SYNTHESIS, CONFORMATIONAL, AND ANTIARRHYTHMIC PROPERTIES OF SELECTED DERIVATIVES OF THE 3,7-DIHETERABICYCLO[3.3.1]-NONANE FAMILY

By

SAMEER TYAGI

Bachelor of Science (B.Sc.)
University of Bombay
Bombay, India
1990

Master of Science (M.S.)
Oklahoma State University
Stillwater, Oklahoma
1995

Submitted to the Faculty of the
Graduate College of the
Oklahoma State University
in partial fulfillment of
the requirement for
the Degree of
DOCTOR OF PHILOSOPHY
May, 1999

SYNTHESIS, CONFORMATIONAL, AND ANTIARRHYTHMIC PROPERTIES OF SELECTED DERIVATIVES OF THE 3,7-DIHETERABICYCLO[3.3.1]-NONANE FAMILY

Thesis approved:

K D Berlin

Thesis Advisor

Neil B Ram

Eldon C Nelson

Warren T Ford

Wayne B. Powell

Dean of the Graduate College

ACKNOWLEDGMENTS

I wish to express my sincere appreciation and upmost respect to Dr. K.D. Berlin, not only for his suggestions and guidance regarding this project, but also for his personal insight and advice on issues outside of the lab. I would like to thank him, not only for his help and patience, but also his care and genuine interest. Appreciation is also extended to my committee members, Dr. Eldon Nelson, Dr. Ziad El Rassi, and especially Dr. Warren Ford for accepting to serve on my committee at short notice. Special thanks goes to Dr. Feng Qiu for his great help in teaching me to do 2D NMR experiments. I wish to thank Dr. Mario Rivera and Dr. Subbiah Sangiah for useful discussions on 2D NMR experiments and cardiovascular physiology respectively. I would like to thank Dr. Dilip Sensharma for performing mass spectral analysis. I am grateful to Dr D. van der Helm and Dr. Elizabeth Holt for their outstanding crystallographic work. I am thankful to Dr. Benjamin Scherlag and Dr. Eugene Patterson for performing the antiarrhythmic screening of our compounds. Efforts by Asif Rahaman and Dr. Lionel Raff in performing the *ab initio* calculations are highly appreciated. I am grateful to the Chemistry Department for giving me an opportunity to continue my education and also the financial support in the form of teaching assistantship during the course of my graduate study.

I am thankful to my colleagues Jagdish Jethmalani, Matora Madler, Jozef Klucik, Chad Brown, Shengquan Liu, Kevin Couch, Asif Rahaman, Kenneth Brown, Karen

Teeter, Spence Pilcher, Paul Miller, Ken Hampton, and Marc Wirtz for being good friends and making life more enjoyable. A special thanks goes to Christie for good friendship and all the help and encouragement in tough times.

No words can suffice to express my deepest gratitude to my parents, brother, and sister. Their love and faith in me has been my greatest strength. Finally, I wish to thank the almighty God for providing me strength and courage to complete my degree.

TABLE OF CONTENTS

Chapter Page

I. HISTORICAL

Introduction. 1
Sudden Cardiac Death and Coronary Artery Disease 2
Myocardial Infarction 3
Electrocardiogram 4
Arrhythmias 6
Classification of Antiarrhythmic Agents 11
Limitations of Vaughan Williams Classification 21
Antiarrhythmic Properties of 3,7-Diheterabicyclo[3.3.1]nonanes 22
Effects of Antiarrhythmic Drugs on Mortality 30
Nitric Oxide in Vascular Regulation 36

II. RESULTS AND DISCUSSION 39

Antiarrhythmic Agents with Multiple Class Action 39
Structure Activity Relationship 40
Synthetic Methodology 46
Antiarrhythmic Activity 59
Conformational Analyses 63
Summary 85
Suggestions for Future Work 86

III. EXPERIMENTAL 89

General Information 89
7-Benzyl-3-oxa-3,7-diazabicyclo[3.3.1]nonane-
Hydroperchlorate (**28**) 91
7-Benzyl-3-oxa-9,9-(1,3-dithiolan-2-yl)-7-azabicyclo[3.3.1]nonane
Hydroperchlorate (**29**) 92
3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (**30**) 92
3,7-Dibenzyl-9,9-(1,3-dithiolan-2-yl)-3,7-diazabicyclo[3.3.1]nonane
Hydroperchlorate (**31**) 93
7-[4-(1*H*-Imidazol-1-yl)benzoyl]-3-oxa-7-azabicyclo[3.3.1]nonane
Hydroperchlorate (**32**) 93
7-(4-Nitrobenzoyl)-3-oxa-7-azabicyclo[3.3.1]nonane (**33**) 94
7-(4-Aminobenzoyl)-3-oxa-7-azabicyclo[3.3.1]nonane (**34**) 95
7-[(4-*N*-Benzoyl)benzoyl]-3-oxa-7azabicyclo[3.3.1]-
nonane (**35**) 96

7-(4-Nitrobenzenesulfonyl)-3-oxa-7-azabicyclo[3.3.1]nonane (**36**) 97
7-(4-Aminobenzenesulfonyl)-3-oxa-7-azabicyclo[3.3.1]nonane (**37**) 98
7-[4-(1*H*-Imidazol-1-yl)benzoyl]-3-benzyl-3,7-diazabicyclo[3.3.1]nonane (**38**) 99
3-Benzyl-7-(4-nitrobenzoyl)-3,7-diazabicyclo[3.3.1]nonane (**39**) 100
3-Benzyl-7-(4-aminobenzoyl)-3,7-diazabicyclo[3.3.1]nonane (**40**) 100
3-Benzyl-7-[4-(dimethylsulfonyl)amino]benzoyl-3,7-diazabicyclo[3.3.1]nonane (**41**) 101
3-Benzyl-7-(4-nitrobenzenesulfonyl)-3,7-diazabicyclo[3.3.1]nonane (**42**) 102
3-Benzyl-7-(4-aminobenzenesulfonyl)-3,7-diazabicyclo[3.3.1]nonane (**43**) 103
Attempted Preparation of 7-[4-(Amino)benzyl]-3-oxa-7-azabicyclo[3.3.1]nonane (**49**) 103
7-[4-(Amino)benzyl]-3-isopropyl-3,7-diazabicyclo[3.3.1]nonane (**52**) 104
7-[4-(*N*-Benzylamino)benzyl]-3-isopropyl-3,7-diazabicyclo[3.3.1]nonane (**53**) 105
7-[4-(*N*-Ethylamino)benzyl]-3-isopropyl-3,7-diazabicyclo[3.3.1]nonane (**54**) 105
7-[4-(*N*-Ethylamino)phenylacetyl]-3-isopropyl-3,7-diazabicyclo[3.3.1]nonane (**55**) 106
7-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (**57**) 107
7-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonane (**58**) 108
7-Benzyl-3-oxa-9,9-(1,3-dithiolan-2-yl)-7-azabicyclo[3.3.1]nonane (**59**) 109
3-Oxa-7-azabicyclo[3.3.1]nonane (**60**) 109
7-(4-Fluorobenzoyl)-3-oxa-7-azabicyclo[3.3.1]nonane (**61**) 110
7-[4-(1*H*-Imidazol-1-yl)benzoyl]-3-oxa-7-azabicyclo[3.3.1]nonane (**62**) 111
7-(4-Fluorobenzenesulfonyl)-3-oxa-7-azabicyclo[3.3.1]nonane (**63**) 112
3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**65**) 113
3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]nonane (**66**) 114
3,7-Dibenzyl-9,9-(1,3-dithiolan-2-yl)-3,7-diazabicyclo[3.3.1]nonane (**67**) 115
3-Benzyl-3,7-diazabicyclo[3.3.1]nonane (**68**) 116
3-Benzyl-7-(4-fluorobenzoyl)-3,7-diazabicyclo[3.3.1]nonane (**69**) 116
3-Benzyl-7-[4-(dimethylsulfonyl)amino]benzoyl-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (**70**) 117
3-Benzyl-7-(2',2',2'-trichloroethoxycarbonyl)-9,9-

(1,3-dithiolan-2-yl)-3,7-diazabicyclo[3.3.1]nonane (**71**) 118
7-Aza-3-benzyl-9,9-(dithiolan-2-yl)-3,7-diazabicyclo[3.3.1]nonane (**72**) 119
4-*N*-Acetylbenzamide (**75a**) 119
4-*N*-Ethylbenzylamine (**76a**) 120
4-*N*-Benzoylbenzamide (**75b**) 120
4-*N*-Benzylbenzylamine (**76b**) 121
Attempted Preparation of 7-[4-(*N*-Ethyl)benzyl]-3-benzyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**77**) 122
4-Nitrobenzylamine (**79**) 122
Attempted Preparation of 7-[4-Nitrobenzyl]-3-benzyl-3,7-diazabicyclo[3.3.1]-nonan-9-one (**80**) 123
Attempted Preparation of 7-[4-(*N*-Ethyl)benzyl]-3-thia-3,7-diazabicyclo[3.3.1]nonan-9-one (**84**) 124

BIBLIOGRAPHY 239

LIST OF TABLES

Table		Page
I.	Vaughan Williams Classification	11
II.	Clinical Subclassification of Class I Antiarrhythmic Drugs	14
III.	Antiarrhythmic Activity of Benzamide Derivatives	24
IV.	Antiarrhythmic Activity of Bispidine Derivatives **20**	25
V.	Antiarrhythmic Activity of Bispidine Derivatives **21**	26
VI.	Antiarrhythmic Activity of 3-Azabicyclo[3.3.1]nonanes **22**	27
VII.	Antiarrhythmic Properties of the Most Active DHBCN Derivatives **23**	29
VIII.	Events in 1,455 Patients Randomly Assigned to Receive Encainide (**7**), Flecainide (**8**), or Matching Placebo	32
IX.	Incidence of Adverse Events Requiring Discontinuation of the Study Drugs in the ESVEM Trial	35
X.	Incidence of Death in the Three Study Groups of the BASIS Study	36
XI.	Interim Results From the CASH Study	37
XII.	Derivatives With Proposed Class I, III, and IV Action	43
XIII.	Antiarrhythmic Data of Compounds **28** and **30**	62
XIV.	^{1}H-NMR Chemical Shifts (ppm) and Multiplicities (Hz) for **57**	78
XV.	Minimum Potential Energy (kcal/mol) Calculation for **57** and **91a**	80
XVI.	Minimum Potential Energy (kcal/mol) Calculation for **22d** and **28**	81

LIST OF FIGURES

Figure Page

1. Illustration of an Electrocardiogram (ECG) Output 5

2. Action Potential of a Cardiac Purkinje Fiber With Five Phases and its Major Ionic Currents 13

3. NOESY Spectrum of **28** 69

4. DQCOSY Spectrum of **28** 71

5. NOESY Spectrum of **22d** 72

6. DQCOSY Spectrum of **22d** 74

7. HMBC Spectrum of **22d** 75

8. HOESY Spectrum of **57** 77

9. ORTEP Diagram of **57** 79

10. ORTEP Diagram of **32** 84

LIST OF PLATES

Plate		Page
I.	IR Spectrum of **28**	126
II.	^{1}H NMR Spectrum of **28**	127
III.	^{13}C NMR Spectrum of **28**	128
IV.	IR Spectrum of **29**	129
V.	^{1}H NMR Spectrum of **29**	130
VI.	^{13}C NMR Spectrum of **29**	131
VII.	IR Spectrum of **30**	132
VIII.	^{1}H NMR Spectrum of **30**	133
IX.	^{13}C NMR Spectrum of **30**	134
X.	IR Spectrum of **31**	135
XI.	^{1}H NMR Spectrum of **31**	136
XII.	^{13}C NMR Spectrum of **31**	137
XIII.	IR Spectrum of **32**	138
XIV.	^{1}H NMR Spectrum of **32**	139
XV.	^{13}C NMR Spectrum of **32**	140
XVI.	IR Spectrum of **33**	141
XVII.	^{1}H NMR Spectrum of **33**	142
XVIII.	^{13}C NMR Spectrum of **33**	143
XIX.	IR Spectrum of **34**	144

XX. ^{1}H NMR Spectrum of **34** 145

XXI. ^{13}C NMR Spectrum of **34** 146

XXII. IR Spectrum of **35** 147

XXIII. ^{1}H NMR Spectrum of **35** 148

XXIV. ^{13}C NMR Spectrum of **35** 149

XXV. IR Spectrum of **36** 150

XXVI. ^{1}H NMR Spectrum of **36** 151

XXVII. ^{13}C NMR Spectrum of **36** 152

XXVIII. IR Spectrum of **37** 153

XXIX. ^{1}H NMR Spectrum of **37** 154

XXX. ^{13}C NMR Spectrum of **37** 155

XXXI. IR Spectrum of **38** 156

XXXII. ^{1}H NMR spectrum of **38** 157

XXXIII. ^{13}C NMR Spectrum of **38** 158

XXXIV. IR Spectrum of **39** 159

XXXV. ^{1}H NMR Spectrum of **39** 160

XXXVI. ^{13}C NMR Spectrum of **39** 161

XXXVII. ^{1}H NMR Spectrum of **40** 162

XXXVIII. ^{1}H NMR Spectrum of **42** 163

XXXIX. ^{13}C NMR Spectrum of **42** 164

XL. IR Spectrum of **43** 165

XLI. ^{1}H NMR Spectrum of **43** 166

XLII. ^{13}C NMR Spectrum of **43** 167

XLIII. ^{1}H NMR Spectrum of **51** 168

XLIV. ^{13}C NMR Spectrum of **51** 169

XLV. IR Spectrum of **52** 170

XLVI. ^{1}H NMR Spectrum of **52** 171

XLVII. ^{13}C NMR Spectrum of **52** 172

XLVIII. IR Spectrum of **53** 173

XLIX. ^{1}H NMR Spectrum of **53** 174

L. ^{13}C NMR Spectrum of **53** 175

LI. IR Spectrum of **54** 176

LII. ^{1}H NMR Spectrum of **54** 177

LIII. ^{13}C NMR Spectrum of **54** 178

LIV. IR Spectrum of **55** 179

LV. ^{1}H NMR Spectrum of **55** 180

LVI. ^{13}C NMR Spectrum of **55** 181

LVII. IR Spectrum of **57** 182

LVIII. ^{1}H NMR Spectrum of **57** 183

LIX. ^{13}C NMR Spectrum of **57** 184

LX. IR Spectrum of **58** 185

LXI. ^{1}H NMR Spectrum of **58** 186

LXII. ^{13}C NMR Spectrum of **58** 187

LXIII. IR Spectrum of **59** 188

LXIV. ^{1}H NMR Spectrum of **59** 189

LXV. ^{13}C NMR Spectrum of **59** 190

LXVI. IR Spectrum of **60** 191

LXVII. ^{1}H NMR Spectrum of **60** 192

LXVIII. ^{13}C NMR Spectrum of **60** 193

LXIX. IR Spectrum of **61** 194

LXX. ^{1}H NMR Spectrum of **61** 195

LXXI. ^{13}C NMR Spectrum of **61** 196

LXXII. IR Spectrum of **62** 197

LXXIII. ^{1}H NMR Spectrum of **62** 198

LXXIV. ^{13}C NMR Spectrum of **62** 199

LXXV. IR Spectrum of **63** 200

LXXVI. ^{1}H NMR Spectrum of **63** 201

LXXVII. ^{13}C NMR Spectrum of **63** 202

LXXVIII. IR Spectrum of **65** 203

LXXIX. ^{1}H NMR Spectrum of **65** 204

LXXX. ^{13}C NMR Spectrum of **65** 205

LXXXI. IR Spectrum of **66** 206

LXXXII. ^{1}H NMR Spectrum of **66** 207

LXXXIII. ^{13}C NMR Spectrum of **66** 208

LXXXIV. IR Spectrum of **67** 209

LXXXV. ^{1}H NMR Spectrum of **67** 210

LXXXVI. ^{13}C NMR Spectrum of **67** 211

LXXXVII. IR Spectrum of **68** 212

LXXXVIII. IR Spectrum of **69** 213

LXXXIX. ^{1}H NMR Spectrum of **69** 214

XC. ^{13}C NMR Spectrum of **69** 215

XCI. IR Spectrum of **70** 216

XCII. ^{1}H NMR spectrum of **70** 217

XCIII. ^{13}C NMR Spectrum of **70** 218

XCIV. IR Spectrum of **71** 219

XCV. ^{1}H NMR Spectrum of **71** 220

XCVI. ^{13}C NMR Spectrum of **71** 221

XCVII. IR Spectrum of **72** 222

XCVIII. ^{1}H NMR Spectrum of **72** 223

XCIX. ^{13}C NMR Spectrum of **72** 224

C. IR Spectrum of **75a** 225

CI. ^{1}H NMR Spectrum of **75a** 226

CII. ^{13}C NMR Spectrum of **75a** 227

CIII. IR Spectrum of **75b** 228

CIV. ^{1}H NMR Spectrum of **75b** 229

CV. ^{13}C NMR Spectrum of **75b** 230

CVI. IR Spectrum of **76a** 231

CVII. ^{1}H NMR Spectrum of **76a** 232

CVIII. ^{13}C NMR Spectrum of **76a** 233

CIX. IR Spectrum of **76b** 234

CX. ^{1}H NMR Spectrum of **76b** 235

CXI. ^{13}C NMR Spectrum of **76b** 236

CXII. ^{1}H NMR Spectrum (600 MHz) of **57**.....237

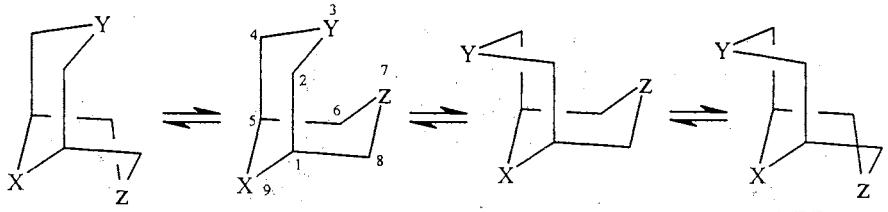
CXIII. ^{1}H NMR Spectrum (600 MHz) of **91a**.....238

CHAPTER I

HISTORICAL

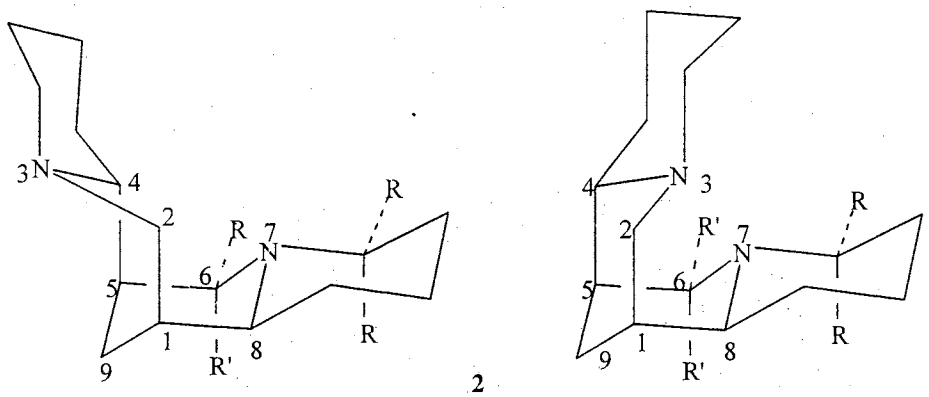
Introduction

The 3,7-diheterabicyclo[3.3.1]nonanes **1** (DHBCNs) family have been of great



1-CB **1-CC** **1-BC** **1-BB**

interest not only for unique conformational and stereochemical considerations, but also as potential antiarrhythmic agents.[1] In addition to being excellent antiarrhythmic agents, DHBCN's have also been found to exhibit good hypotensive activity[2] and local anesthetic properties.[3] The DHBCN's have also been of great interest due to their unique conformational preferences.[1c,4a-b] DHBCNs possess conformational mobility and, as a result can adopt four different conformations, namely a chair-chair (**1-CC**), boat-chair (**1-BC**), chair-boat (**1-CB**) and/or boat-boat (**1-BB**). The boat-boat conformation, however, appears to be rare, possibly due to energetically unfavorable interactions and has not been confirmed.[4c] The dynamic properties of the DHBCN ring may result in equilibration between the above four conformers. The conformational preferences of these systems appear critical for their biological action. The DHBCN ring moiety is found in naturally occuring C-15 lupine alkaloids like sparteine (**2a**), aphylline (**2b**), lupanine (**2c**), and α-isosparteine (**2d**).[5] Sparteine (**2a**), the most common among the four alkaloids, has been used in the management of cardiac arrhythmias.[6]



2

a R, R' = H [Sparteine]
b R', R' = O, R = H [Aphylline]
c R, R = O, R' = H [Lupanine]
d R, R' = H [α-Isosparteine]

Sudden Cardiac Death and Coronary Artery Disease

The term "sudden cardiac death" (SCD) broadly refers to the unexpected cessation of breathing and circulation caused by an underlying heart disease. Under such conditions, victims often experience shortness of breath, sweating, chest pain, and/or loss of consciousness. Usually, within a few minutes to hours from the onset of these symptoms, death occurs. SCD has occurred in people who have had a history of heart disease, even though they were successfully treated by the physician. In many other cases, SCD has struck individuals with no prior known or diagnosed heart disease.[7a] The major challenges in prevention of SCD depends on a better understanding of the clinical settings in which it occurs, as well as the pathologic and electrophysiologic mechanisms. About 20% of all natural deaths in the industrially-developed world are sudden cardiac deaths.[7b,c] In the United States each year, 400,000-500,000 persons die of cardiovascular disease.[7a,b] Of the more than 700,000 deaths from the coronary artery disease (CAD)

each year, 60%-65% are sudden, usually occurring when the victim is engaged in normal, routine activities.[7a-c]

Extensive studies have now shown that people with CAD, a prior history of a myocardial infarction (MI), or ventricular arrhythmias [originating from CAD or non-CAD factors] are at great risk for SCD.[7,8] Some other factors which have been linked to the SCD are aortic stenosis,[7c,] hypertrophic cardiomyopathy,[9] cardiomyopathy,[10] mitral valve prolapse,[11] prolonged QT syndrome,[12] Wolff-Parkinson-White syndrome,[13] and drug-induced ventricular arrhythmias.[8f,14] Evidence for chronic ischemic heart disese is found at autopsy, with healed MI having been reported in 40% to 75%.[7b] Acute, coronary occlusion may result in ventricular tachycardia (VT) or ventricular fibrillation (VF) or less commonly in mechanical dysfunction, leading to sudden death.[7,8] Some studies have reported acute thrombosis in 40% of sudden deaths.[7b]

Myocardial Infarction

The typical MI begins with the rupture of an atherosclerotic plaque[15] A thrombus or blood clot forms at the site and over time fills the lumen of the coronary artery, interfering with or abolishing blood flow. Thromboemboli and vasopasm may also precipitate blockage or thrombus formation. Regardless of the initiating event, tissue downstream from an occlusion is deprived of arterial blood with its life-sustaining oxygen and nutrients, and metabolic wastes accumulate. The lack of oxygen inhibits mitochondrial oxidative phosphorylation, the major source of the adenosine triphosphate (ATP) used to power excitation-contraction coupling and maintain intracellular homeostatis. As a result, the tissue becomes energy starved and contractile function

declines. Further, if the tissue downstream from a coronary occlusion is not reperfused, affected cells will eventually die and be replaced by scar tissue. This impairs overall cardiac pump function because cardiac myocytes are terminally differentiated and cannot replicate.[15b] The lack of blood flow also allows for the buildup of metabolic wastes, particularly lactic acid and amphilic fatty acid metabolites, and the tissue becomes acidotic. The increased intracellular H^+ concentration favors intracellular Na^+ accumulation via the sarcolemnal Na^+/H^+ exchange and this, in turn, favors excess Ca^{2+} accumulation via the reverse mode of the electrogenic sarcolemmal Na^+/Ca^{2+} exchanger.[16] Intracellular free Ca^{2+} concentration gradually increases and cytosolic Ca^{2+} overload activates proteases[17] and lipases[18] which, in turn, degrade important cellular components.

Electrocardiogram

The electrophysiological events of the heart are recorded in the form of an electrocardiogram (ECG) resulting from myocardial fiber depolarization and repolarization (Figure 1). Typically, there are six waves in the ECG: P, Q, R, S, T, and sometimes U. Some of the important components of the ECG are:

(1) QRS complex: The QRS interval signifies the depolarization of the cardiac muscle cells and is defined as the time alloted for a polarized cell to become fully depolarized in which there is a sudden loss of semipermeability of the membrane around the cell so that there is a flow of ions (Na^+ and Ca^{2+}) across the cell. It is usually never greater than 0.10 s.

(2) QT interval: The QT interval refers to the time to complete the process of depolarization

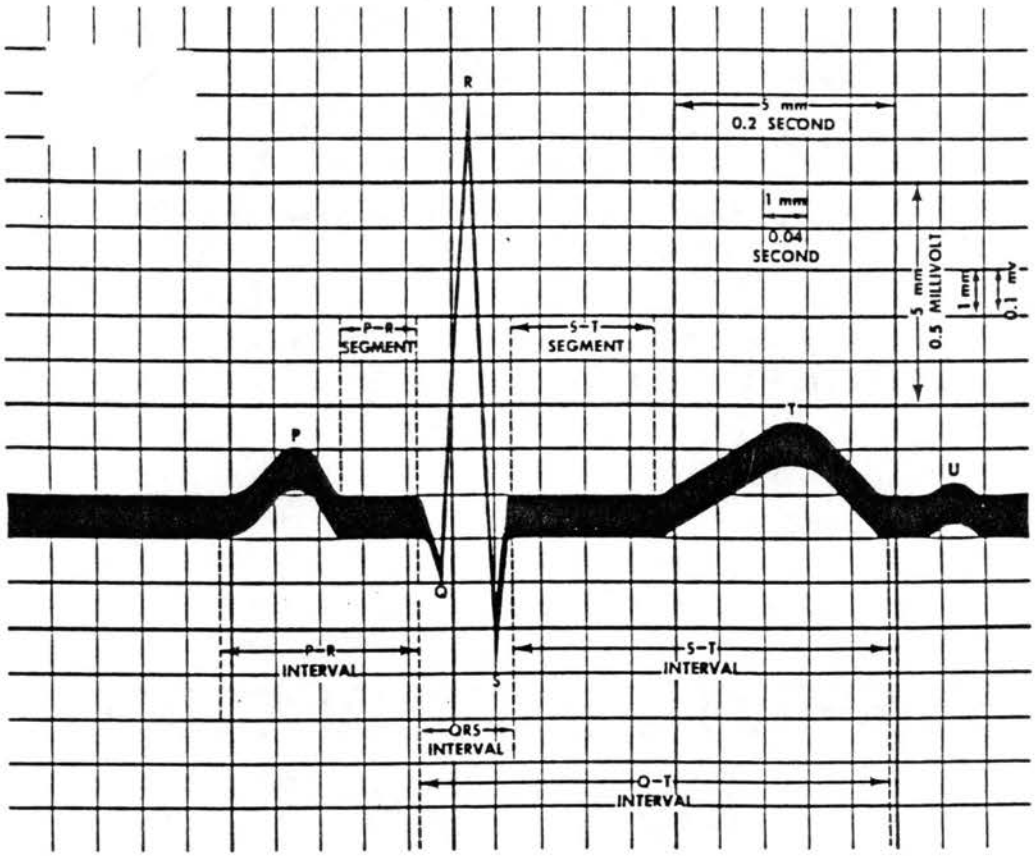


Figure 1. Illustration of an Electrocardiogram (ECG) Output

and repolarization. It is measured from the onset of any QRS activity to the end of the T wave.

(3) P-R interval: The PR interval results from the atrial depolarization, impulse delay at the atrioventricular (AV) node, and transmission of the impulse through the bundle of His, right and left bundles, and Purkinje fibers. It is measured from the beginning of the P wave to the onset of any QRS activity and is normally 0.12-0.20 s.

(4) P-R segment: The origin of the P-R segment is the same as the P-R interval and is also measured from the beginning of the P wave to the onset of any QRS activity. It is usually not greater than 0.08 s.

Abnormalities in a normal cardiac rhythm affect the appearance of these waves, intervals, and overall appearence of the ECG. Arrhythmias are characterized by such abnormalities.

Arrhythmias

As stated earlier, myocardial ischemia provokes abnormalities in the biochemical homeostatis of individual cardiac cells. These intracellular changes ultimately culminate in the disruption of cellular electrophysiological properties and life-threatening alterations in the cardiac rhythm. A large amount of chemical substances, including catecholamines, amphilic products of lipid metabolism, various peptides, cytosolic Ca^{2+} accumulation, and an increase in extracellular K^{+}, have been proposed as possible causative factors in the genesis of such life-threatening cardiac rhythms or arrhythmias.[19]

Disturbances in the cardiac rhythm may be divided into two categories: (1) arrhythmias and (2) conduction abnormalities.[20] The category of arrhythmias include

ectopic beats, brady- and tachyarrhythmias, and rhythms other than the normal sinus rhythm. Conduction abnormalities include atrioventricular (AV) nodal blocks, bundle branch blocks, and pre-excitation syndromes. Some of the common clinically encounterd arrhythmias include:

Atrial arrhythmias: The atrial arrhythmias include: (1) sinoatrial block/arrest; (2) atrial premature contraction, (3) atrial tachycardias, (4) atrial flutter, and (5) atrial fibrillation.

Sinoatrial (SA) block/arrest: In SA block, sinus node impulse generation occurs but its propagation to the atrial conduction system and/or atrial musculature fails to occur, i.e., its exit from the SA node is blocked. In sinus arrest, on the other hand, there is total failure of the SA node. Either of two mechanisms may be responsible: (1) complete SA exit block in which the SA node fires without resultant atrial capture or (2) total failure of impulse formation in which the SA node fails to function at all.

Electrocardiographically, SA block/arrest is characterized by the absence of an expected P-QRS-T cycle for one or more cycles.[20] Often, atrial pacing is resumed by a release of the exit block, and thus a normal P wave occurs as the result of atrial depolarization arising from the SA nodal discharge. Occasionally, an atrial, atrioventricular junctional, or ventricular escape beat, may occur as their order of hierarchy is surpassed. Should the normal pacemaker take over following the escape beat, normal P-QRS-T complexes will resume.

Atrial Premature Contraction (APC): APC is an atrial contraction arising from an ectopic focus somewhere in either the right atrium or left atrium, but not the sinus node.[20] Electrocardiographically, APC's are characterized by : (1) an atrial conduction (P wave) occurring before the next normal beat is due and (2) an associated QRS-T identical or

very similar to the QRS-T of preceding beats. The PR interval may be longer or shorter than the PR interval of a normal sinus beat. On occassion, the advancing stimulus of a APC may reach the AV node during its absolute refractory period. Should this occur, the AV node is unable to accept the impulse and a blocked atrial beat occurs. This would appear as an early P wave not followed by the expected QRS-T complex.

Atrial Tachycardia: Atrial tachycardia may be sustained or paroxysmal.[20] It is defined as a run of three or more consecutive APC's. Electrocardiographically, atrila tachycardia is characterized by :(1) atrial and ventricular, i.e., P-QRS-T, rate of 150 to 250 beats/min, (2) a generally regular rhythm, (3) an abnormal P wave morphology, and (4) a normal QRS-T complex associated with each P wave.

Atrial Flutter: Atrial flutter is an advancement along the continum of atrial tachycardia.[20] Whereas atrial tachycardia are the rapid, consecutive firings of an atrial focus between 150-250 beats/min, atrial flutter is the rapid, consecutive firing of antrial focus between 250-350 beats/min. Atrial conduction is so rapid that AV block is usually the rule rather than the exception. Thus, the ventricular rate is considerably slower than the atrial rate and generally in the range of 75 to 150 beats/min.

Electrocardiographically, atrial flutter is characterized by (1) an atrial rate of 250-350 beats/min, (2) P waves appearing as sawtooth in nature , and (3) a ventricular rate usually at a discernible ratio of the atrial rate, i.e., 1/2, 1/3, or 1/4. This would produce 2:1, 3:1. or 4:1 atrioventricular conduction.

Atrial Fibrillation: Atrial fibrillation is a further advancement along the continuum of atrial tachyarrhymias.[20] Atrial fibrillation, however, is the rapid firing of several atrial foci resulting in an irregular atrial rate. Electrocardiographically, it is characterized by

multiple irregular P waves with an atrial rate of greater than 350 beats/min. The ventricular rate is almost always irregular.

Venricular arrhythmias include: (1) ventricular premature beats (PVC), (2) ventricular tachycardia, (3) idioventricular rhythm, (4) ventricular flutter, (5) ventricular fibrillation, and (6) ventricular asystole.

Premature Ventricular Contractions (PVC): PVC, also commonly known as ventricular premature beats, may occur via three mechanisms: (1) re-entry, (2) enhanced automaticity, or (3) parasystole.[20] In re-entry, a supraventricular, usually sinus, impulse conducts normally until it reaches the Purkinje fiber system. It then proceeds to activate the ventricular myocardium, after which, it reenters the ventricular conduction system to reactivate the ventricles. The initiating complex will have a normal narrow QRS. The reentry impulse, however, will have an aberrant, wide and often bizzare complex as compared to its predecessor. Due to dependence on its predecessor, re-entrant ventricular ectopics tend to have a relatively constant interval between themselves and their predecessor-a phenomenon known as fixed coupling.[20]

PVC's due to enhanced autorhythmicity are random and unpredictable. Ventricular parasystole, on other hand, refers to the firing of an autonomous ectopic focus within the ventricles with measurable periodicity.[20] Since parasystolic ectopics and those due to enhanced autorhythmicity are non-dependent on a predecessor beat and arise on their own, coupling intervals are variable. Electrocadiographically, PVC's are charaterized by their bizarre, aberrantly conducted QRS waves without a preceding P wave. The QRS duration usually exceeds 0.1 s and is commonly associated with a T wave opposite in direction to the main coordinate directive of the QRS.

Ventricular Tachycardia (VT): VT is defined as three or more consecutive PVC's.[20] VT usually occurs as a result of rapid, repetitive re-entry impulses within the ventricular conductive system. Electrocardiographically, VT is characterized by three or more consecutive PVC's ranging usually between 150 and 200 beats/min. A parasystolic mechanism is suggested when the rate falls below 140 beats/min and a re-entrant mechanism when the rate exceeds 140 beats/min.

Idioventricular Rhythm: An idioventricular rhythm is one in which some portion of the ventricles, usually within the Purkinje system, takes over the role of pacing when higher mechanisms along the pacing hierarchy fail to operate.[20] Electrocardiographically, idioventricular rhythm is characterized by wide, bizarre QRS complexes, occurring 20 to 120 beats/min accompanied by absence of P wave.

Ventricular Flutter: Ventricular flutter is a variant of ventricular tachycardia in which discrete QRS-T morphology is lost.[20] A single ventricular ectopic focus fires ar rate of 200 to 300 beats/min. Electrocardiographically, ventricular flutter is characterized by smooth biphasic waves, 200 to 300 per min, and a sine wave in appearance. Often, ventricular flutter is an intermediary rhythm and/or predecessor to ventricular fibrillation.

Ventricular Fibrillation (VF): VF usually occurs following premonitory ventricular ectopic activity, i.e., PVC's, ventricular tachycardia or ventricular flutter.[20] The likelihod of a normal sinus rhythm being converted to a VF is greatest during myocardial infarction. Electrocardiographically, VF is characterized by bizzare oscillations without evidence of discrete QRS-T morphology. The oscillations are very coarse and irregular between 150 and 300 beats/min.

Classification of Antiarrhythmic Agents

In recent years, with the discovery of new antiarrhythmic agents and development of the sophisticated electrodes for recording the intracellular electrical events, it became necessary to develop a classification scheme for antiarrhythmic drugs. Several criteria have appeared in the literature in attempt to classify such agents.[21] Among these is the Vaughan Williams (VW) classification,[22] which is based upon the fundamental electrophysiological effects of drugs on myocardial tissues. This approach is widely accepted by most physicians. The VW scheme classifies most antiarrhythmic drugs into five types (Table I).

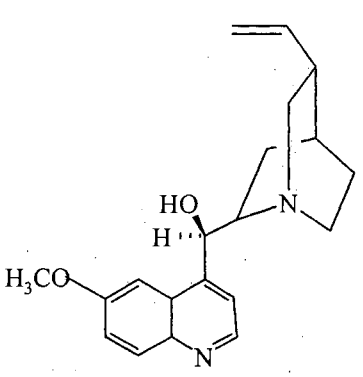
Table I[a]

VAUGHAN WILLIAMS CLASSIFICATION

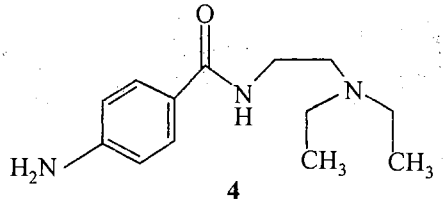
class	electrophysiological action	drugs
I	Sodium channel blockade	lidocaine, procainamide, diisopyramide
II	β-Blockers/antagonism of sympathetic nervous system	propranolol, esmolol
III	Prolong action potential duration/ increased refractoriness	amiodarone, sotalol, bretylium
IV	Calcium channel blockers	verapamil, diltiazem
V	Cl^- channel blockers	alinidine

[a]Reference 22

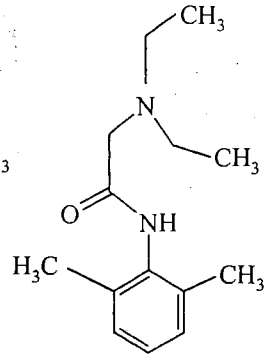
Class I: Class I antiarrhythmic agents alter the transmembrane action potential and have been found to retard the maximum upstroke (Phase 0, Figure 2) velocity of the cardiac action potential maximum (the maximum rate of rise of depolarization) V_{max} (dV/dt_{max}). This is interpreted as an inhibition of the fast sodium influx across the cell membrane. The electrophysiological and clinical differences between various class I drugs led to a Sub-classification into three categories, namely Ia, Ib, Ic (Table II). This sub-classification is based upon the varying effects which each agent has on the QRS complex, conduction, effective refractory period (ERP), and action potential duration (APD). The common properties of all class I drugs are inhibition of the fast sodium inward current and, more generally, the membrane stabilizing effect of local anesthetic agents. Class I agents like quinidine (**3**), procainamide (**4**), lidocaine (**5**), and diisopyra-



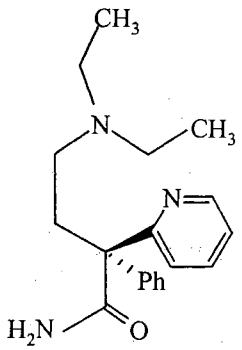
3



4



5



6

mide (**6**) have been shown to suppress ventricular arrhythmias in the acute phase of MI.[23] Interestingly, a great majority of drugs in this family possess amide functionalities.

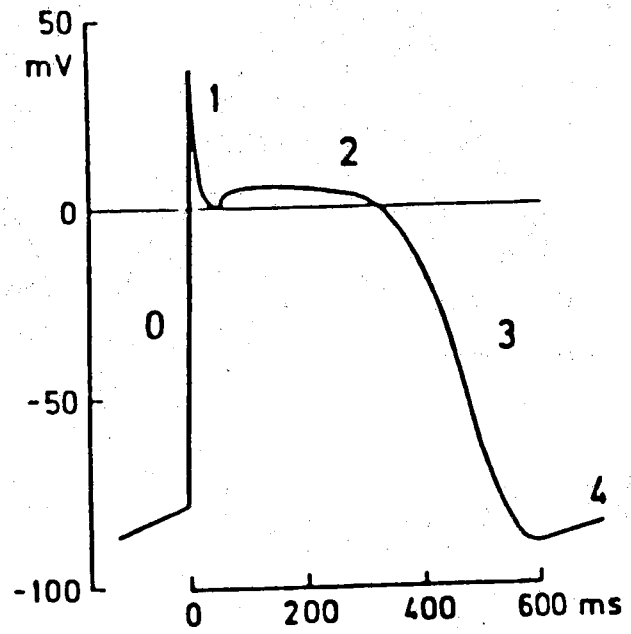


Figure 2. Action potential of a cardiac Purkinje fiber with five phases and its major ionic currents. Phase 0: rapid upstroke (Na^+ in); phase 1: initial repolarization (K^+ out); phase 2: plateau (Ca^{2+} and Na^+ in); phase 3: repolarization (K^+ out); phase 4: pacemaker depolarization (in part K^+).

Class Ia: These agents prolong the APD and slow conduction at high concentrations, lengthen the ERP absolutely and relatively to APD, and widen the QRS complex in the ECG. Quinidine (**3**), procainamide (**4**), and diisopyramide (**6**) are typical representatives of the Ia group.

Class Ib: Class Ib agents shorten the APD in parts of the ventricular conduction system.

Table II[a]

CLINICAL SUB-CLASSIFICATION OF CLASS I ANTIARRHYTHMIC DRUGS

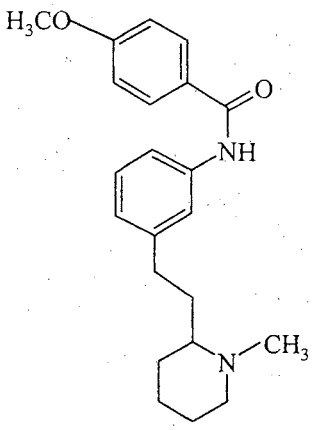
Effect on	Ia	Ib	Ic
	quinidine procainamide diisopyramide	lidocaine mexiletine tocainide	lorcainide encainide flecainide
1. QRS	widen at high concentration	none in sinus rhythm	widen at low concentration
2. Conduction	slowed at high concentration	none in sinus rhythm	slowed at low concentration
3. ERP	lengthened absolutely and relative to APD	lengthened in relation to APD	very little change
4. APD	lengthened at high concentration	shortened	very little change

[a]Reference 22

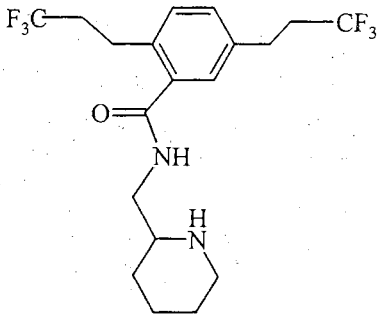
In sinus rhythm, no effect is observed on the QRS and conduction velocity. The effective refractory period (ERP) is lengthened relative to the APD. Class Ib agents may have more pronounced effects in areas of ischemic myocardium than in normal myocardium.[24] Typical representatives of class Ib are lidocaine (**5**) and its derivatives mexiletine and tocainide, diphenylhydantoin, aprindine, and ethmozine. In addition, prolongation of

atrial-His Bundle (AH) and His Bundle-ventricular (HV) conduction is also a measure of class Ib action.

Class Ic: Agents in the class Ic category have only slight effects on the APD and repolarization. The dominant action is the slowing of conduction even at low concentrations, resulting in an increase of QRS complex duration. Prototypes in this class include encainide (**7**), flecainide (**8**), both of which are no longer used.

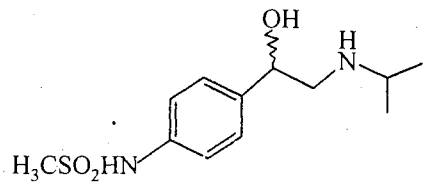


7



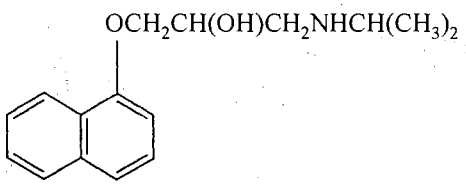
8

Class II (β-blockers): A detailed design and uses of class II drugs have been reviewed.[25] This group of drugs mainly bring about a reduction in the cardiac sympathetic tone.[26] These drugs can therefore interact at a number of electrophysiological and vascular sites which might contribute to the end profile of the antiarrhythmic effect. The primary agents in this class are the β-adrenergic receptor-blocking drugs (acting on any of the subclasses of β-receptors) as well as those that have an indirect sympatholytic effect by preventing release of norepinephrine from the sympathetic nerve endings. Electrophysiologically, β-blockers reduce more or less the maximun rate of depolarization (MRD), slow conduction, and increase the ERP. Class II drugs do not affect the APD, except sotalol (**9**), although the long term treatment with class II agents



9

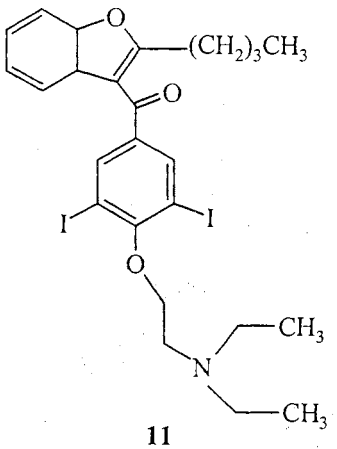
may induce a marked prolongation of APD in atria and ventricles.[22] Class II agents are useful in the prevention and treatment of supraventricular arrhythmias, especially in patients with Wolff-Parkinson-White syndrome.[25] In patients with the prolonged QT syndrome, class II agents are effective in reducing the number and complexity of premature ventricular complexes.[12a,27] In acute MI, β-blockers are usually effective in reducing the number and complexity of premature ventricular complexes.[28] The prototype in this family is propranolol (**10**). A specific class II agent found to have



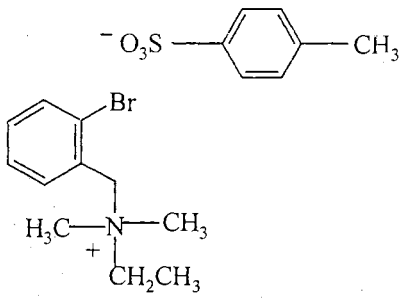
10

multiple class action is sotalol (**9**). One interesting and common structural feature of class II drugs is the presence of a hydroxyl group.

Class III: Class III agents prolong the APD and ERP (phase 3, repolarization phase) without significantly altering the V_{max}. This property of class III drugs is believed to play an important role in the prevention and termination of developing atrial and ventricular fibrillation.[29] The most commonly known members of this family are sotalol (**9**),[30] amiodarone (**11**),[31] and bretylium (**12**).[23b,32] Unlike class I and II agents, the chemical structure of most class III drugs is quite heterogenous. The efficacy, potency, and



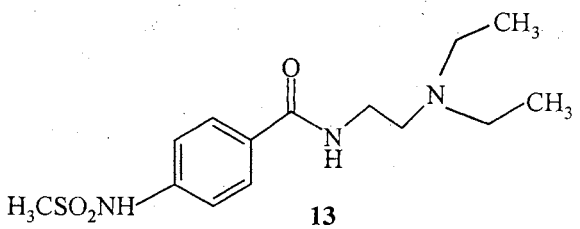
11



12

antiarrhythmic action are not often uniform, and the ionic mechanisms by which the agents delay the repolarization are also frequently different. As a result, members of class III drugs vary significantly in their physiological actions but appear to have in common the ability to prolong ventricular repolarization and ERP.

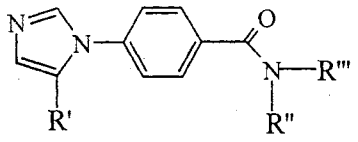
Although sotalol (**9**) and amiodarone (**11**) are good class III agents, they are not selective in their action for this class. As mentioned earlier, sotalol (**9**)[30,33] and amiodarone (**11**)[31] have been shown to possess both class II and class III action.[30,31,33] This may or may not be desirable, depending upon the nature of arrhythmias to be treated. Currently, efforts are underway in our laboratory and others to develop agents that may be selective in class III action. Lumma and co-workers[34] prepared a series of benzamide derivatives in an attempt to achieve class III antiarrhythmic activity. Screening of the compounds [such as sematilide (**13**)] was performed *in vitro* on isolated



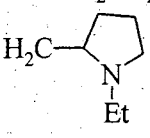
13

canine Purkinje fibers to determine the effects on APD at 95% repolarization (APD_{95}) and the maximun rate of depolarization (V_{max}). As mentioned earlier, active class III agents prolong APD_{95} and ERP with a minimal effect on V_{max}.[29-32] All compounds screened displayed no significant decrease in V_{max}, and the conduction times were essentially unchanged, while prolonging the APD and ERP. Results of the structure-activity relationship (SAR) studies indicated that replacement of the methyl group on the sulfonamide moiety in **13** with another alkyl group greatly reduced decreased the activity.[34] Replacement of the N-H hydrogen in the sulfonamide with a methyl group resulted in a complete loss of activity. In view of its overall profiles, including low toxicity (LD_{50} ~250-300 mg/kg, ip, mouse), **13** was further developed for therapy involving ventricular arrhythmias.[35]

Similar efforts in this direction were reported by Morgan and coworkers[35] for a family of benzamides **14a-d** to determine their selective class III activity using sematilide



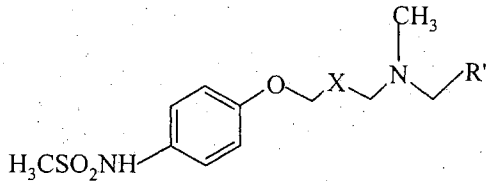
14

(a) R' = H; R" = H; R"' = $CH_2CH_2NEt_2$
(b) R' = CH_3; R" = H; R"' = $CH_2CH_2NEt_2$
(c) R' = H; R" = 1-napth; R"' = CH_2CH_2NEt
(d) R' = H; R" = H; R"' = 

(**13**) as a standard. Results of the SAR analysis indicated that imidazole moiety could be a suitable replacement for the sulfonamide group to enhance the class III AAA.[35] Substitutions on the imidazole ring resulted in active agents, but attachement of the

imidazole functionality to the benzene ring via the C(2) bond of the imidazole ring, resulted in very weak class III activity relative to **13**.

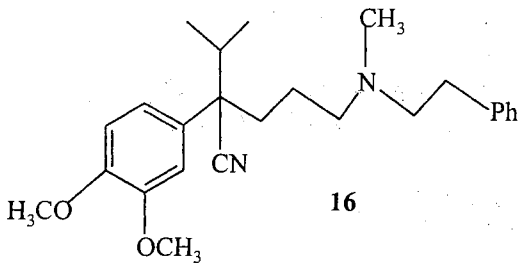
More recently, Butera and co-workers[36] reported a series of (aryloxy)propanolamine **15a-c** which displayed good selective class III action.



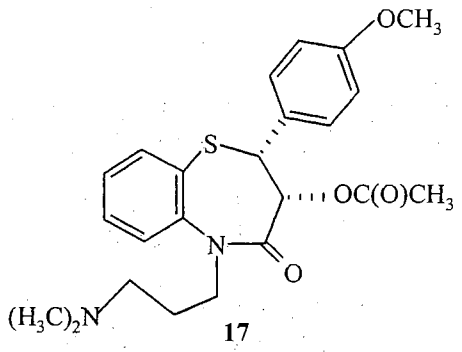
15

(a) X = CHOH; R = quinolin-2-yl
(b) X = CH_2; R = quinolin-2-yl
(c) X = CH_2; R = 6-[(methylsulfonyl)-amino]quinolin-2-yl

Class IV: Class IV drugs inhibit the slow inward current (phase 2) carried by the calcium ions that is responsible for the depolarization of sinoatrial (SA) and atriventricular (AV) nodal cells under normal conditions.[37] In addition, certain class IV agents like verapamil (**16**)[38] and diltiazem (**17**)[39] also suppress arrhythmias that have origin elsewhere than in



16



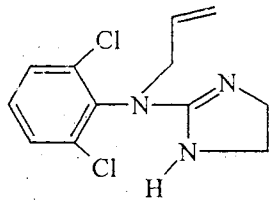
17

the SA or AV node. This effect may be explained by considering that conducting tissue and myocardial muscle become depolarized by local damage or ischemia. If the membrane is partially depolarized, then the sodium channels become partially inactivated

and may not contibute to the action potentials or impulse conduction. However, action potentials carried by the slow inward calcium current are still elicitable, and subsequent slow conduction may initiate reentry arrhythmias.[40] Those arrhythmias should be treatable with calcium channel blockers. Although this hypothesis appears to be logical, most known calcium antagonists are not as strongly effective as expected or are even ineffective in the treatment of arrhythmias associated with ischemia.

An additional mode of antiarrhythmic action of class IV agents was suggested by Vaughan Williams.[22] It was proposed that cell-to-cell conduction via gap junctions may be influenced by the intracellular calcium concentrations. Dahl and Isenberg[41] and DeMello[42] found that increasing free intracellular calcium concentrations led to cell decoupling, possibly modulated by cAMP specific kinases. If the changes in intracellular calcium concentrations that are associated with the myocardial contractions are sufficient to influence intercellular gap junction resistance, then negative inotropic concentrations of calcium antagonists that decrease intracellular calcium concentrations should also decrease intercellular resistance and consequently improve conduction velocity. The prototypes in this family are verapamil (**16**) and diltiazem (**17**). Reduction of ventricular rate by verapamil (**16**)[38] and diltiazem (**17**)[39] in cases of atrial tachycardia or fibrillation, is probably due to slowing of AV conduction.

Class V: The class V agents are chloride channel blockers. The only known example in this family is alinidine (**18**). In SA-nodal tissue, the effect of alinidine could be explained by inhibition of chloride permeability, thus reducing the slope of the diastolic depolarization and prolonging SA action potential duration.[43] Any vagal or β-blocking activity, as well as sodium or calcium antagonist effects of alinidine, were ruled out.[43] In



18

experimental arrhythmias, alinidine (**18**) was found to have antiarrhythmic activity in arrhythmias associated with enhanced SA nodal activity, but **18** was much less active in ventricular arrhythmias due to ischemia.[44] These findings are interestingly correlated with different anion permeability in atrial and ventricular cells.[45] However, whether restriction of anion currents constitutes a fifth class of antiarrhythmic activity remains to be proven.[22]

Limitations of VW Classification

The VW classification has recently received criticism.[21g,21f,46] It is obvious that each antiarrhythmic drug in this classification scheme may have multiple actions at different concentrations and potentially different effects, depending on the nature of the underlying cardiac rhythm, e.g. heart rate, neurohormonal tone, sympathetic activation, and the pressure loading state of the heart. One drug can belong to more than one VW class, and most inevitably do. Alternatively, a range of drugs can share the same class property but achieve this by a variety of cellular mechanisms. In general, the beneficial effects of any drug on a given arrhythmia cannot always be ascribed to its primary VW class. In most instances, the mechanisms linking antiarrhythmic drug action in the form of a VW class to the mechanisms of arrhythmogenesis and clinical effectiveness are not

clear. Further reservations for the VW classification were raised, particularly where the rate constants of ion channel interaction started to be a feature of discussion.[47] Most of these concerns were crystallized in the results of cardiac arrhythmias suppression trial (CAST) where available classification systems failed to predict the adverse effects of treatment in the relatively low-risk population studied.[48]

More recently, an alternative agent-based system of drug classification (Sicilian Gambit) was proposed by the working group established for this purpose by the European Society of Cardiology.[49] This incorporated an appreciation of likely arrhythmia mechanisms, targets of drug effect (receptors as well as ion channels) and clinical considerations derived from the prospective patient population for a given drug. With a deeper understanding of the mechanism of arrhythmias and the actions of antiarrhythmic drugs, better classification of antiarrhythmic agents will appear in the near future. Inspite of several drawbacks of the VW classification, it is still currently a method of choice for classifying antiarrhythmic drugs until a more suitable method is developed.

Antiarrhythmic Properties of 3,7-Diheterabicyclo[3.3.1]nonanes

Sparteine (**2a**), which is one of the earliest known members of the DHBCN family, was used in treatment of arrhythmias but was discontinued later due to toxicity although it has since been recognized that the study was flawed.[5] It was believed that by changing substituents on the outer rings of sparteine with various groups could result in agents with improved antiarrhythmic activity and less toxicity. Ruenitz and Mokler[6] synthesized several 3,7-dialkylbispidines from the DHBCN family. Screening of the compounds [using diisopyramide (**6**) as the clinical standard] was performed using the

mouse-chloroform fibrillation assay. Although the potency of these derivatives were high, their acute toxicities were negative factors.[6] Considering these results, slight structural modifications were incorporated into the framework of the bispidines system by including the benzamide functionality to form compounds **19a-c** (Table III). These amides possessed greater potency[50] and two fold less toxicity when compared to the earlier reported bispidines.[6]

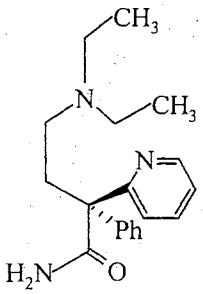
Binnig and co-workers synthesized several bispidines analogues **20** (Table IV) that were tested for antiarrhythmic action in guinea pigs and were found to be active when compared to quinidine (**3**).[51] Table IV illustrates a few examples of the most active derivatives. Interestingly, these derivatives displayed antiphlogistic and thrombocyte aggregation-inhibition properties in addition to the antiarrhythmic activity.[51]

Several DHBCN derivatives **21** were prepared with an alcohol or an ether functionality in the 9-position and showed enhanced activity (Table V).[52] To assay for an antiarrhythmic effect, rats were pretreated intravenously with aconitine to induce arrhyhmias. Compounds **21a-c** exhibited therapeutic activity several times more potent than lidocaine (**5**), which was used as the standard. In addition, these compounds increased the refractory period.

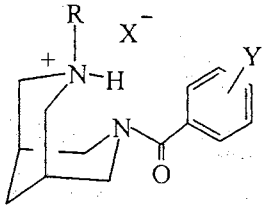
Our group has synthesized several members of the DHBCN family (Table VI).[53] The compounds **22** were examined for antiarrhythmic properties in anesthetized dogs in which myocardial infarction were induced by ligating the left coronary descending artery. In the predrug or control state, sustained ventricular tachycardia (SVT) were induced by ventricular paced beats at rates above 300 beats/min. It was found that most agents at dosages 3 mg/kg and 6 mg/kg abolished the SVT.[53] In addition, select members caused a

TABLE III[a]

ANTIARRHYTHMIC ACTIVITY OF BENZAMIDE DERIVATIVES



6 (Diisopyramide)



19

Agent[b]	R	Y	ED_{50}[c]	LD_{50}[d]	T.I.[e]
6			90	517	5.77
19a	CH_3	H	85	621	7.29
19b	CH_3	4-OCH_3	78	463	5.93
19c	CH_3	4-Cl	49	535	10.89

[a]Reference 50; X = Br^-, Cl^-.

[b]Mouse-chloroform fibrillation assay in adult mice.

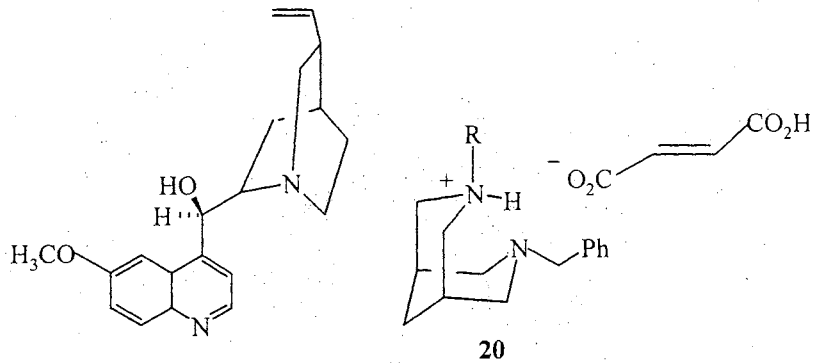
[c]ED_{50} = Effective dose (μmole/Kg ip) in which 50% are affected; mean potency.

[d]LD_{50} = Dose (μmole/Kg ip) causing mortality in 50% of mice; mean toxicity.

[e]Therapeutic Index (T.I.) = LD_{50}/ED_{50}.

TABLE IV[a]

ANTIARRHYTHMIC PROPERTIES OF BISPIDINE DERIVATIVES **20**



3 (Quinidine) **20**

Agent	R	ED_{50}[b]	MED[c]	TD[d]	Q[e]
3		42.7	215	464	10.9
20a	$CH_2C_6H_3$-3,4-$(Cl)_2$	15.6	215	464	29.7
20b	$CH_2C_6H_4$-4-F	20.2	100	215	10.6
20c	$CH(Ph)_2$	20.4	215	464	22.8

[a]Reference 51.

[b]Effective dose (mg/Kg) for the increase by 50% in the duration of aconitine infusion.

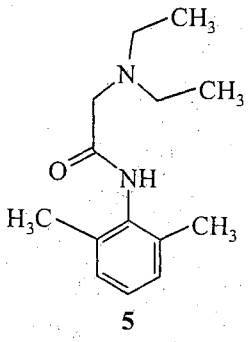
[c]Maximum Effective Dose (MED, mg/Kg) to achieve duration effect.

[d]Toxic Dose (TD, mg/Kg) at which toxic side effects such as cyanosis or electrocardiograph (ECG) change occur.

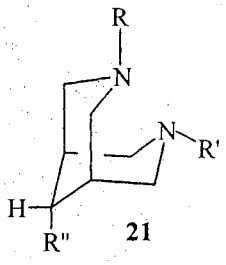
[e]Q = Toxic Dose/ED_{50}.

TABLE V[a]

ANTIARRHYTHMIC ACTIVITY OF BISPIDINE DERIVATIVES **21**



5



21

Agent[b]	R	R'	R''	ED_{50}[c]	LD_{50}[d]	T.I.[e]	R.I.[f]
5				10.0	28.5	3	1
21a	CH_3	CH_3	O_2C-2-Naphthyl	0.11	17.0	154	58
21b	CH_3	CH_3	O_2CPh	0.08	9.0	112	39
21c	CH_3	CH_3	OC_6H_4-4-Cl	0.9	52.0	58	21

[a]Reference 52.

[b]Aconotine-induced arrhythmias in rats.

[c]Effective dose (mg/Kg) to restore normal sinus rhythm in 50% of rats tested.

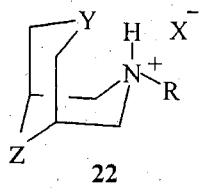
[d]Dose (mg/Kg) causing mortality in 50% of tested rats.

[e]Q = Therapeutic Index (T.I.) = LD_{50}/ED_{50}.

[f]Relative Index (R.I.) = T.I. (agent)/t.I. [lidocaine (**5**)].

TABLE VI[a]

ANTIARRHYTHMIC ACTIVITY OF 3-AZABICYCLO[3.3.1]NONANES **22**



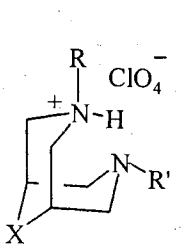
22

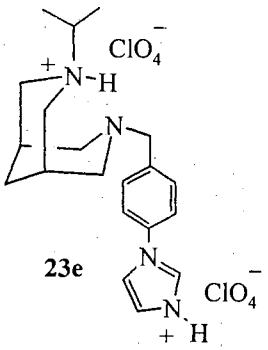
Comp[b]	R	Y	Z	Effect on SVT[c]	
				3 mg/Kg	6 mg/Kg
5 (lidocaine)				reduced[d]	reduced
22a	$CH(CH_3)_2$	NC(O)Ph	CH_2	NSVT[e]	NSVT
22b	$CH(CH_3)_2$	$NCH_2C_6H_4$-3,4-$(OCH_3)_2$	CH_2	NSVT	NSVT
22c	$CH(CH_3)_2$	NCH_2Ph	CH_2	NSVT	NSVT
22d	NCH_2Ph	S	CH_2	NSVT	NSVT
22e	NCH_2Ph	S	$C(OCH_3)_2$	NSVT	NSVT
22f	NCH_2Ph	$CHCO_2Et$	CH_2	NSVT	NSVT
22g	NCH_2Ph	$CHCO_2Et$	$C(SCH_2)_2$	NSVT	NSVT
22h	NCH_2Ph	Se	CH_2	NSVT	NSVT

[a]Reference 53.
[b]X = ClO_4^-, Cl^-, Br^-, citrate, fumarate, HSO_4^-.
[c]SVT = Sustained ventricular tachycardia induced by programmed electrical stimulation (PES) of infarcted dog heart.
[d]Reduced sustained ventricular tahycardia.
[e]NSVT = Nonsustained ventricular tachycardia (or abolished VT).

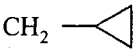
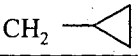
moderate increase in mean blood pressure (MBP). In addition, several DHBCN derivatives substituted at the 2-, 4-, 9-positions were synthesized and screened for their ability to abolish SVT.[54] Results of SAR demonstrated clearly that DHBCNs substituted with aryl groups alpha to the heteroatoms (3-, 7-positions) were less effective in controlling the SVT and that CC systems were more effective than BC systems.[54] In all experiments, lidocaine (**5**) was used as the standard for comparison.

More recent work in our laboratory has focused upon classifying the DHBCNs via different class actions based upon their observed electrophysiological actions as viewed in single agents with multiple class action.[53a] Compounds **23a-e**, (Table VII) were





23e

23a	R = $CH(CH_3)_2$, R' = $(O)CC_6H_4$-3,4$(OCH_3)_2$, X = CH_2
23b	R = $CH(CH_3)_2$, R' = $CH(CH_3)_2$, X = SCH_2CH_2S
23c	R = CH_2  R' = $(O)CC_6H_4$-4-Cl, X = CH_2
23d	R = CH_2  R' = $(O)CC_6H_5$, X = CH_2

examined for their ability to abolish pace-induced and SVT or prevent induction of ventricular tachycardia (Table VII).[53a] Most compounds displayed a predominant class III activity, via a prolongation of the ventricular ERP, although there may be an underlying class Ib action present as illustrated by the ability of several agents to slow conduction in the myocardial infarcted dog hearts. In addition, several other electro-

TABLE VII[a]

ANTIARRHYTHMIC PROPERTIES OF THE MOST ACTIVE DHBCN DERIVATIVES **23**

	HR[b]		MBP[c]		QT interval[d]		AH interval[e]		HV interval[f]		VERP[g]	
Comp	pre[h]	post[i]	pre	post	pre	post	pre	post	pre	post	pre	post
5 (lidocaine)	NE[j]	NE	105	84	NE	NE	NE	NE	NE	NE	NE	NE
23a	150	110	110	55	NM	NM	64	70	NE	NE	170	230
23b	154	105	61	76	136	170	56	75	30	40	140	180
23c	125	105	88	98	215	250	60	68	NE	NE	170	220
23d	120	111	92	83	NE	NE	65	70	NE	NE	170	190
23e	152	110	94	84	222	288	57	66	30	37	142	187

[a]Antiarrhythmic properties are compared to lidocaine (**5**) using doses (3 mg/Kg) in which SVT was non-inducible in the DHBCN system while lidocaine (**5**) only reduced the rate of the VT.

[b]HR = Heart rate (beats/min).

[c]MBP = Mean blood pressure (mm Hg).

[d]QT = Time (msec) required for the cell to undergo depolarization and repolarization.

[e]AH interval = (msec) measures conduction time.

[f]HV interval = (msec) measures sodium channel action.

[g]VERP = (msec) elapsed time to complete the QRS complex of ECG.

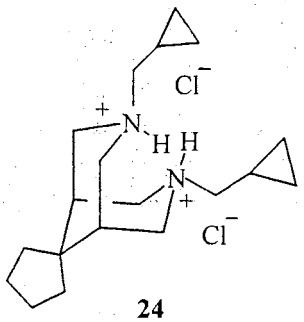
[h]Pre = Predrug or drug free state; mesurements before administration of the drug.

[i]Post = Post drug; mesurement after the administration of the drug.

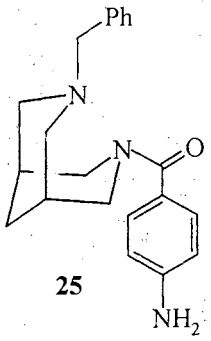
[j]NE = No effect.

physiological parameters like QT, AH, and HV intervals were measured to assess class III action. Most compounds displayed good class III action, with **23e** being one of the best class III agents. Interestingly, compounds **23a** and **23d** displayed class IV action (decrease in MBP and heart rate). The underlying feature of these agents, however, is a class Ib antiarrhythmic action which is most likely associated with the heterabicyclo[3.3.1]nonane unit present in these molecules.[53a]

Recently, Tedisamil (**24**)[55] and Ambasalide (**25**)[56] which belongs to the DHBCN



24



25

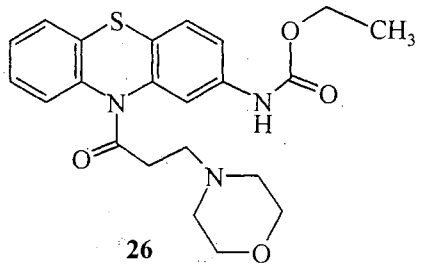
family were reported. Tedisamil (**24**) was found to have a predominant class III action (prolongation of APD, QT interval, and the refractory period) with slight class I action. Similarly, Ambasalide (**25**) was found to be a predominantly class III agent. Many DHBCN derivatives discovered by our group[53] and by others[6,50,51] have exhibited good class Ib action, the origin of which was speculated to be from the diheterabicyclo-[3.3.1]nonane nucleus. For such reasons, it appears that diheterabicyclo[3.3.1]nonane nucleus may also contribute significantly to the class III action.

Effects of Antiarrhythmic Drug Therapy on Mortality

Pharmacologic therapy for treatment of arrhythmias has expanded dramatically in the recent years. The results of multiple clinical trials using either spontaneous or induced arrhythmias as endpoints for guiding the therapy have caused a reevaluation of antiarrhythmic therapy.[8e,f,14] Although the potential benefits of antiarrhythmic therapy are a reduction in mortality, or in symptoms due to arrhythmias, these trials have clearly delineated the risks associated with antiarrhythmic drug therapy.[8e,f,14] There is no conclusive evidence from appropriately designed clinical trials which demonstrate that suppression of arrhythmias results in a reduction in sudden cardiac death or mortality from any cause.[8e,f]

The CAST Study: The Cardiac Arrhythmia Suppression Trial (CAST) was designed to test antiarrhythmic drug therapy via the suppression of asymptomatic or mildly symptomatic ventricular arrhythmias, subsequent to MI, to determine if there occurred a reduction in mortality from such arrhythmias.[57] Prior to the CAST study, results from the Cardiac Arrhythmia Pilot Study (CAPS)[58] showed that encainide (**7**) and flecainide (**8**) suppressed arrhythmias in the targeted population of their experiments. Encainide (**7**) and flecainide (**8**), both class Ic agents, were thus chosen to be two of the drugs evaluated in the more elaborate CAST study. Initial trials identified patients who would respond to treatment with one of the drugs to be tested. Those who responded were then randomly assigned to receive either the therapy with the agent or the placebo. The experiment was comprised of 2,309 patients in which only 1,727 showed a suppression of their arrhythmias. Those patients were then assigned the blind therapy: 1,455 were assigned

to encainide (**7**), flecainide (**8**), or a placebo, with a further 272 assigned to morcizine (**26**).[57]



26

The results of the CAST showed a statistically significant two- to threefold increase in both total and sudden arrhythmic death in the patients treated with encainide (**7**) or flecanide (**8**), as compared with those the placebo. Table VIII shows the number of

TABLE VIII[a]

EVENTS IN 1,455 PATIENTS RANDOMLY ASSIGNED TO RECEIVE ENCAINIDE (**7**), FLECANIDE (**8**), OR MATCHING PLACEBO

Variable	Encainide (**7**) or Flecainide (**8**) (N = 730)	Placebo (N = 725)
Average exposure (days)	293	300
Death from arrhythmia or cardiac arrest	33	9
Other cardiac death	14	6
Noncardiac or unclassified death or cardiac arrest	9	7
Total deaths or cardiac arrests	56	22

[a]Reference 58

deaths caused by arrhythmias and a nonarrhythmic cardiac events.[58] The increase in total mortality is of importance, given the difficulty in clearly defining arrrhythmic death. The substantial increase in presumed arrhythmic deaths and nonfatal cardiac arrests implies a

proarrhythmic action of these drugs. The increase in nonarrhythmic cardiac mortality suggests that the drugs may also have other adverse consequence such as precipitation of heart failure.

As an extension of the CAST study, the CAST II study, was undertaken to evaluate morcizine (**26**), which is class I agent.[57] In the two-week period of morcizine (**26**) therapy initiation, 17 of 665 patients died or had cardiac arrest. All were receiving morcizine (**26**) as compared with 3 of 660 patients which received placebo.[57] In a long-term follow-up, there was no significant difference in cardiac death, sudden death, or total mortality among patients taking morcizine (**26**) or placebo. At the completion of the long-term phase of CAST II, there were 49 deaths or cardiac arrests due to arrhythmias in patients assigned to morcizine (**26**) and 42 in patients assigned to placebo. The trial was terminated prematurely due to the disappointing results in regards to any survival benefit from morcizine (**26**) therapy.[57]

The results of the CAST study has several important implications for assessment of antiarrhythmic therapy. First, although the drugs were found to be associated with an increased risk of death, they were quite effective in suppressing arrhythmias. Therefore, studies using only suppression as the primary endpoint can be misleading. Second, although limited extrapolations might be made to other class I agents, it may not be appropriate at the current time to generalize the CAST findings to all antiarrhythmic drugs. Each agent may need to be evaluated for its effects on clinical outcomes. Because the risk-benefit ratio of antiarrhythmic drugs may vary in different types of patients who may have different underlying conditions and arrhythmic substrate, there may be additional need to evaluate these drugs in different populations.

The ESVEM Trial: In the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) trial seven antiarrhythmic drugs, including quinidine (**3**), procainamide (**4**), mexiletine, sotalol (**9**), and propafenone, were used to test the predictive accuracy of electrophysiologic study as compared to electrocardiographic monitoring.[59] The study was conducted with the goal of improving patient monitoring and thus improve patient care as well as to determine the long term tolerance, safety, and efficacy of the drugs. The ESVEM trial involved a total of 486 patients, each one on one of the agents being tested in accordance with the response of patients to that drug. Many of the drugs tested caused adverse side effects, which required the discontinuation of those agents in the patient. Table IX illustrates such results for five of the seven drugs examined. Among all the drugs examined, only sotalol (a, nonselective class II/III agent) offered a low risk for proarrhythmia and noncardiac adverse effects while at the same time, providing efficacy against ventricular tachyarrhythmias.[59,33a]

The Basis Study: The Basel Antiarrhythmic Study of Infarct Survival (BASIS) study was designed as randomized trial in patients at high risk for mortality after MI.[60] The patients were randomly allocated to one of three treatment regimens: (i) individualized antiarrhythmic treatment, starting with class I agents selected on the basis of suppression of ventricular ectopic activity and patient tolerance; (ii) standardized antiarrhythmic treatment with low dose of amiodarone ; and (iii) no antiarrhythmic therapy (control group). Over a one year follow-up period, clinical events, antiarrhythmic drug effects, and side effects were recorded to assess whether one or both of the antiarrhythmic drug regimens given prophylactically could actually reduce mortality (Table X).[60]

During the study,[60] 1220 consecutive patients <71 years of age were screened for persisting complex ventricular ectopic activity before hospital discharge. Of this group, 312 patients had qualifying asymptomatic arrhythmias and consented to study. Then 100 of these patients were consigned to group 1 (individual treatment), 98 to group 2 (low dose amiodarone), and 114 to group 3 (control). The incidence of death in the three study groups is shown in Table X. Overall 30 patients died, 27 from cardiac related events, while 22 of the cardiac deaths were sudden.

The CASH Study: The Cardiac Arrhythmia Study Hamburg (CASH) was designed to compare the effects of various kinds of drug therapy with the implantable cardioverter

TABLE IX[a]

INCIDENCE OF ADVERSE EVENTS REQUIRING DISCONTINUATION OF THE STUDY DRUG IN THE ESVEM TRIAL

	Mexiletine	Procainamide (**4**)	Sotalol (**9**)	Quinidine (**3**)	Propafenone
Titration[b]					
No. of patients receiving the drug	226	158	234	157	220
Adverse events (%)					
Cardiovascular	8	6	14	13	24
All	27	24	16	24	26
Long-term follow-up					
No. of patients receiving the drug	15	39	85	38	45
Adverse events (%)					
Cardiovascular	2	3	6	8	11
All	19	31	7	32	13

[a]Reference 59
[b]Refers to the period before the completion of the efficacy tests.

TABLE X[a]

INCIDENCE OF DEATH IN THE THREE STUDY GROUPS OF THE BASIS STUDY

	Individual treatment	Amiodarone (**11**)	Control (placebo)	Total
Sudden death	8	4	10	22
Nonsudden cardiac death	1	1	3	5
Noncardiac death	1	0	2	3
Total	10	5	15	30

[a]Reference 60

defibrillator (ICD) on total mortality and sudden death in survivors of cardiac arrest.[61] CASH, which is still in progress has a planned enrollment of 400 patients, with randomization of 100 patients each to four therapies, including amiodarone (**11**), propafenone, and metaprolol, versus the use of ICD. An analysis of early results of the CASH study representing 230 patients is given in Table XI The propafenone group shows a trend toward increased mortality (20%-significantly higher than other forms of therapy in the test) causing the discontinuation of the propafenone treatment limb of the study.[61]

Nitric Oxide in Vascular Regulation

In recent years, nitric oxide (NO) has received widespread attention due to its involvement in biological systems.[62] It was named molecule of the year in 1992, and the 1998 Nobel prize in medicine was awarded to Drs. Robert F. Furchgott, Ferid Murad, and Louis J. Ignarro for their outstanding work in elucidating different biological roles of NO.

TABLE XI[a]

INTERIM RESULTS FROM THE CASH STUDY

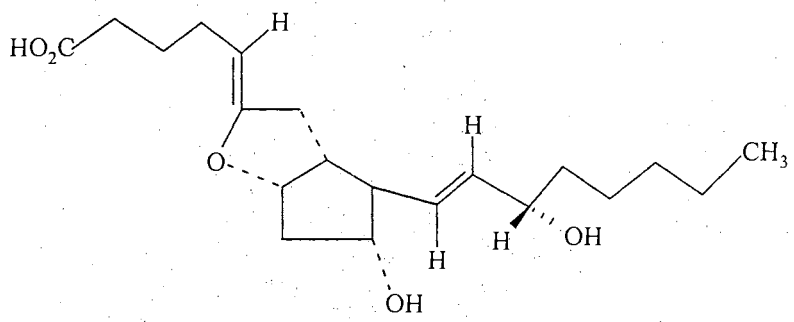
Therapy	No. of Patients	Sudden Death (%)	Total Mortality (%)
Amiodarone (**11**)	56	8.8	14.7
Metaprolol	59	11.4	14.3
Propafenone	56	11.4	20.0
ICD[b]	59	0.0	14.3

[a]Reference 61
[b]ICD = implantable cardioverter defibrillator.

The vascular endothelium is now regarded as an endocrine gland and not simply as an inert vessel. One of the most potent substances released by the vascular endothelium is NO.[63] The second messenger is released by the action of several endothelium dependent vasodilators which cause a rise in intracellular calcium leading to the activation of nitric oxide synthase (NOS)-III. The NO diffuses from the endothelial cell to the adjacent vascular smooth muscle cells activating guanylate cyclase (sGC), producing cGMP, which then mediates further signal transduction and ultimately leads to vasorelaxation.[64] The NO dependent relaxation has been demonstrated in isolated arteries, veins, and microvasculature.[62c] Local infusion of NOS inhibitors into the brachial artery of humans has reduced blood flow by as much as 40%.[62c] Thus, resistance vessels are continually modulated by NO and NOS activity is responsible for the maintance of a basal dilatory vascular tone which vasoconstrictors then modulate.

Mechanical stimuli, such as shear stress, are also sufficient to evoke changes in intracellular calcium amd NO synthesis which may act to minimize cardiac load by optimally dilating local systemic vasculature.[65]

In addition to its effect on smooth muscle within the blood vessel wall, Moncada and co-workers showed that NO inhibits platelet aggregation.[66] Prostacyclin and NO act



Prostacyclin

synergistically to inhibit platelet aggregation and to disaggregate platelets, but there is no parallel synergism in platelet adhesion. The role of NO in this area appears to be as a feedback mechanism to counteract the effect of the substances in the body, produced after injury, which promote aggregation and adhesion. The NO utilized by the platelets is derived from endothelia cells with which the platelets come in contact, but there is also an enzyme system in the platelets themselves which acts on arginine to produce NO. Recently, it was shown that human platelets possess a specific *L*-arginine transport system able to provide adequate amounts of *L*-arginine for endogenous NO production.[67] *L*-arginine uptake takes place through a saturable high affinity, carrier-mediated, Na^+-independent process which is significantly inhibited by *L*-ornithine, *L*-lysine and *L*-omega-methyl-*L*-arginine.[67] The kinetic data suggested a possible role for arginine plasma levels in the regulation of platelet NO production.

CHAPTER II

RESULTS AND DISCUSSION

Antiarrhythmic Agents With Multiple Class Action

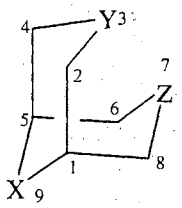
As described earlier, most arrhythmias are accompanied with disruption of cellular electrophysiology, which includes increases in intracellular $Na^+$and Ca^{2+} and extracellular K^+.[15] A reasonable approach to treatment of arrhythmias would be to develop agents that will resuscitate a normal transport of Na^+, Ca^{2+}, and K^+ ions across the membrane. Thus, an ideal agent would have the ability to inhibit the fast Na^+ and Ca^{2+} ions (class I and IV, respectively) across the membrane and inhibit the K^+ eflux across the membrane (class III). Development of such agents with multiple class action is one of the current objectives in our laboratory. Moreover, incorporation of class II action in these agents may have further benefits as numerous studies have clearly demonstrated extensive benefits of class II drugs in reduction of mortality in post myocardial infarction patients.[8e,f] However, the mechanism of action of class II agents is not well understood and poses a hindrance in design and development of multiple class agents with class II properties. For such reasons, our approach towards the treatment of arrhythmias has been to incorporate class I, III, and IV action in a single molecule.

It was recently proposed by Hondegham and Snyder[68] that an ideal AAA drug would have the ability to block the fast sodium channel with fast diastolic recovery (class Ib) and use-dependent prolongation of the APD, that is, the agent would only prolong the action potential at an accelerated heart rate (class III). Agents which block the potassium channels are indicated as having use dependent prolongation of the APD.[68] The term

"use dependence" implies that the agent prolongs the action potential at accelerated heart rates with no prolongation of the APD being observed at lower heart rates.

Structure-Activity Relationships (SAR)

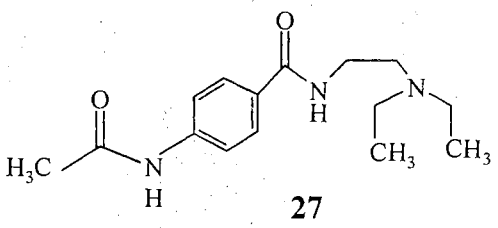
Our group has synthesized several derivatives of the DHBCN family with more than one class action. Variations in substituents at the 3-, 7-, and 9-positions can significantly alter the antiarrhythmic activity of a DHBCN.[53,54] The current work has focussed upon developing DHBCN agents with class Ib, III, and IV action in a single molecule. Such agents are likely to have an impact in the treatment of life-threatening arrhythmias which involve conduction abnormalities due to imbalance of intracellular and extracellular Na^+, K^+, and Ca^{2+} ions. With the available antiarrhythmic data, a SAR can be developed and conclusions can be drawn as to which functional groups are important for useful class Ib, III, and IV antiarrhythmic activity, a minimum proarrhythmic effect, and a multiple class action.



1

Work by our group[53a] and that of Morgan and co-workers[35] implied that the imidazole might be responsible for strong class III action, while sulfonamide group might also impart class III action to the molecule, but to lesser extent as compared to imidazole. In addition, as stated earlier, the diheterabicyclo[3.3.1]nonane nucleus may contribute to the class Ib and slight III action. Based upon some of our earlier work, it was also realized that hydrophobic nature of 9-position may be essential in maintaining the

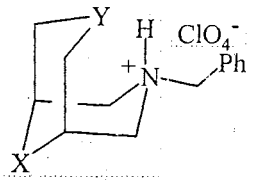
antiarrhythmic activity.[53] Good class Ib antiarrhythmic activity was obtained when X = CH_2, SCH_2CH_2S, OCH_2CH_2O in **1**. *N*-Acetylprocainamide (**27**) has been found to be an active metabolite of procainamide (**4**) and to possess class III action.[70] It thus appeared



27

that the *N*-acetyl group might impart class III activity to a molecule. Some of the current work in our laboratory has established that amide and sulfoxide moieties contribute significantly to the class III action.[53,71] It was further realized that perchlorates of DHBCNs exhibited much better class Ib and III activity in comparison to chloride and bromide salts.[53a,71] An additional feature of some perchlorates was slight class IV activity. Although there is no substantial evidence that perchlorate anion contributes to class IV action, it appears that certain electron-withdrawing groups, like NO_2, may contribute to class IV activity in addition to the perchlorate anion. By class IV, it is meant that the agents may induce lowering of mean blood pressure (MBP) and heart rate (HR). The presence of *N*(3)-isopropyl, *N*(3)-cyclopropylmethyl, and S(3) has preserved good class Ib and III activity in a majority of DHBCNs investigated.[53] Interestingly, the toxicity of most derivatives of DHBCN prepared in our laboratory has been low,[71] which suggests the role of the substituents at the 3-position in other DHBCN derivatives should be investigated.

Based upon the above mentioned SAR results, a series of DHBCN derivatives were prepared in an effort to induce more than one class action in a single agent. It was anticipated that perchlorates **28-31** might also exhibit class Ib and III activity in one



Class Ib and III

	X	Y
28	CH_2	O
29	SCH_2CH_2S	O
30	CH_2	NCH_2Ph
31	SCH_2CH_2S	NCH_2Ph

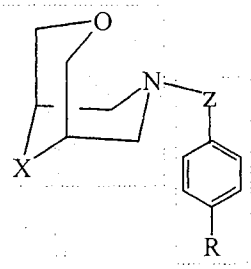
agent. As stated earlier, class Ib and III activity of DHBCN derivatives possibly originates from the diheterabicyclo[3.3.1]nonane nucleus and perchlorate anion. Examples of DHBCN heterocycles with Y = O and NCH_2Ph are rare, and, to our knowledge, very few have been synthesized or investigated for their antiarrhythmic properties. It thus seemed reasonable to synthesize DHBCN derivatives with Y = O, NCH_2Ph and evaluate their antiarrhythmic properties as compared to the known examples in which Y = $NCH(CH_3)_2$, NCH_2-cyclopropyl, and S. In addition, several amide and sulfoxide derivatives **32-43** were prepared with varying R, X, and Z groups with the aim to incorporate class Ib, III and IV action in a single molecule (Table XII). In certain cases, perchlorates of these derivatives were also prepared.

Recently, we have been interested in nitric oxide (NO) due to its involvement in the vasorelaxation[63-65] and antiplatelet aggregation.[62] processes. As stated earlier, most life threatening arrhythmias originate due to coronary artery disease (CAD) or myocardial infarction (MI), which is accompanied by constriction of the coronary arteries.[78] It thus appeared reasonable to us to develop antiarrhythmic drugs which could

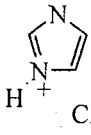
TABLE XII

DERIVATIVES WITH PROPOSED CLASS I, III, and IV ACTION

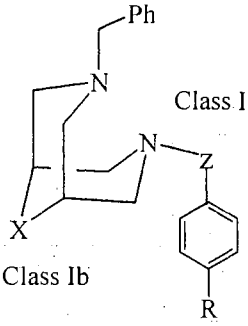
Class Ib



Class III and IV

	R	X	Z
32		CH_2	C(O)
33	NO_2	CH_2	C(O)
34	NH_2	CH_2	C(O)
35	NHC(O)Ph	CH_2	C(O)
36	NO_2	CH_2	SO_2
37	NH_2	CH_2	SO_2

Class III and IV



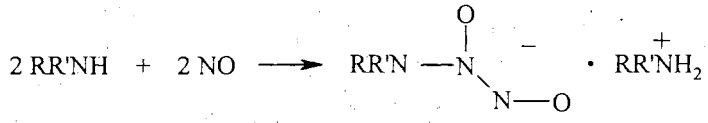
Class Ib

	R	X	Z
38		CH_2	C(O)
39	NO_2	CH_2	C(O)
40	NH_2	CH_2	C(O)
41	$N(SO_2CH_3)_2$	CH_2	C(O)
42	NO_2	CH_2	SO_2
43	NH_2	CH_2	SO_2

alleviate or abolish the symptoms of arrhythmias and at the same time release NO in a highly controlled manner to dilate the coronary arteries and to resuscitate the blood flow through the lumen to prevent further infarction. Controlled release of NO is very critical since an excess dilation of the arteries could lower the blood pressure significantly and induce a state of shock in the patient and eventually death. It is also conceivable that such novel agents might help in the reduction of mortality by preventing platelet aggregation/adhesion (clot or thrombus formation, which typically occurs as a result of CAD) considering that NO counteracts the effect of the substances (usually fibrin)

produced in the ischemic zones of the lumen.[72] This prediction is based upon some of the randomized trials of the antiplatelet drugs, which suggested a significant reduction in nonfatal cardiac death or sudden cardiac death.[72]

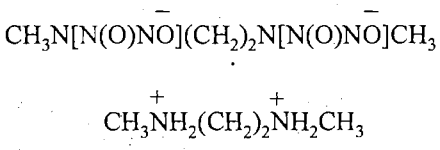
The reaction of NO with amines to produce salts of structure **44** was first



44

demonstrated by Drago several years ago.[73] The anionic portion of these salts are of great interest but they spontaneously decompose in solution to release NO.[73,74] Although NO release was a desirable feature of these salts, the rate of decomposition was very fast with the molecules having a short half life. Decomposition occurred even in the solid state unless stored at -78 °C.[73]

Drago also studied the reaction of two diamines with NO and reported the production of intermolecular salts **45**.[73] Interestingly, the stability of these intermolecular



45

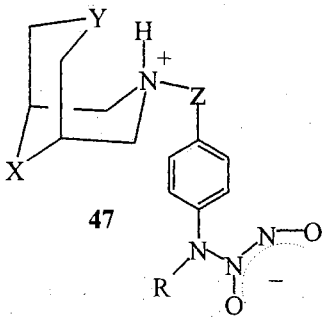
salts was slightly greater than **44** which was obtained by reaction of a monoamine with NO. However, it was realized by Hrabie and Keefer that by performing the reaction of diamines or polyamines with $NO_{(g)}$ under dilute and polar aprotic solvent conditions, more stable intramolecular zwitterionic salts **46** could be obtained.[74] This new class of

$RN[N(O)NO](CH_2)_xNH_2R'$

46

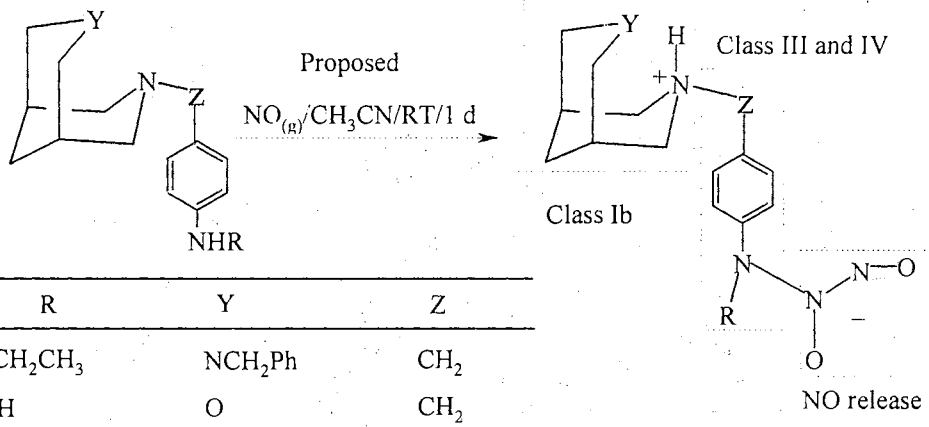
intramolecular zwitterionic salts proved to have many advantageous properties when compared to previously known materials **44** and **45**. Under an NO pressure of 70-80 psig, **46** formed at room temperature in excellent yields with short (< 1 d) reaction times. As solids, members of **46** were stable for weeks at room temperature in closed containers and yet released NO rapidly in acidic solutions or more slowly in near-neutral buffered solutions.

A close examination of the diheterabicyclo[3.3.1]nonane system reveals that some of the derivatives in this family are di- or triamines, and hence the intriguing possibility exists of producing such zwitterionic salts as **47** from the diheterabicyclo[3.3.1]nonane



47

ring system. It was hypothesized that such salts would exhibit class Ib, III, and IV action and NO releasing properties in a single molecule. It was also speculated that variations in the R group could lead to better agents with controlled release of NO. Based upon such reasoning, several DHBCN di- and triamines **48-55** were prepared. Hopefully, such systems will react with $NO_{(g)}$ to produce the zwitterionic salts with antiarrhythmic and



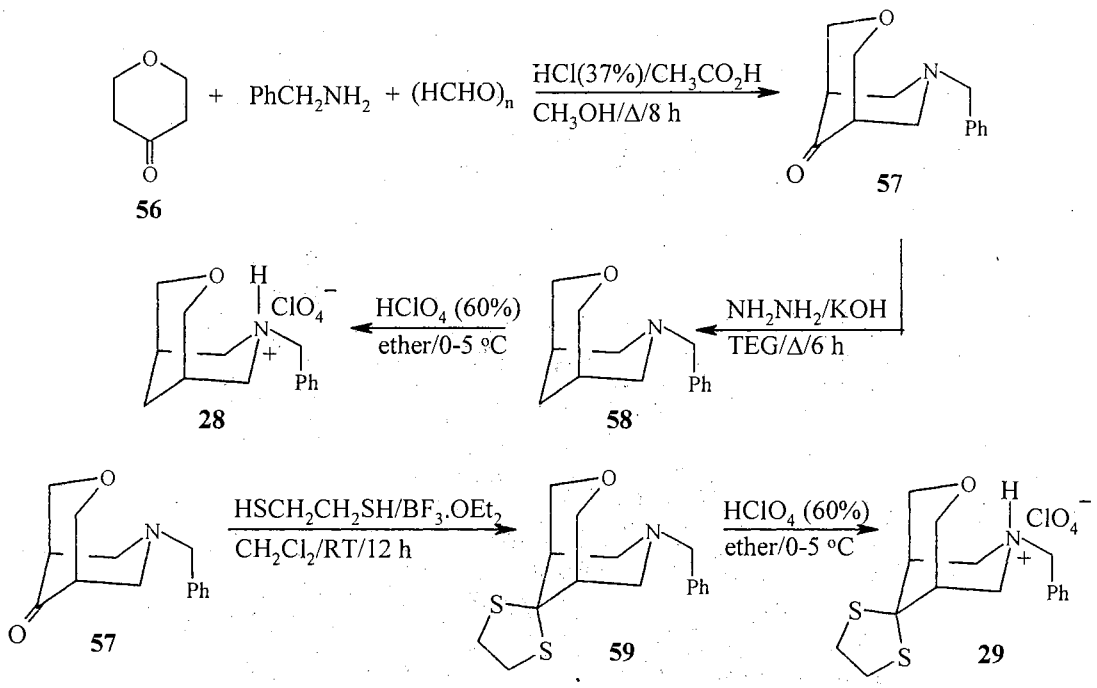
	R	Y	Z
48	CH_2CH_3	NCH_2Ph	CH_2
49	H	O	CH_2
50	CH_2CH_3	S	CH_2
51	CH_2Ph	O	CH_2
52	H	$NCH(CH_3)_2$	CH_2
53	CH_2Ph	$NCH(CH_3)_2$	CH_2
54	CH_2CH_3	$NCH(CH_3)_2$	CH_2
55	CH_2CH_3	$NCH(CH_3)_2$	CH_2CH_2

NO releasing properties. Efforts are currently underway in our laboratory to execute the reactions of these amines with $NO_{(g)}$, the results of which will be reported shortly.

Synthetic Methodology

Synthesis of derivatives **28** and **29** (Scheme I) was initiated by performing a double Mannich condensation[75] with tetrahydro-4*H*-pyran-4-one (**56**), benzylamine, paraformaldehyde, glacial acetic acid, and one half equivalent (with respect to benzylamine) of conc HCl. The reaction gave bicyclic ketone **57**. It had been previously shown that performing the double Mannich reactions under forcing conditions (addition of excess HCl) increased the yield of certain diheterabicyclo[3.3.1]nonane ketones from

SCHEME I

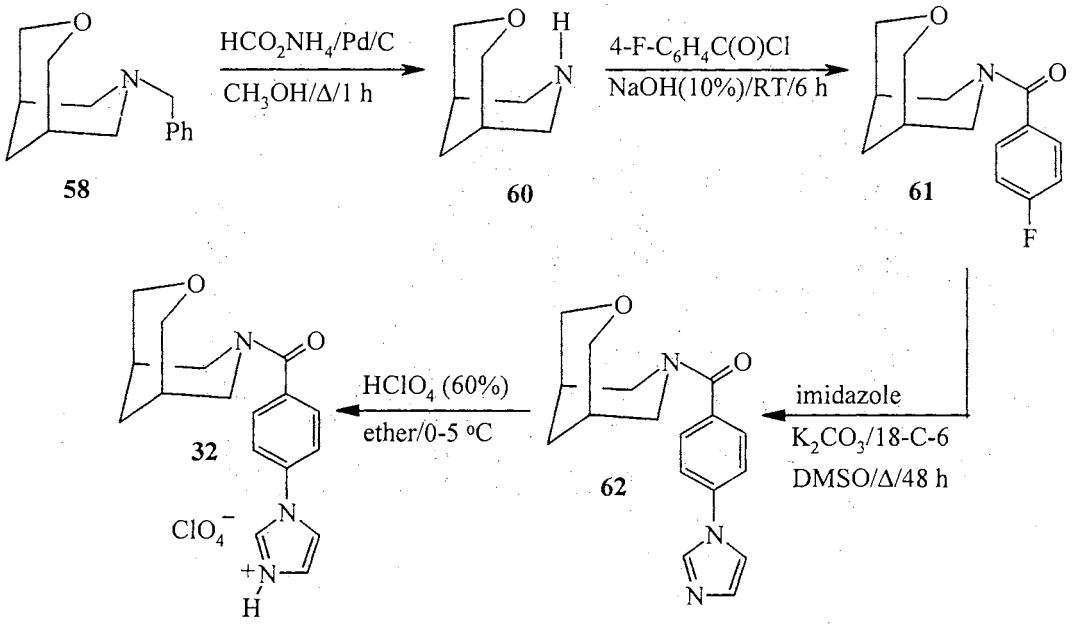


25% to 56%.[76] The phenomenon is difficult to explain, but it is speculated that pH plays an important role in the reaction kinetics, possibly in accelerating the formation of an intermediate imininum ion. Wolff-Kishner reduction of the Mannich ketone **57** under strongly basic conditions involved the use of KOH pellets and hydrazine in triethylene glycol and gave the tertiary amine **58**, which upon treatment with perchloric acid, gave the desired salt **28**. Synthesis of perchlorate **29** was accomplished by the reaction of the ketone **57** with 1,2-ethanedithiol in the presence of boron trifluoride etherate to give the protected thioketal **59**,[77] which was treated with perchloric acid to form the desired salt **29**.

As stated earlier, the amide and sulfoxide derivatives **32-43** were anticipated to exhibit multiple class action based upon earlier work.[53,71] Debenzylation of **58** (Scheme

II) was performed with ammonium formate and fresh Pd/C (10%) in boiling methanol to give the secondary amine **60** as a light yellow oil, which was used without further

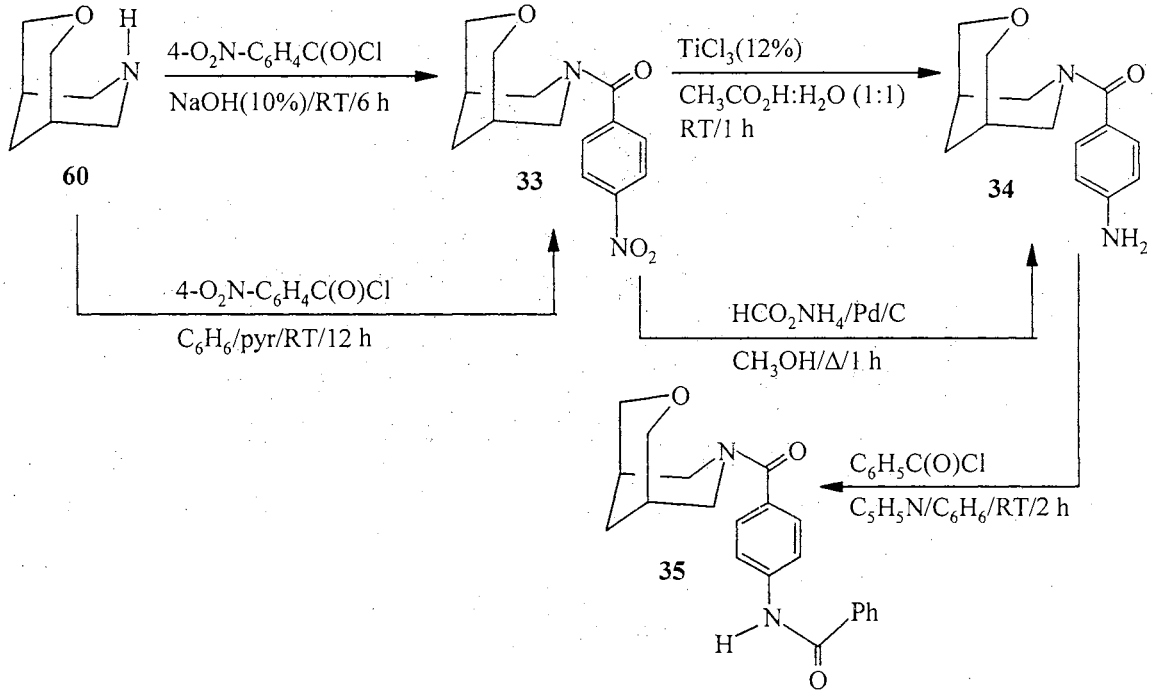
SCHEME II



purification. This reaction has been reviewed, and it is believed that ammonium formate acts as hydrogen source in the reaction procedure.[78] The order of addition of reagents appears to be critical in this reaction. After the Pd/C is placed in the flask and the system is flushed with nitrogen, methanol is slowly added, followed by the addition of the amine and ammonium formate to afford the best yields. A modified Schotten-Baumann acylation of **60** with 4-fluorobenzoyl chloride in a biphasic reaction mixture of H_2CCl_2 and NaOH (10%) gave the amide **61**. Nucleophilic substitution on the aromatic ring of benzamide **61** was achieved in the presence of imidazole, K_2CO_3 (dry and powdered), DMSO, and 18-C-6 at a constant temperature (110 °C) for 48 h and formed the amide **62**, which, upon treatment with perchloric acid, gave salt **32**.

Preparation of derivatives **33-35** was initiated by reaction of secondary amine **60** under modified Schotten-Baumann acylation conditions with 4-nitrobenzoyl chloride to form amide **33** (Scheme III). This reaction was also performed by condensation of **60**

SCHEME III

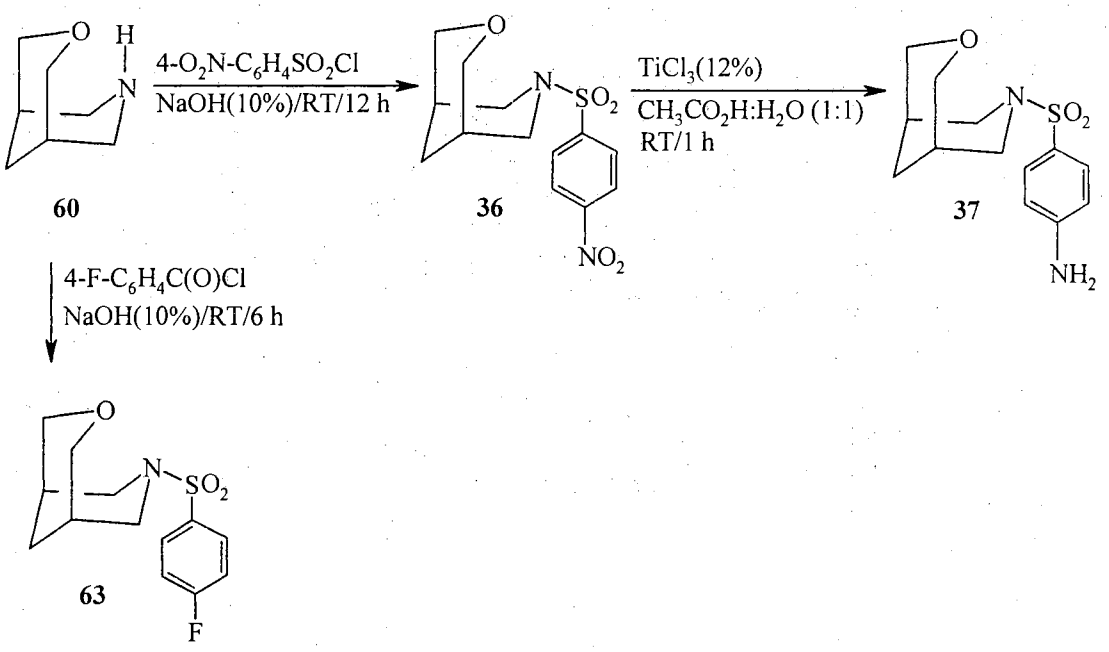


with 4-nitrobenzoyl chloride in presence of pyridine and gave **33** in comparable yields. The nitro group in amide **33** was reduced to a primary amine with $TiCl_3$ (12% solution in HCl) at RT in acetic acid:H_2O (1:1) and gave the reduced product **34**. This reduction of the aromatic nitro group is not fully understood, although it is believed that $TiCl_3$ acts a complexing agent in this redox reaction.[79] An alternative method to obtain **34** was developed and involved the treatment of **33** with ammonium formate and Pd/C.[78] This reaction, which involved the same conditions as debenzylation, gave pure **34** in excellent yields (95.4%) and hence was deemed the better approach for synthesis of **34**.

Conversion of **34** to **35** was effected by acylation of **34** with benzoyl chloride in the presence of pyridine as a scavenger of HCl and yielded the desired diamide **35**.

Recent work has indicated that certain sulfonamides of the DHBCN family may display excellent antiarrhythmic action in different classes.[71] The derivative **36** was prepared (Scheme IV) by a modified Scotten-Baumann acylation of **60** with 4-nitro-

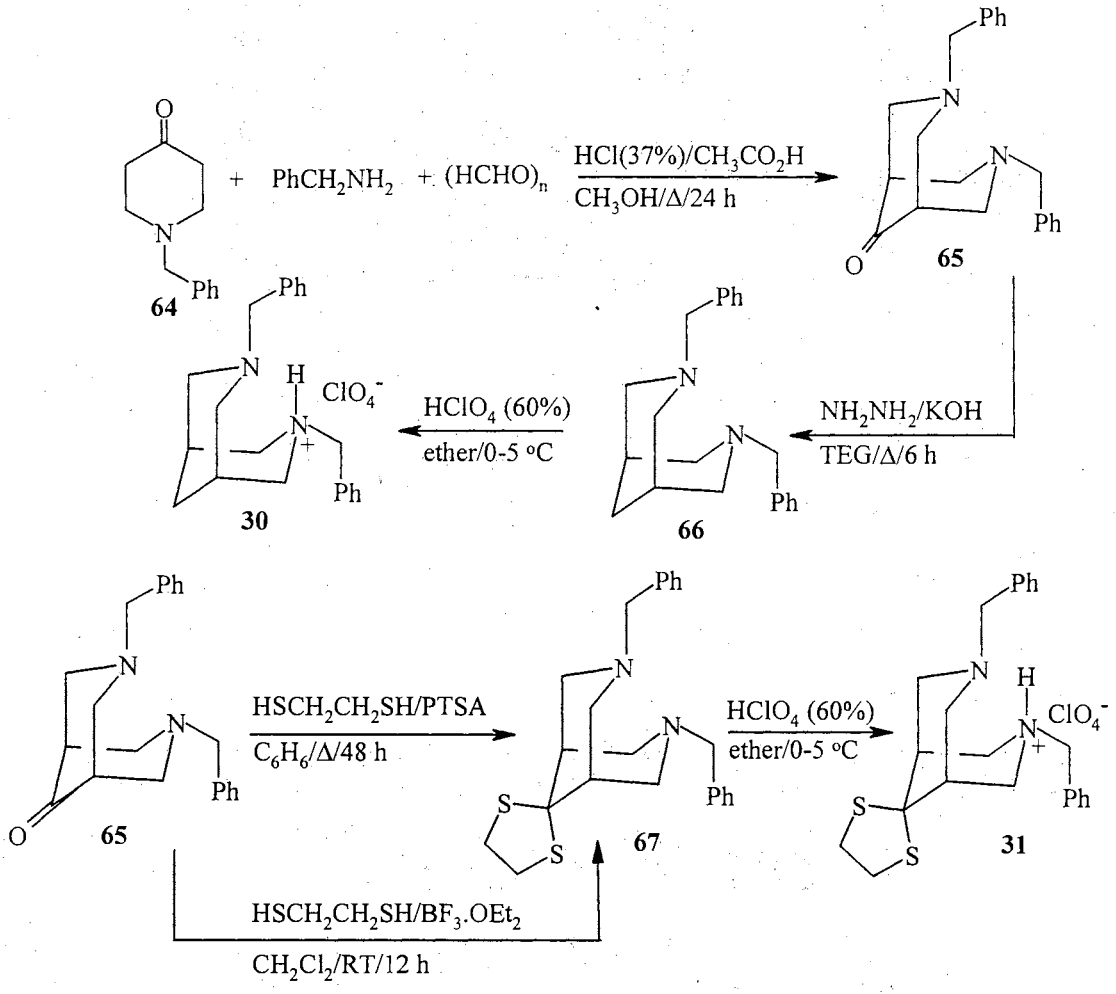
SCHEME IV



benzenesulfonyl chloride to form the corresponding sulfonamide **36.** Treatment of a solution of **36** in CH_3CO_2H:H_2O (1:1) with $TiCl_3$ (12%) gave **37**. The solution of **36** in CH_3CO_2H:H_2O (1:1) was stirred vigorously for almost 1 h to ensure complete homogeneity before the addition of $TiCl_3$ solution. Reaction of **60** with 4-fluorobenzenesulfonyl chloride produced the sulfonamide **63**. The fluoro-substituted sulfonamides in the DHBCN family have not been investigated for their antiarrhythmic properties. The lack of such biological data on such sulfonamides prevents any predictions about their antiarrhythmic class actions at this time.

The synthesis of the DHBCN derivatives with Y = NCH_2Ph was accomplished using *N*-benzyl-4-piperidinone (**64**), which was an important synthon for the preparation of other useful derivatives in this family. Preparations of derivatives **30** and **31** (Scheme V) were achieved by first synthesizing ketone **65** as shown via a double Mannich condensation of *N*-benzyl-4-piperidinone (**64**) with benzylamine and paraformaldehyde.

SCHEME V

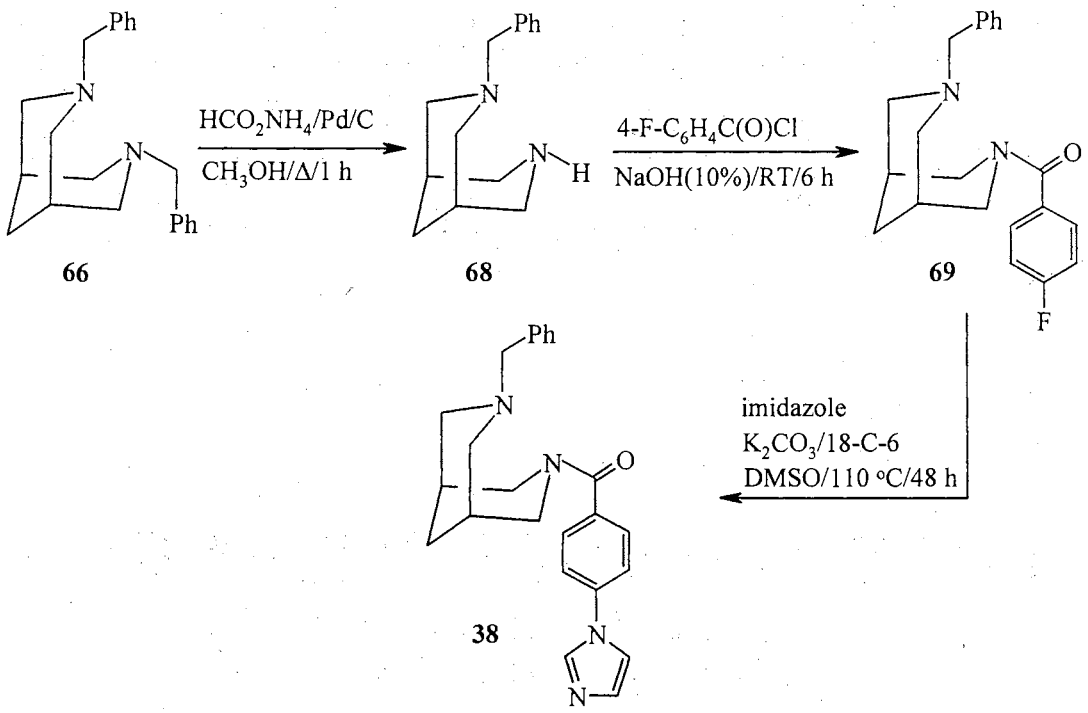


Wolff-Kishner reduction of **65** with hydrazine and KOH pellets gave the corresponding tertiary amine **66**. Treatment of **66** with perchloric acid produced the desired salt **30**. Reaction of **65** with 1,2-ethanedithiol and *p*-toluenesulfonic acid (anhydrous) formed the

masked thioketal **67**. The water formed in this reaction as byproduct was removed via the use of a Dean-Stark trap. Since the yield of the reaction was low (47%), an alternative method, which involved the 1,2-ethanedithiol and boron trifluoride etherate with stirring at RT for 12 h, was developed to produce **67** in higher yields (79%).[77] Treatment of **67** with perchloric acid (60%) resulted in formation of **31** as a white solid.

As the starting point to obtain derivative **38**, debenzylation of the tertiary amine **66** was employed using anhydrous ammonium formate and Pd/C (Scheme VI). The reaction was performed using 1.5 equivalents of ammonium formate to prevent or mini-

Scheme VI

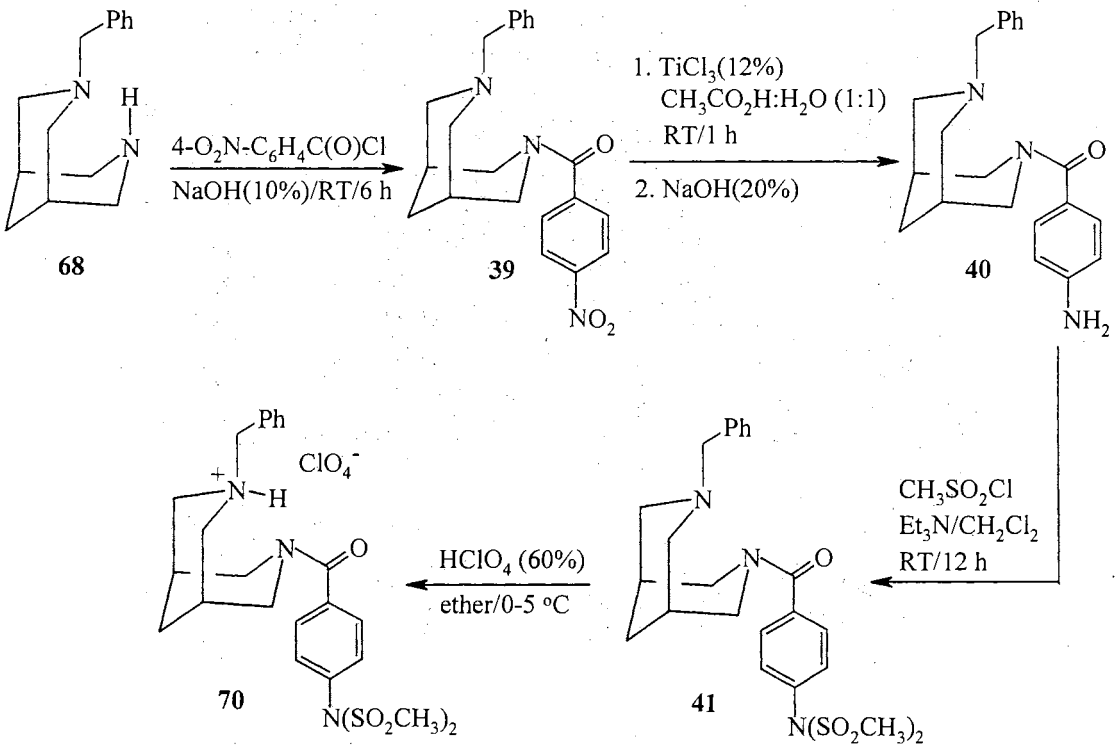


mize debenzylation of both the benzyl groups. Under such conditions, it was possible to selectively isolate secondary amine **68**, which, upon treatment with 4-fluorobenzoyl chloride, gave the corresponding tertiary amide **69** (82%). Replacement of fluorine in **69**

was achieved by a nucleophilic aromatic substitution reaction with imidazole, K_2CO_3 (dry and powdered), and 18-C-6 to afford the target compound **38** (52%).

Preparation of amides **39-41** (Scheme VII) was accomplished by acylation of **68**

Scheme VII

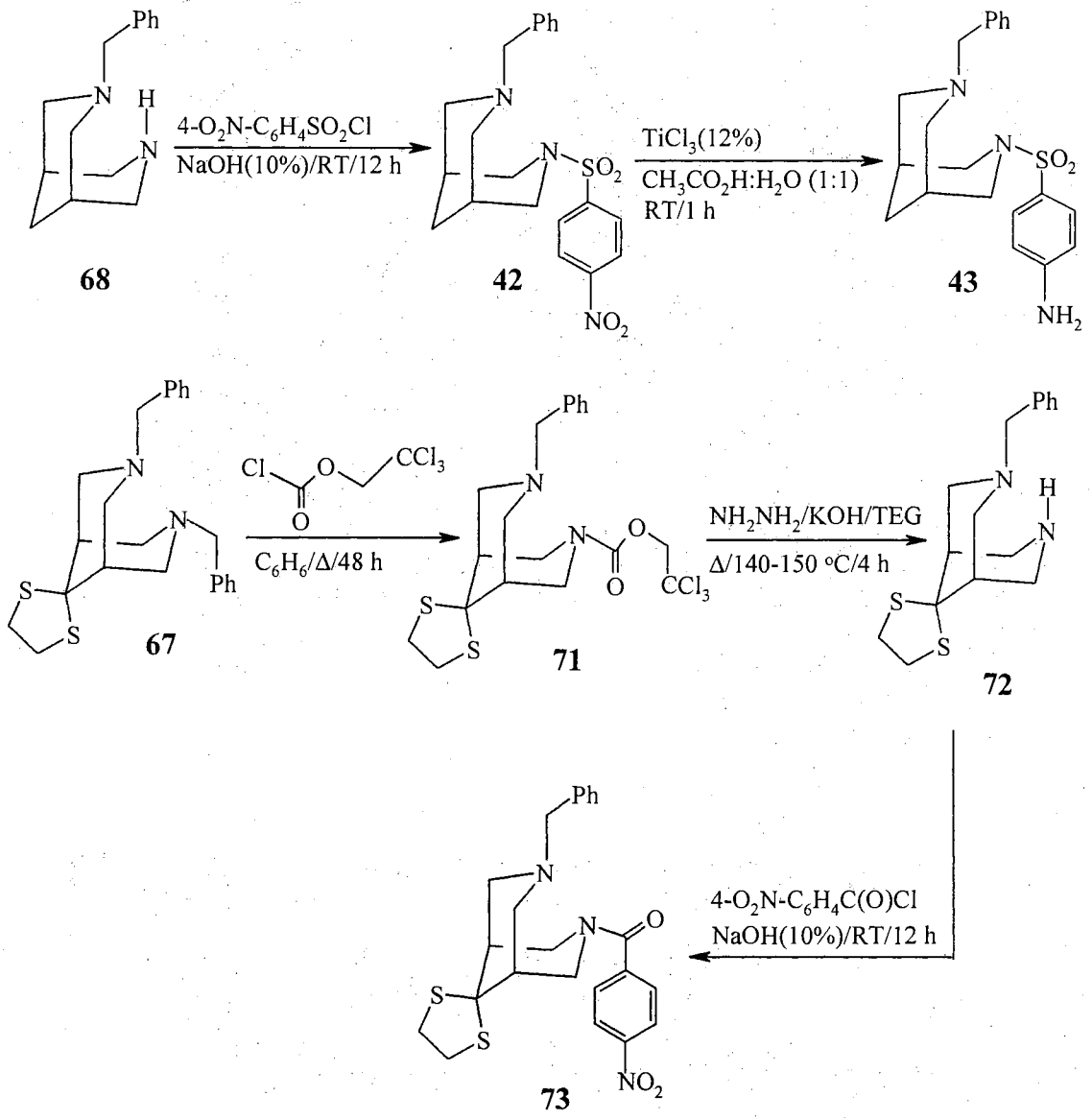


with 4-nitrobenzoyl chloride, under modified Schotten-Baumann conditions to produce **39** as a yellow solid (92%). Reduction of the nitro group in **39** occurred by treatment with $TiCl_3$ in acetic acid:water (1:1) to afford **40** (49%). Reaction of **40** with 2 equivalents of methanesulfonyl chloride and triethylamine resulted in the formation of the unusual disubstituted sulfonamide **41**, which, upon treatment with perchloric acid, produced the desired product **70** (59%).

The synthesis of the sulfonamides **42** and **43** was achieved by Schotten-Baumann acylation of the secondary amine **68** with 4-nitrobenzenesulfonyl chloride to form the

corresponding sulfoxide **42** (87%) (Scheme VIII). Reduction of the nitro group in **42** proceeded normally with $TiCl_3$ to form the desired product **43** (53%). Preparation of derivative **73** (Scheme VIII) was initiated by debenzylation of one of the benzyl groups

Scheme VIII



in **67** via the use of trichloroethyl chloroformate in boiling benzene to form the carbamate **71**.[80] It was realized that the standard debenzylation conditions involving the use of ammonium formate and Pd/C would not be useful in affecting the debenzylation of **67** as

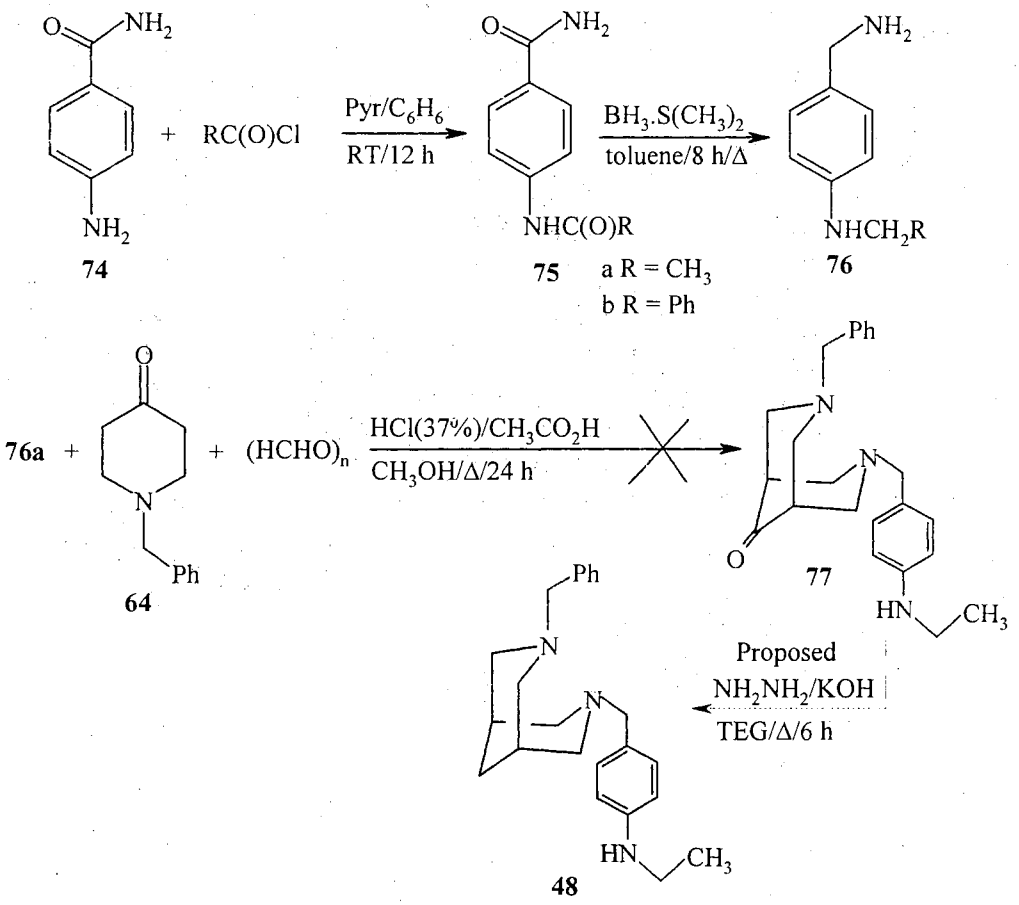
the presence of a sulfur atom in **67** would likely deactivate the Pd/C catalyst. Cleavage of the carbamate linkage in **71** was attempted by reaction with zinc/acetic acid. However, this resulted in cleavage of not only the carbamate group but also of the thioketal moiety. Thus, an alternative method involving the use of KOH pellets and hydrazine under strongly basic conditions was employed to cleave the carbamate group and to form the desired secondary amine **72**, which, upon treatment with 4-nitrobenzoyl chloride, gave the desired amide **73**.

As stated earlier, incorporation of NO releasing feature to the DHBCNs in addition to the antiarrhythmic properties, is one of the current interest in our laboratory. As a part of ongoing efforts in this direction, di- and triamine precursors **48-55** were conceived (page 47), which, upon reaction with $NO_{(g)}$ are likely to produce the corresponding zwitterionic salts **47**. Such salts would hopefully decompose in slightly acidic medium to release NO in a slow and controlled manner.

Synthesis of compound **48** was envisioned as outlined in Scheme IX. 4-Aminobenzamide (**74**) was acylated by reaction with acetyl chloride to form the diamide **75a**. Pyridine was used as a scavenger of HCl, which is formed as a side product in the reaction. The primary and tertiary amide fuctionalities in **75a** were reduced by reaction with 6 equivalents borane dimethyl sulfide to form the corresponding diamine **76a**.[81] The next step involved a double Mannich condensation of *N*-benzyl-4-piperidinone (**64**) with **76a** and paraformaldehyde under forcing conditions via the use of conc HCl and glacial acetic acid, hopefully, to form the desired Mannich ketone **77**, which could eventually be reduced under Wolff-Kishner conditions to form **48**. The workup and purification, however, revealed the presence of only the starting materials and other

unidentifiable complex by-products. This process was repeated by executing the reaction for 48 h, but only starting materials and complex side products were found. Preparation

SCHEME IX

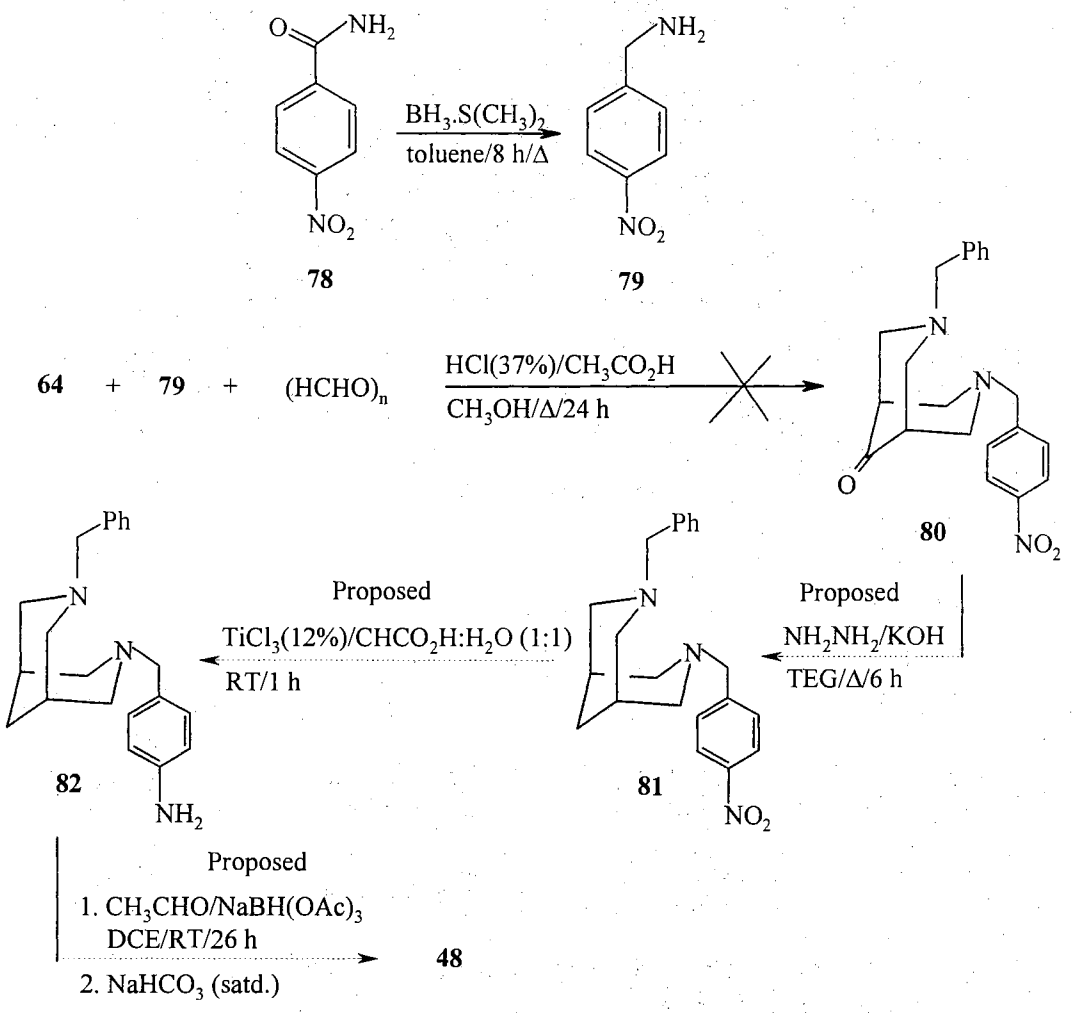


of **75b** was achieved by acylation of **74** with benzoyl chloride under similar conditions described for preparation for **75a**. Reduction of amide functionalities in **75b** produced **76b**. A double Mannich condensation of **76b** with **64** and paraformaldehyde under forcing conditions however resulted in isolation of only the starting materials and complex side products.

Thus, an alternative strategy for the preparation of **48** was employed as outlined in Scheme X. It was envisioned that a double Mannich condensation of 4-nitrobenzylamine

(**79**) with **64** would form the ketone **80**, which, upon reduction under Wolff-Kishner conditions, would produce **81**. Reduction of the nitro group in **81** could be accomplished by reaction with $TiCl_3$ to form the corresponding reduced product **82**, which, upon treatment with acetaldehyde and sodium triacetoxyborohydride, would form **48**.[82] In order to accomplish the above mentioned scheme, 4-nitrobenzamide (**78**) was reduced by

SCHEME X

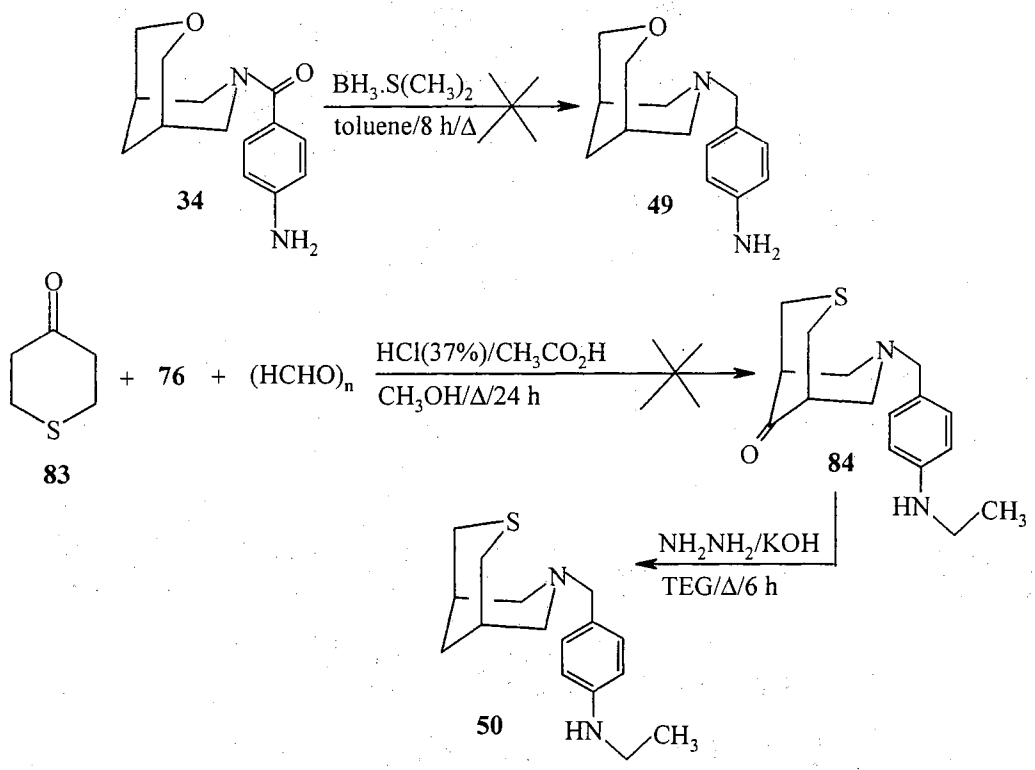


treatment with borane dimethyl sulfide to 4-nitrobenzylamine (**79**). A double Mannich condensation of **64** with **79** and paraformaldehyde under forcing conditions was performed only to recover the starting materials. The reaction was also performed by

increasing the reaction time to 48 h and with less forcing conditions by avoiding the use of conc HCl. However, only to recover the starting materials were recovered. Efforts are currently underway to devise alternative strategy to obtain **48**, the results of which will be reported soon.

Preparation of derivative **49** (Scheme XI) was attempted by reaction of **34** with borane dimethyl sulfide only to recover the starting material. This reaction was also attempted via the use of lithium aluminum hydride (LAH) but only **34** was recovered. Synthesis of compound **50** (Scheme XI) was attempted by a double Mannich conden-

SCHEME XI

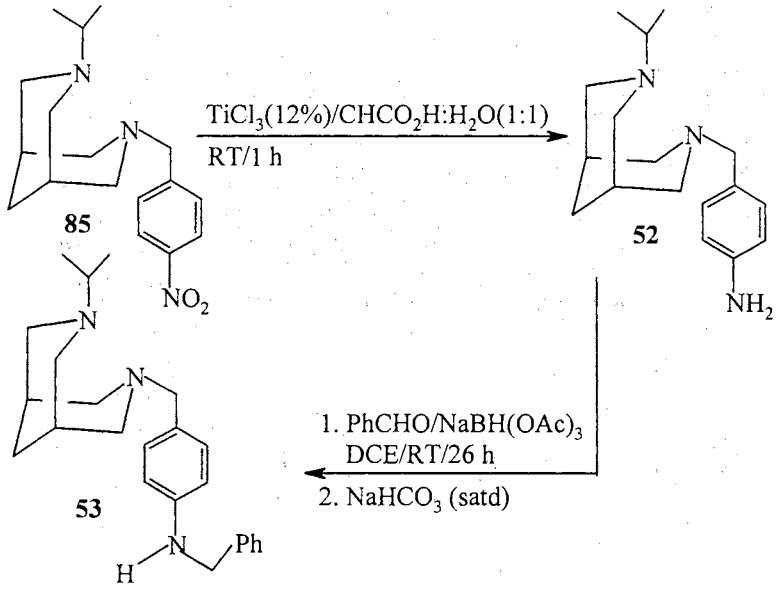


sation of tetrahydrothiopyran-4-one (**83**) with **76** and paraformaldehyde via the use of conc HCl and glacial acetic acid. Examination of the reaction mixture, however, revealed

the presence of starting materials and complex side products. Currently, efforts are underway to devise alternate synthetic strategy to obtain compounds **49** and **50**.

Preparation of derivatives **52** and **53** (Scheme XII) was accomplished by the reduction of the nitro group in **85** to produce **52**. Treatment of **52** with benzaldehyde generated the corresponding imine *in situ*, which was reduced to the desired product **53**

SCHEME XII

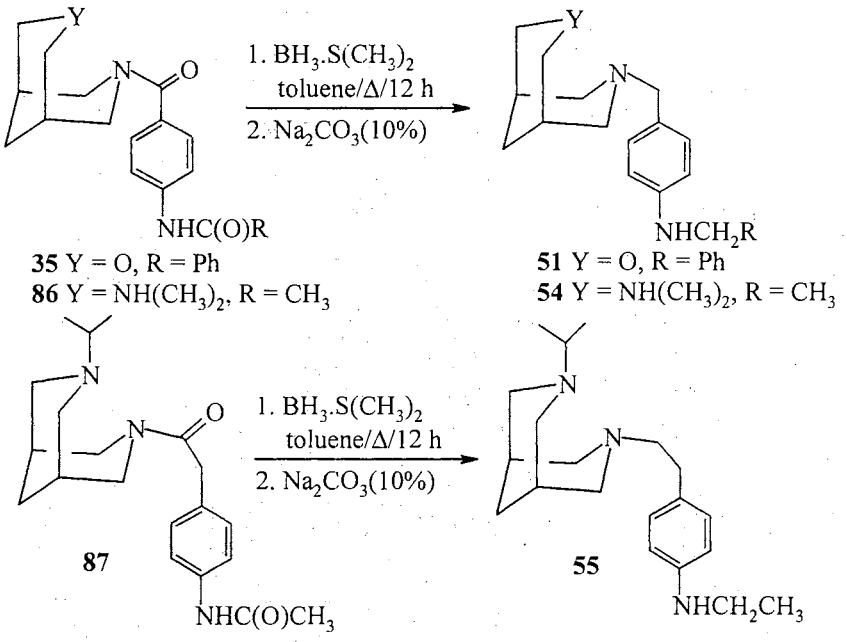


via reaction of the imine with sodium triacetoxyborohydride. Synthesis of derivative **51** as outlined in Scheme XIII was achieved by reaction of the diamide **35** with borane dimethyl sulfide to form **51**. Similarly, amine **54** was obtained by the reduction of amide **86** with borane dimethyl sulfide. Derivative **55** was obtained by treatment of **87** with borane dimethyl sulfide (Scheme XIII).

Antiarrhythmic Activity

The antiarrhythmic properties of **31** and **47** were evaluated by Drs. Scherlag and Patterson at the VAMC/OUHSC in Oklahoma City, Oklahoma. The compounds were

SCHEME XIII



studied in anesthetized mongrel dogs which were examined after the occlusion of the left anterior descending coronary artery and after the dogs were allowed to recover for 24-96 h.[53] This occlusion results in a transmural myocardial infarction of the heart in which accelerated idioventricular rhythms are observed interdispered with the beats of the normal sinus rhythm. Electrical output of the heart was monitered using a 12-lead electrocardiogram (ECG) to ascertain the presence and the extent of myocardial infarction. Induction of sustained ventricular tachycardia (SVT is defined as a series of ventricular beats which are usually uniform at a rate of 250 or more) was initiated using programmed electrical stimulation (PES) which followed with the test agents at doses of 3 and 6 mg/kg and administered intravenously (i.v.). The agent's ability to terminate SVT or to prevent the induction of SVT was measured in all experiments. Lidocaine (**5**) was used as the standard for comparsion purposes since it is currently agent of choice in the treatment of SVT.[83]

Several parameters were measured in the experiments to determine the different class actions of each agent. These parameters include AH interval (Atrial His bundle conduction time), HV interval (His bundle to ventricular activation; measures sodium channel action), QT interval (time to complete the process of depolarization and repolarization), QRS interval (depolarization), PR interval (atrial depolarization, impulse delay at the AV node and transmission of impulse through the His bundle, right and left bundles, and Purkinje fibers), sinus cycle length (SCL), and the ability of each agent to abolish SVT. Prolongation of AH and HV intervals suggests that the agent has class I action while the prolongation of PR, QRS, and QT interval infers a class III action. In the experiments, lidocaine (**5**) was found to exhibit no class III action and only reduced the rate of SVT. Lidocaine (**5**) is known to possess class Ib action.[83]

The antiarrhythmic data of compounds **31** and **47** are reported in Table XIII. A careful analysis of the antiarrhythmic data reveals that both the compounds prolong the AH, HV interval (slowing of conduction), QRS, and QT intervals. Based upon such observations, it may thus be concluded that both the compounds exhibit class I and III antiarrhythmic properties.

TABLE XIII[a]

ANTIARRHYTHMIC PROPERTIES OF THE MOST ACTIVE DHBCN DERIVATIVES **28** & **30**

Comp	SCL[b]		QRS[c]		QT interval[d]		AH interval[e]		HV interval[f]		PR[g]		HR[h]		MBP[i]	
	pre[j]	post[k]	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post
DOSE = 3 mg/kg																
5 (lidocaine)	445	470	43	46	445	470	71	72	37	37	109	101	NM[l]	NM	NM	NM
28	467	468	42	47	467	468	70	77	37	37	111	94	NM	NM	NM	NM
30	465	504	42	56	465	504	82	84	35	44	123	107	NM	NM	NM	NM
DOSE = 6 mg/kg																
5 (lidocaine)	445	476	43	48	445	476	71	79	37	38	109	110	NM[l]	NM	NM	NM
28	467	482	42	46	467	482	70	72	37	38	111	96	NM	NM	NM	NM
30	465	429	42	64	465	429	82	99	35	46	123	125	NM	NM	NM	NM

[a]Antiarrhythmic properties were measured compared to lidocaine (**5**) using doses (3 and 6 mg/Kg) in which SVT was non-inducible in the DHBCN system while lidocaine (**5**) only reduced the rate of the VT.

[b]SCL = Sinus Cycle Length (msec).

[c]QRS = Time (msec) needed for depolarization.

[d]QT = Time (msec) required for the cell to undergo depolarization and repolarization.

[e]AH interval = (msec) measures conduction time.

[f]HV interval = (msec) measures sodium channel action.

[g]PR = (msec) Atrial depolarization, impulse delay at the AV node, and transmission of impulse through the His bundle-Purkinje fiber.

[h]HR = Heart Rate (beats/min).

[i]MBP = Mean Blood Pressure (mm Hg).

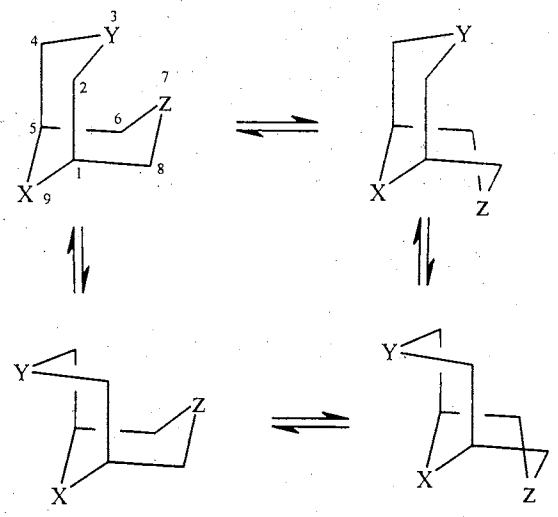
[j]Pre = Predrug or drug free state; mesurements before administration of the drug.

[k]Post = Post drug; mesurement after the administration of the drug.

[l]NM = Not measured

CONFORMATIONAL ANALYSES

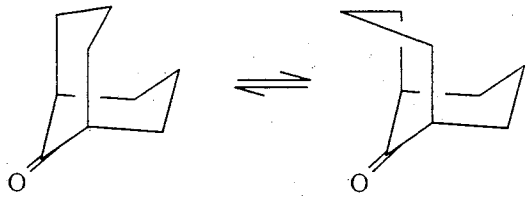
Conformational mobility, a unique property which is inherent to the diheterabicyclo[3.3.1]nonane ring system, has stimulated a variety of studies concerning the stereochemical and conformational preferences.[1a,,4a,53e,84,85] Not only are such analyses useful as diagnostic probes for structure elucidation, but such data are also important to understand the observed biological properties and possibly the mode of action of these agents. As described earlier, DHBCNs can exist in four possible



conformations. Some of the factors that probably lead to the preferred conformation of these systems are (i) steric repulsion of the heteroatoms, (ii) dipole repulsion, (iii) lone pair orbital repulsion, and/or (iv) intramolecular hydrogen bonding involving a proton on one heteroatom at the 3-position, for example, with the heteroatom at the 7-position.

The diheterabicyclo[3.3.1]nonan-9-ones (DHBCN-9-ONEs) also exist as mixtures of conformers in solution. The DHBCN-9-ONEs are excellent precursors of DHBCNs, and are thus valuable. A solid state ^{13}C NMR analysis of bicyclo[3.3.1]nonan-9-one (**88**) at 42 °C suggested the existence of the CC form predominantly.[86] This was further

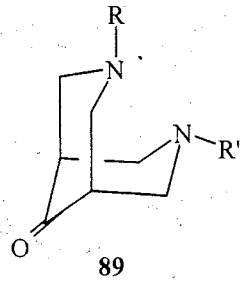
supported by the analysis of the ^{1}H NMR shifts induced by the lanthanide shift reagent $Eu(fod)_3$ on **88** in CCl_4.[87] A distribution of 78:22 favoring the CC conformer was



88

observed by comparing the experimental shifts with those predicted by the pseudocontact equations using geometries obtained from empirical force field (EFF) calculations.

Conformational analyses of several 3,7-diazabicyclo[3.3.1]nonan-9-ones (DABCN-9-ONEs) **89a-g** using ^{1}H, ^{13}C NMR, and IR spectral techniques were

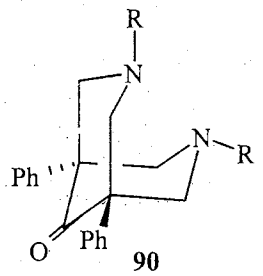


89

	R	R'		R	R'
a	CH_3	CH_3	e	CH_3	CH_2Ph
b	CH_3	CH_2CH_3	f	CH_2Ph	CH_2Ph
c	CH_3	$CH(CH_3)_2$	g	CH_3	CH_2CH_2Ph
d	CH_3	$CH_2CH_2CH_3$	h	$CH(CH_3)_2$	CH_2Ph

performed by Galvez and co-workers.[85] Their analyses suggested that ketones **89** adopt a primarily a flattened CC conformation in solution, but increased distortion from an ideal CC occurs in the series from R = methyl to where R = isopropyl.[85] This was deduced from an increase in the $[\delta_{C(6,8)} - \delta_{C(2,4)}]$ values in the ^{13}C NMR data observed in the series

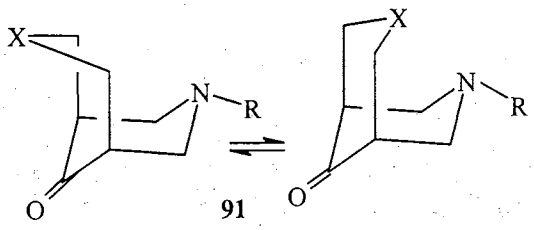
89a-c, which was taken as an indication of a more flattened CC conformation as the size of the N-alkyl substituents increased. This "flattening is presumed to be with respect to the corresponding 4-heteracyclohexanone or cyclohexanone. It was implied that rings with R,R' > Me were more flattened than the ring containing R,R' = Me. However, an X-ray analysis of **89e**, for example, showed a BC conformation in the solid state.[85c] On the other hand, variable temperature (VT) ^{13}C NMR spectral studies performed by Takeuchi on **90a-b** suggested a BC⇌CC equilibrium at -63 °C.[88]



90

a R = Me
b R = *t*-Bu

Our group has done extensive NMR studies on several members of the 3-hetera-7-



91

	X	R
a	S	CH_2Ph
b	Se	CH_2Ph
c	S	CH_2CH_2Ph
d	Se	CH_2CH_2Ph
e	O	CH_2Ph

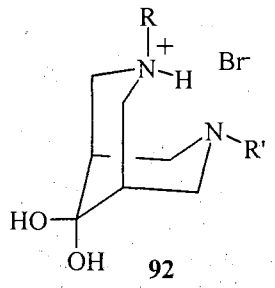
azabicyclo[3.3.1]nonan-9-ones[84a-c] which include ketones **91**. An X-ray diffraction analysis of solid ketones **91a** and **91b** showed a preference of a BC conformation which

was further supported by VT NMR studies of **91a** in the solution.[53e] A flattened CC conformation was suggested in solution for **91e** in solution.[84a] More recently, an enhanced population of the BC conformation in D_3CCN solution at 70 °C was assigned to ketones **89h** and **91a** by ^{17}O NMR spectroscopy.[84c] In each case, the ring bearing the benzyl group existed in a chair form and thus appeared to be somewhat biased. This assignment was derived on the basis of the observation that an upfield shift for C=O of 5-7 ppm [due to increased shielding at C(9)] was observed for each system. This observation appeared defensible only if a significant interaction existed between the lone pair on the heteroatom and the pi orbital of the carbonyl group. Thus, it was tentatively concluded that a BC conformer could give rise to such an effect.

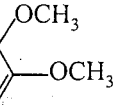
Based upon the studies carried out by our group[84] and others,[85] it is reasonable to believe that many 3,7-DABCNONs may have a high population of a BC conformation in solution with a BC⇌CC equilibrium. The existence of this equilibrium is likely in all systems, but where one of the fused rings has large substituents, there appears to be a conformational bias. This hints that systems like **89a-h** and **91a-d** may not exhibit an easily detectable BC⇌CC equilibrium at RT since large groups are attached to N. It appears that some simple 3,7-DABCNONs exhibit a BC⇌CC equilibrium in solution with an increased population of a BC form at higher temperatures (greater than or equal to that at RT) and an increased population of a CC form at low temperatures (-50 °C to –100 °C).[84a-c]

As part of this work, an investigation was made of conformational preferences of 3,7-DABCN-9,9-diols of the type **92** which were derived from the appropriate DHBCN-9-ONEs.[84d] The ^{13}C NMR spectral analyses of **92** indicated an upfield shift of C(2,4)

signals in comparison to the C(6,8) signals. This was explained by a gamma shielding effect involving the C(6)-N(7) and N(7)-C(8) bonds on C(2,4), which can occur only if



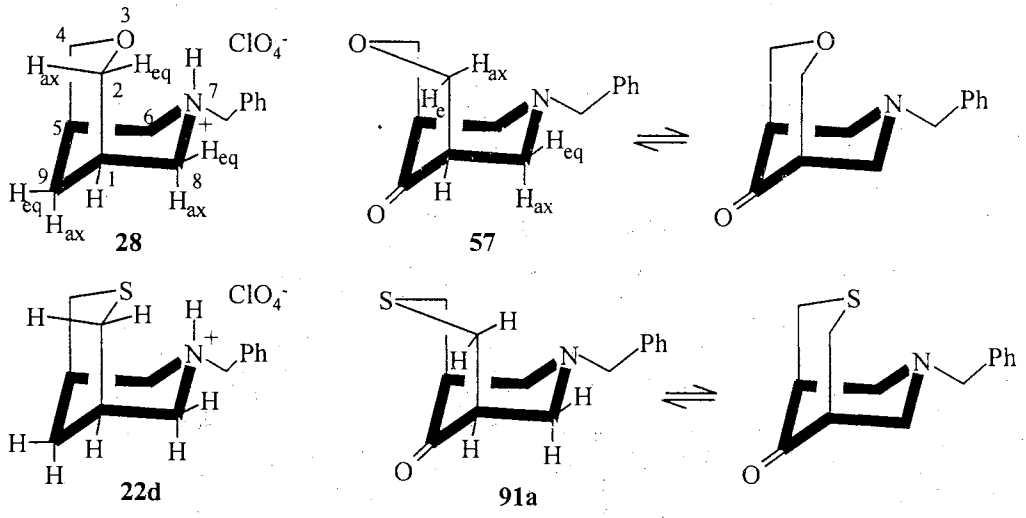
92

	R	R'
a	$CH(CH_3)_2$	CH_2Ph 
b	$CH(CH_3)_2$	H_2C
c	$CH(CH_3)_2$	$CH(CH_3)_2$
d	H_2C 	CH_2Ph

the CC conformer predominates in solution. This shielding offsets to some degree any deshielding contribution which results from the protonation of the nitrogen atom.

For only the first time, we have investigated the conformational preferences of DHBCNs via 2D NMR methods, namely using Nuclear Overhauser Enhancement Spectroscopy (NOESY), Double Quantum Correlation Spectroscopy (DQCOSY), and Heteronuclear Multiple Bond Correlation (HMBC). In this work, the conformations of some of the biologically important DHBCNs **22d** and **28** were investigated and their corresponding precursor ketones **57** and **91a**, respectively, at 400 MHz. As described earlier, perchlorates **22d** and **28** have demonstrated excellent antiarrhythmic activity in canine models.[84b]

Initially, the conformational preferences of **28** were deduced by NOESY data and further corroborated by DQCOSY and HMBC experiments. The NOESY spectrum



was best explained by assuming a CC conformation for **28**. The bold face ring above will serve as the base chair form for the following discussion. Distinguishing the signals originating from $H(2,4,6,8)_{ax,eq}$ was accomplished by choosing the signal at δ 4.22 as the entry point in the NOESY spectrum (Figure 3). This signal is for the CH_2 in CH_2Ph. Crosspeaks were observed between CH_2Ph and signals at δ 3.24 and 3.40. Since $H(6,8)_{ax,eq}$ protons are closer in space to CH_2Ph than $H(2,4)_{ax,eq}$, it was concluded these two signals must be associated with $H(6,8)_{ax,eq}$ protons. This is contrary to what may be expected since the deshielding effect due to the protonation on N(7) might be anticipated to exceed the electronegative effect due to the oxygen. A crosspeak was observed between HN(7) [δ 8.65] and the signal at δ 3.40. Since $H(6,8)_{eq}$ is closer to HN(7) than $H(6,8)_{ax}$, it follows that signal at δ 3.40 is due to $H(6,8)_{eq}$, and hence the signal at δ 3.24 is for $H(6,8)_{ax}$. The signals at δ 1.81 and δ 1.91 were assigned to $H(9)_{ax,eq}$. A crosspeak was observed between $H(6,8)_{ax}$ and δ 1.81. Since $H(9)_{ax}$ is closer to $H(6,8)_{ax}$ than is $H(9)_{eq}$, the signal at δ 1.81 is assigned to $H(9)_{ax}$ and hence δ1.91 is for $H(9)_{eq}$. The signals at δ 3.67 and δ 3.93 were assigned to $H(2,4)_{ax,eq}$. Since a crosspeak was observed

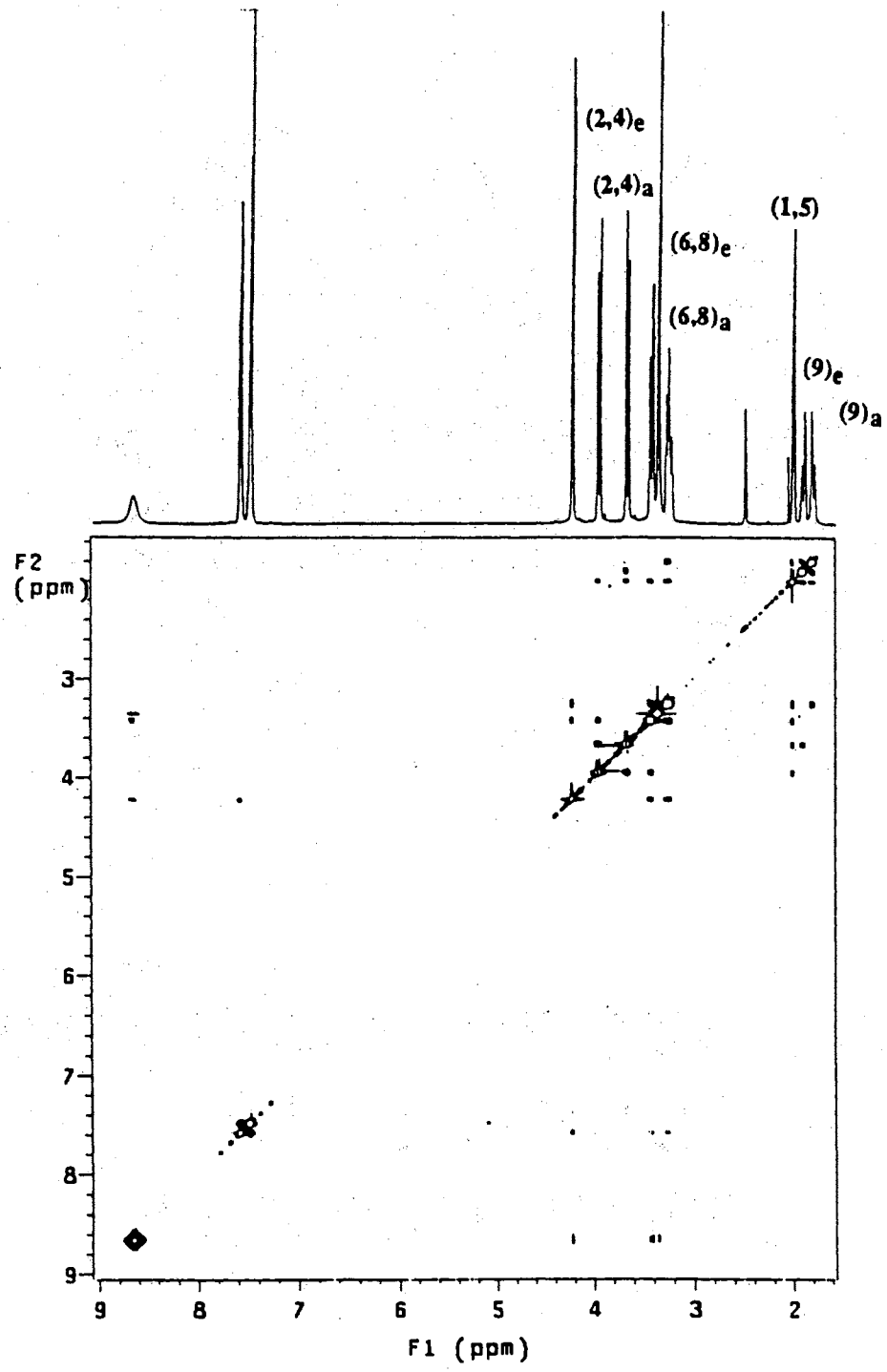


FIGURE 3. NOESY Spectrum of **28**

between $H(9)_{eq}$ and δ 3.67, it was concluded that $H(2,4)_{ax}$ appears at δ 3.67, and hence $H(2,4)_{eq}$ appears at δ 3.93. Furthermore, a crosspeak was observed between $H(2,4)_{eq}$ and $H(6,8)_{eq}$. The above observations support the predominance of a CC conformation for **28** in solution.

The DQCOSY spectrum (Figure 4) displayed several long range 'W' (4 bond couplings). Such couplings have been documented in some rigid ring systems where the rings are locked in chair conformations.[89] Some of the dominant 4-bond couplings are between $H(9)_{ax}$-$H(2,4)_{eq}$, $H(9)_{eq}$-$H(6,8)_{eq}$, and $H(6,8)_{ax}$-$H(2,4)_{ax}$ in **28**. The W coupling depends upon the tails of the orbitals of the first and the fourth bond to overlap. In the case of **28**, such an overlap can only occur when both the rings adopt a CC conformation. For instance, a suitable overlap of orbitals between the tails of $H(2,4)_{ax}$ and $H(6,8)_{ax}$ can occur readily when both the rings are in chair form. On the contrary, such an overlap is not possible when the top ring adopts a boat form since the tails of the orbitals are no longer aligned for a suitable overlap. The presence of 'W' couplings supports a CC conformation as dominant for **28** in solution.

Similar to **28**, the entry point in the NOESY specrum (Figure 5) of **22d** was chosen at δ 4.28, which corresponds to the methylene protons of the CH_2Ph. Crosspeaks were observed between CH_2Ph and signals at δ 3.33 and δ 3.55. Since $H(6,8)_{ax,eq}$ are closer in space to CH_2Ph than are $H(2,4)_{ax,eq}$, it was concluded these two signals were associated with $H(6,8)_{ax,eq}$ protons. A crosspeak was observed between HN(7) [δ 9.25] and the signal at δ 3.55. Since $H(6,8)_{eq}$ is closer in space to HN(7) than is $H(6,8)_{ax}$, it follows that signal at δ 3.55 is due to $H(6,8)_{eq}$, and hence the signal at δ 3.33 is due to

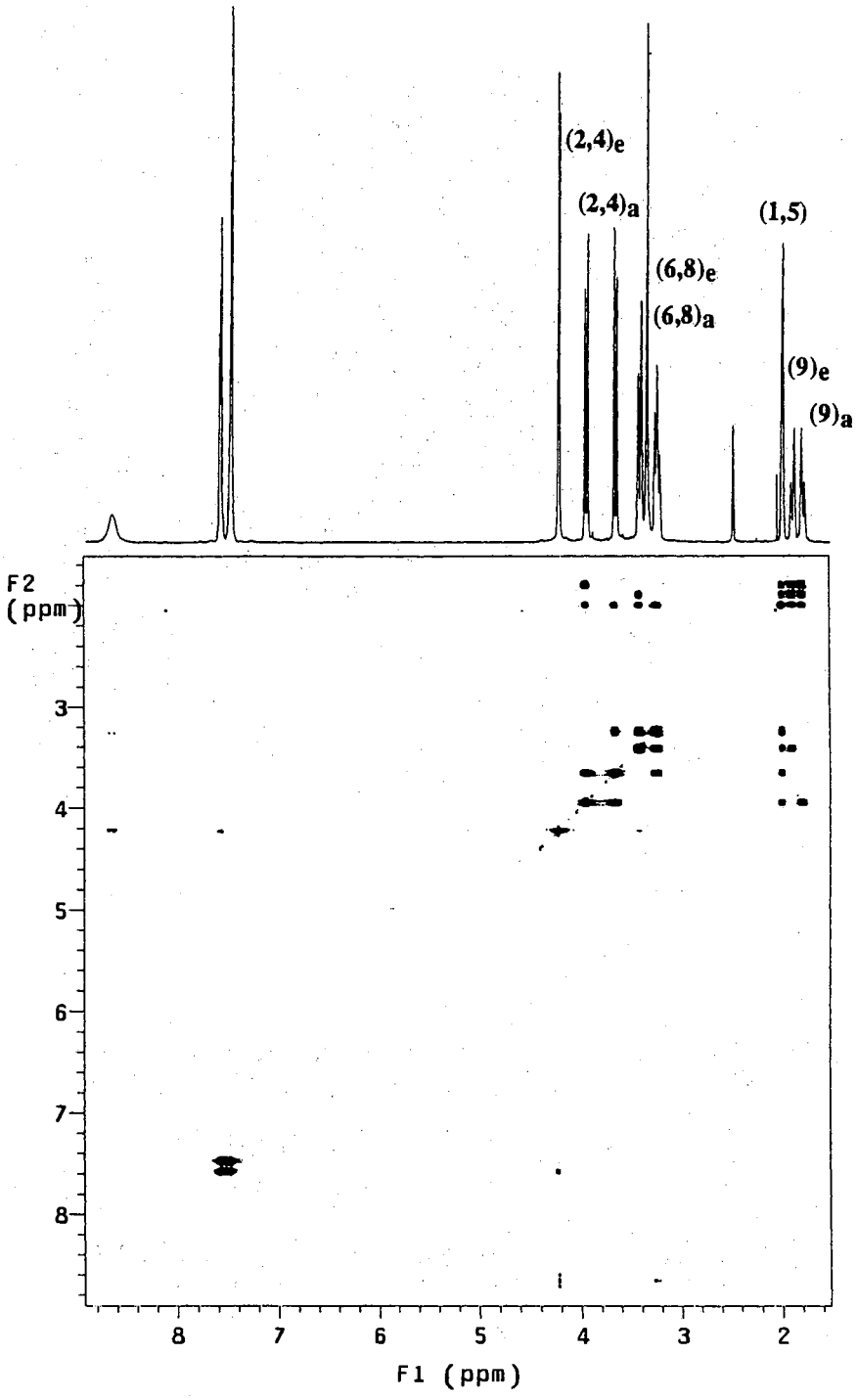


FIGURE 4. DQCOSY Spectrum of **28**

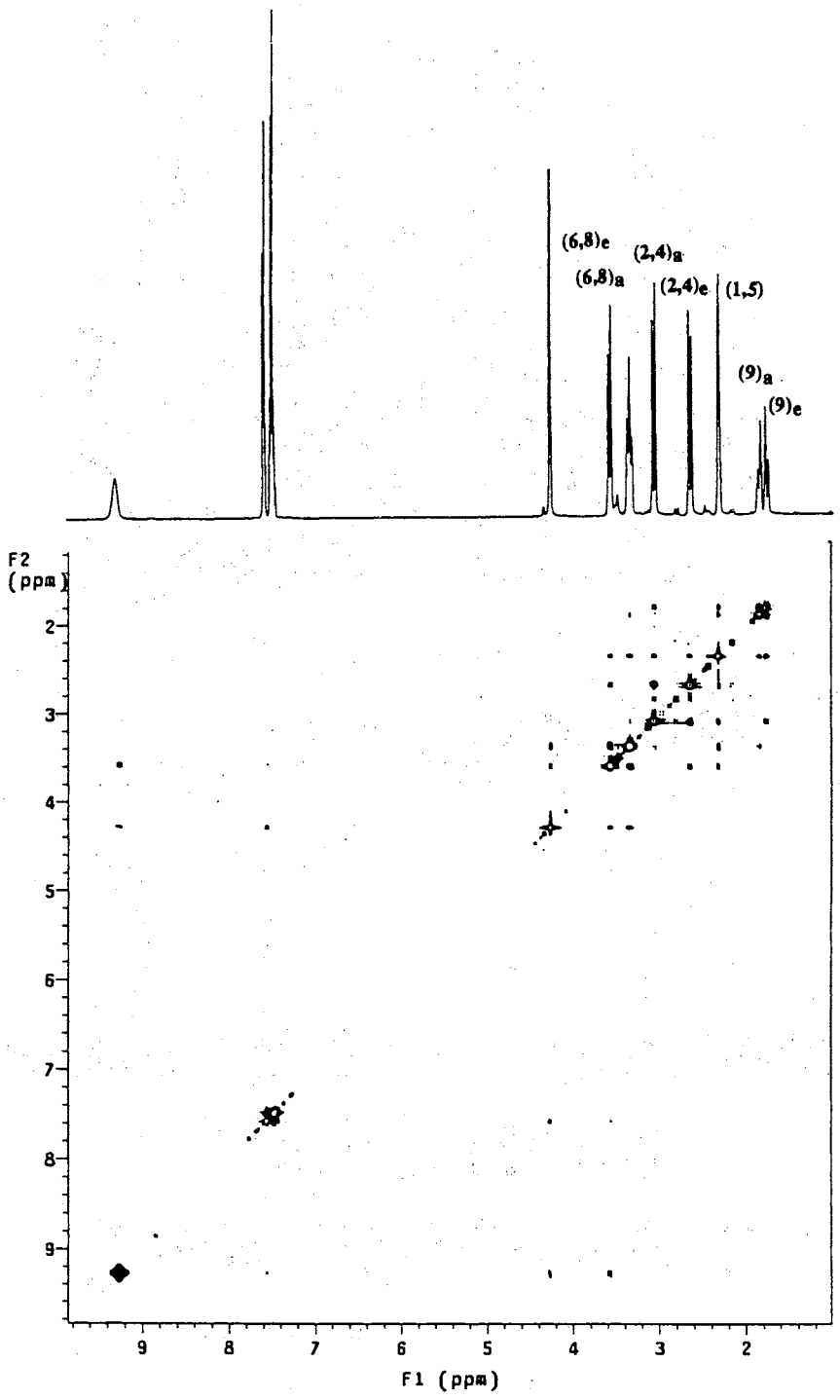


FIGURE 5. NOESY Spectrum of **22d**

$H(6,8)_{ax}$. The signals at δ 1.79 and δ 1.84 were assigned to $H(9)_{ax,eq}$. A crosspeak was observed between $H(6,8)_{ax}$ (δ 3.33) and the signal at δ 1.84. Since $H(9)_{ax}$ is closer in space to $H(6,8)_{ax}$ than is $H(9)_{eq}$, the signal at δ 1.84 was assigned to $H(9)_{ax}$ and hence δ 1.79 was assigned to $H(9)_{eq}$. The signals at δ 2.69 and δ 3.10 were assigned to $H(2,4)_{ax,eq}$. Since crosspeaks were observed between $H(9)_{eq}$ (δ 1.29) and the signal at δ 3.10, it was concluded that $H(2,4)_{ax}$ appeared at δ 3.10, and hence $H(2,4)_{eq}$ occurred at δ 2.69. This is contrary to what has been predicted in some bicyclo[3.3.1]nonanes ring systems where axial protons appear upfield compared to equatorial protons in cyclohexane rings.[89] Furthermore, a crosspeak was observed between $H(2,4)_{eq}$ and $H(6,8)_{eq}$. Such observations strongly support a CC conformer as the major form for **22d** in solution.

In the case of **22d**, the DQCOSY spectrum (Figure 6) was also informative. The 'W' couplings were observed between between $H(9)_a$-$H(2,4)_e$, $H(9)_e$-$H(6,8)_e$, and $H(6,8)_a$-$H(2,4)_a$ which also suggests that a CC conformation is the preferred form for **22d** in solution. Interestingly, several long range (three-bond) couplings were observed between protons and carbons in the HMBC spectrum (Figure 7). Some dominant ones include $H(9)_{a,e}$-C(6,8), $H(2,4)_e$-C(9), $H(2,4)_a$-C(6,8), $H(6,8)_a$-C(2,4), $H(6,8)_e$-C(9), and CH_2benzyl-C(6,8). Such observations also support the CC conformation for **22d**.

In ketones **57** and **91a**, a greater conformational mobility is expected compared to that in salts **28** and **22d** where an intramolecular H-bonding can occur between HN(7) and the heteroatom O or S.[84] In addition, repulsion of the nonbonded electron pairs on the heteroatoms in the ketones could reduce the energy barrier for ring reversal, thus making possible a rapid BC⇌CC equilibrium at RT. In the case of ketone **57**,

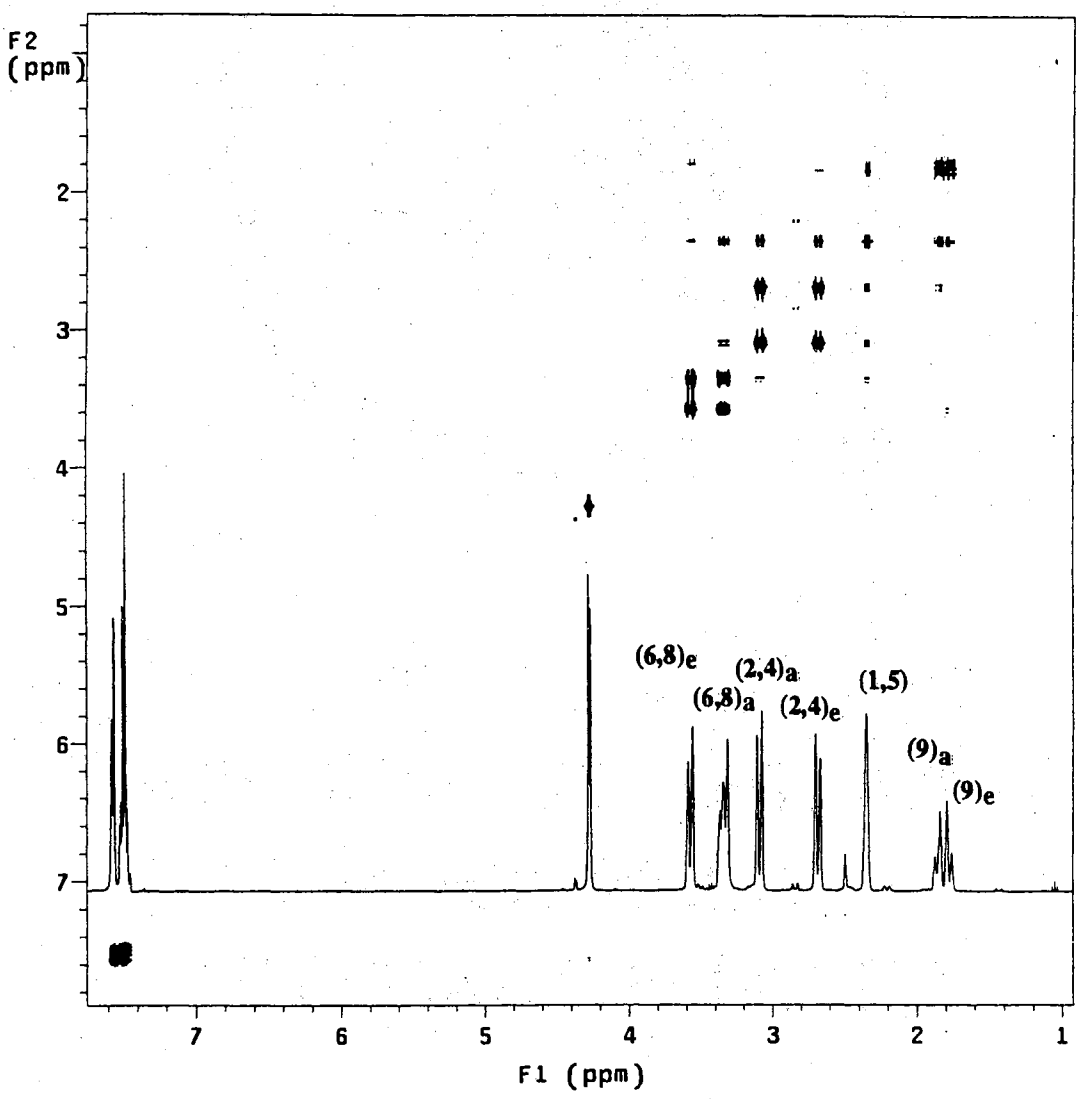


FIGURE 6. DQCOSY Spectrum of **22d**

FIGURE 7. HMBC Spectrum of **22d**

homonuclear NOESY and DQCOSY experiments were not informative. However, a heteronuclear NOESY (HOESY)[90] and coupling constant analysis proved to be useful. In an ^{1}H-^{13}C HOESY experiment (Figure 8), a significant proton-proton correlation was detected for H(2,4) and C(6,8) in **57**. This was manifested in a crosspeak between the signal at δ 3.87 [$H(2,4)_{eq}$] and that observed for C(6,8) [57.57 ppm]. Since the distance from $H(2,4)_{eq}$ to C(6), for example, is greater in **57-CC** than is the distance between $H(2,4)_{ax}$ and C(6) in **57-BC** (as found by *ab initio* calculations not reported herein), it is tentatively concluded that such evidence supports the BC form for **57** in solution. The interatomic distances between for $H(2)_{eq}$-C(6) in **57-CC** and $H(2)_{ax}$-C(6) in **57-BC** are 2.777 Å and 2.543 Å, respectively. Note that $H(2,4)_{eq}$ in **57-CC** refers to $H(2,4)_{ax}$ (pseudo axial) in the **57-BC** conformation. The ^{2}J and ^{3}J coupling constants in the Table XIV are also best rationalized by assuming the BC conformation as dominant in solution. In the **57-BC** form, the angle between $H(2,4)_{ax}$ and H(1,5) approaches 90° while the angle between $H(2,4)_{eq}$ and H(1,5) is closer to 0°. Thus, a small vicinal ^{3}J coupling is expected for the former case and a larger ^{3}J coupling for the latter case. Such couplings were indeed observed, and hence it may be tentatively concluded that a BC form predominates for **57** (600 MHz, Plate CXIII) in solution. This agrees with the former ^{17}O NMR study.[84c]

In case of sulfur ketone **91a**, overlap of the signals for the methylene protons was extensive at 400 MHz. The signals for $H(2,4)_{ax}$ and $H(6,8)_{eq}$ were found to overlap and appeared as a multiplet at δ 3.08 and could not be resolved even at 600 MHz (Plate CXII). However, we wish to speculate that a possibly BC form probably predominates in solution for **91a** as was found in the solid state by single crystal X-ray diffraction

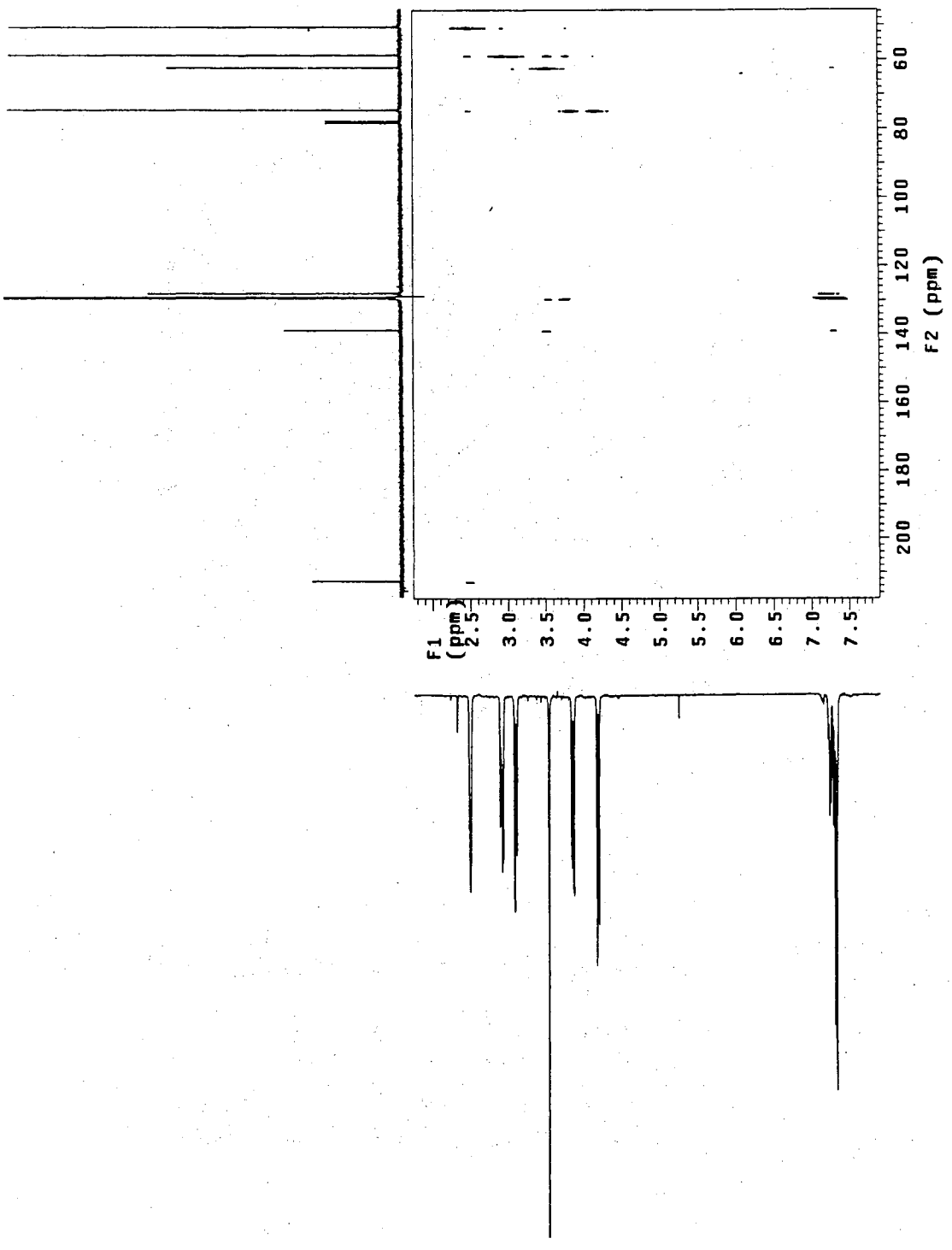


FIGURE 8. ^{1}H-^{13}C NOESY (HOESY) of **57**

TABLE XIV

^{1}H-NMR Chemical Shifts (ppm) and Multiplicities (Hz) for **57**

	ppm	*J*
H(1,5)	2.53	
$H(6,8)_a$	2.93 (dd)	$^2J = 11.17$ $^3J = 6.04$
$H(6,8)_e$	3.11 (dd)	$^2J = 10.98$ $^3J = 2.56$
$H(2,4)_a$	4.21 (d)	$^2J = 10.98$
$H(2,4)_e$	3.87 (dd)	$^2J = 11.17$ $^3J = 2.74$

analysis.[53e] An X-ray diffraction analysis was performed on a single crystal of **57** which was shown to have a CC conformation (Figure 9). This is in contrast to the crystal structure of **91a** which is a BC form.[53e] Ketone **57** crystallizes with two molecules in the asymmetric unit. The structure of one of the molecules is shown in Figure 9. The bond distances are very similar for both molecules. However, there is a significant difference in the conformational angles for C(6)-C(7) which are –53.6° (3) in molecule I and –21.1° in molecule II. Angles for C(7)-N(1) are 171.3° (2) and 162.5° (2) in I and II, respectively. The tricyclic systems in both molecules are in CC conformations. The conformation for related bonds in I and II differ by 1.6° or less. Most puckering occurs around bonds C(9)-C(10) [C(1)-C(9)] and C(10)-C(11) [C(5)-C(9)], with average conformational angles of 64°, and the least occurs for the N(1)-C(12) and N(1)-C(8) angles (53°) as well as for O(2)-C(13) and O(2)-C(14) (54°). The numbering in brackets refers to the normal numbering of such positions in the text.

To determine the relative stabilities of the conformers of **28**, **22d**, **57**, and **91a** in gas phase, *ab initio* methods with GAUSSIAN 94[91] were employed. To reduce

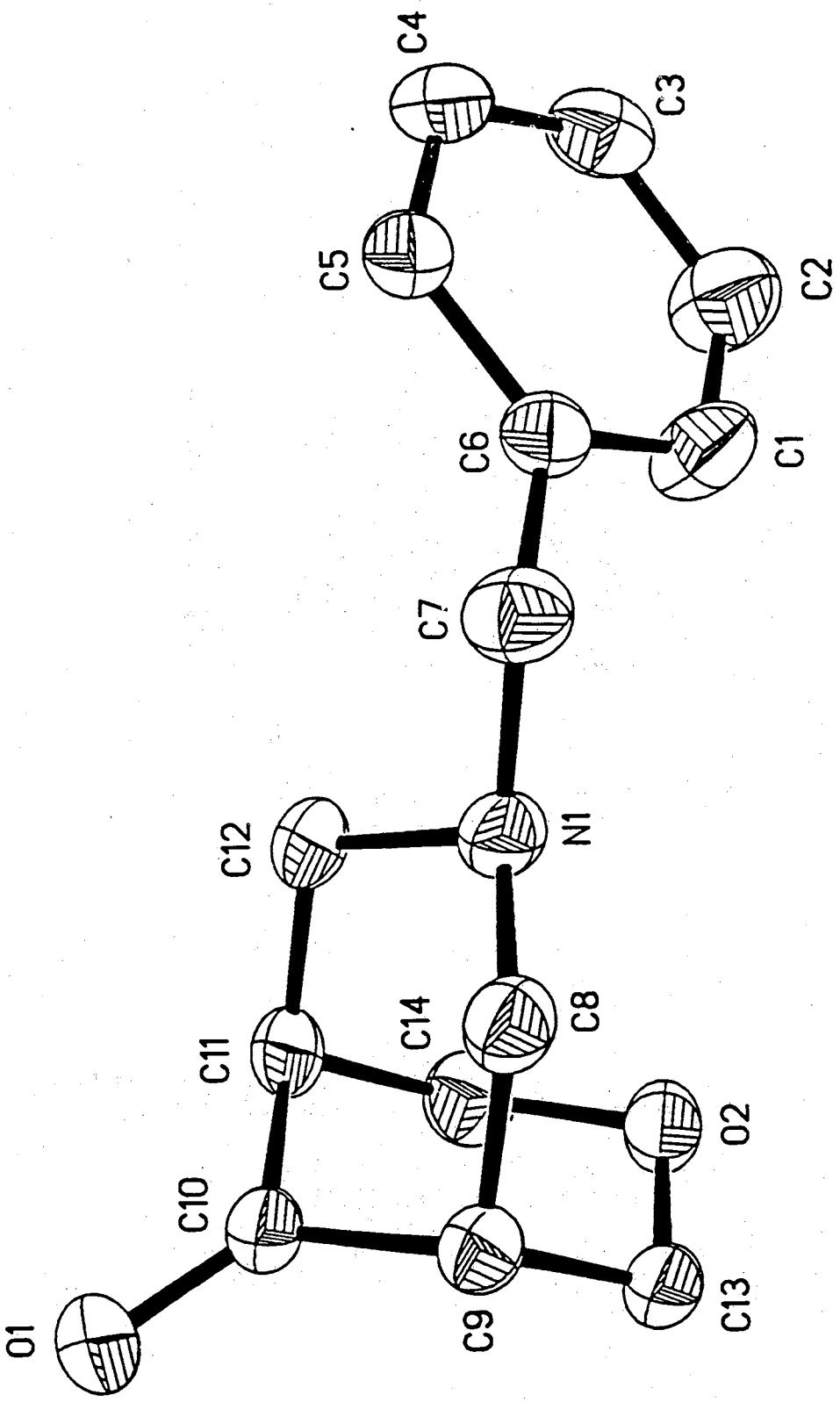


Figure 9. ORTEP Diagram of **57**

computational time, the phenyl (Ph) group in all the four compounds under investigation was replaced by hydrogen (H) in the calculations, since this change produced only a negligible variation in the minimum potential energy (P.E.) values (not shown). The geometries of **28**, **22d**, **57**, and **91a** were fully optimized at the Hartree-Fock (HF) level of theory with a 6-31G basis set. The results of the minimum P.E. data for ketones **57**

TABLE XV

Minimum Potential Energy (Kcal/mol) Calculation for **57** & **91a**

	Theory Level/ Basis Set	CC	BC	
57	HF/6-31G	-322803.7043	-322804.2484	[ΔE = 0.544 Kcal/mol]
91a	HF/6-31G	-525278.5930	-525279.4852	[ΔE = 0.892 Kcal/mol]

and **91a** (Table XV) clearly indicate that a BC form is energetically favored, but only by a small difference in energy. In the case of **91a**, the energy difference (0.892 Kcal/mol) between the CC and BC form is greater than that in the case of ketone **57** where the difference is only 0.544 Kcal/mol. The P.E. values were not affected when the calculations were performed at the MP2 level of theory and 6-31G basis set. Thus, it is speculated that in solution a rapid equilibrium occurs between the CC and BC form with a slight preference for the BC form at room temperature.

On the contrary, the *ab initio* calculations for the corresponding perchlorates **22d** and **28** showed a much greater propensity for the CC conformation as compared to the BC form (Table XVI). The P.E. difference between the CC and BC form in the case of **28** is higher than that for **22d**. Thus, it suggests that a CC conformation may predominate for salts **22d** and **28** in solution. Such stability may be partially attributed to a weak intra-

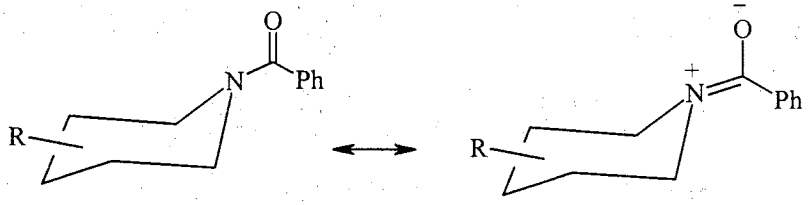
TABLE XVI

Minimum Potential Energy (Kcal/mol) Calculation for **22d** & **28**

		CC	BC	
22d	HF/6-31G	-479314.1682	-479302.6091	[ΔE = 11.55 Kcal/mol]
28	HF/6-31G	-276843.1707	-276827.7789	[ΔE = 15.39 Kcal/mol]

molecular hydrogen bonding between the heteroatom O or S and the proton on N(7).

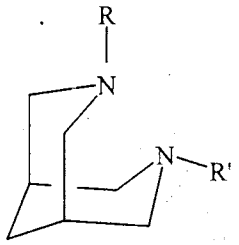
As stated earlier, certain amides and their corresponding salts of the DHBCN family have displayed excellent antiarrhythmic activity.[53a] Such amides have displayed unique conformational properties in solution as well as solid state.[92] Simple model amides, such as *N*-benzoylated piperidines **93**, apparently prefer flattened chair conformations in solution as assessed by analysis of variable temperature ^{1}H NMR[93] and ^{13}C NMR[94] data. Conformational preferences may be due, in part, to a minimum energy arrangement in which the p orbital of the carbonyl π system and the lone pair on nitrogen overlap (atom attached to the amide system will assume a nearly planar arrangement). Resonance forms of this familiar phenomena are illustrated for **93**.



93

Rotational barriers in simple benzamide systems have been reported to be approximatley 14-16 kcal/mol via ^{1}H and ^{13}C NMR experiments.[94] DHBCN amides

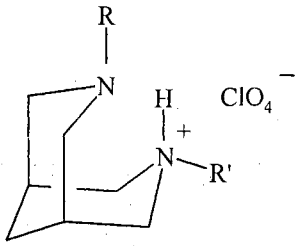
94a-h demonstrate this effect in that all the bicyclic ring carbon signals in the ^{13}C NMR



94

	R	R'
a	$C(O)C_6H_4$-4-Cl	CH_2-cPr
b	$C(O)C_6H_4$-4-NH_2	$CH(CH_3)_2$
c	C(O)Ph	CH_2-cPr
d	$C(O)C_6H_4$-4-NO_2	$CH(CH_3)_2$
e	$C(O)C_6H_4$-4-$NHC(O)CH_3$	$CH(CH_3)_2$
f	$C(O)C_6H_4$-4-$NHSO_2CH_3$	$CH(CH_3)_2$
g	$C(O)C_6H_4$-4-F	$CH(CH_3)_2$
h	$C(O)C_6H_4$-4-(1*H*-imidazol-1-yl)	$CH(CH_3)_2$

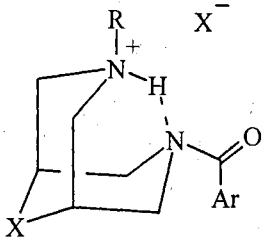
spectra are nonequivalent (thus the energy barrier to rotation of the amides is not reached at RT).[92] In contrast, the ^{13}C NMR spectra of the corresponding salts **95a-h** were found to be completely different in that the environmental nonequivalency seen for the ring carbon signals in the unprotonated amides was not observed in the protonated species.[92] In addition, VT ^{13}C NMR studies of **95** indicated that at low temperatures (-35 °C), the amide salts prefer one conformation while at room temperatures and above, an average conformation is reflected.[92] Thus, the barrier to amide rotation is much lower in the amide salts compared to that in the unprotonated amides. An explaination for this effect can be viewed by analysis of previous work where an intramolecular hydrogen bonding was found to occur between the N-H proton and the lone pair of electrons on the



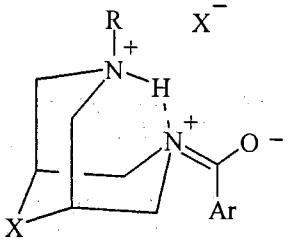
95

	R	R'
a	$C(O)C_6H_4$-4-Cl	CH_2-cPr
b	$C(O)C_6H_4$-4-NH_2	$CH(CH_3)_2$
c	C(O)Ph	CH_2-cPr
d	$C(O)C_6H_4$-4-NO_2	$CH(CH_3)_2$
e	$C(O)C_6H_4$-4-$NHC(O)CH_3$	$CH(CH_3)_2$
f	$C(O)C_6H_4$-4-$NHSO_2CH_3$	$CH(CH_3)_2$
g	$C(O)C_6H_4$-4-F	$CH(CH_3)_2$
h	$C(O)C_6H_4$-4-(1*H*-imidazol-1-yl)	$CH(CH_3)_2$

nitrogen atom of the amide functionality.[53a] It is believed that such an effect may result in the loss of double bond character of the amide N-C(O) bond and thus lead to increased



A



A'

rotation at RT. This implies that of the resonance forms A and A', A' make a smaller contribution to the hybrid in the amide-salts than in the simple amides. A single crystal X-ray diffraction analysis of the amide salt **32**, revealed a CC conformation (Figure 10)

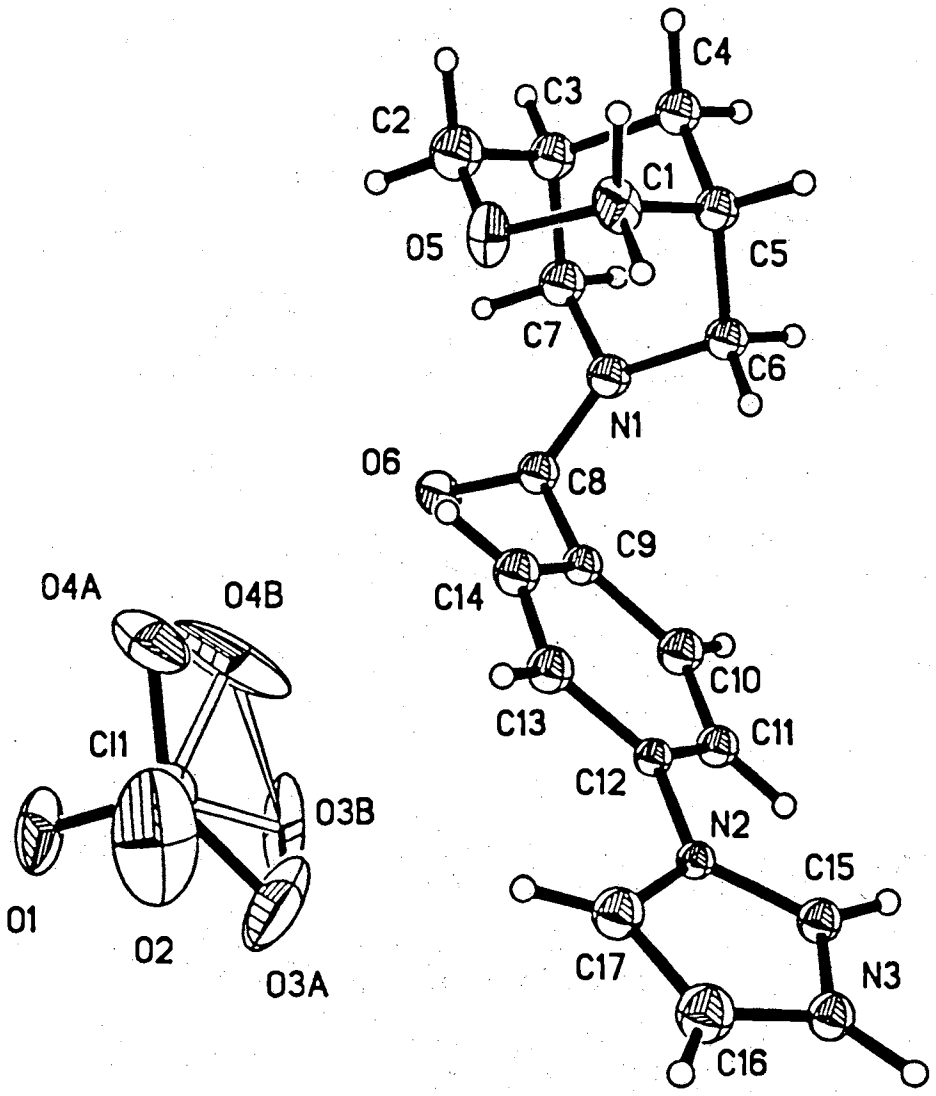
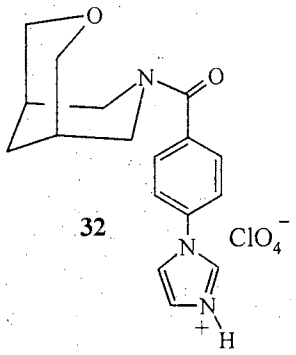


FIGURE 10. ORTEP Diagram of **32**

with a considerable flattening of the bicyclic ring system. It thus appears that the amide members of the DHBCN family prefer a CC conformation in the solid state. The ^1H NMR spectrum indicates that ring protons of the nitrogen ring are nonequivalent.



32

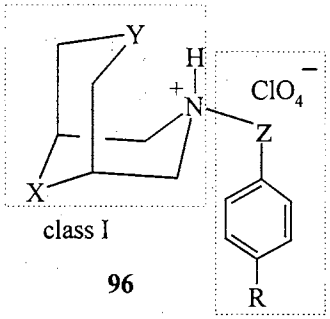
Summary

Several derivatives of the DHBCN family have been synthesized and evaluated for their ability to abolish artificially-induced ventricular tachycardia in canine models. In addition, some of the derivatives displayed antiarrhythmic action of more than one class based upon their effects on different electrophysiological parameters like QRS, QT, AH, and HV intervals. More recent efforts have resulted in the synthesis of certain DHBCNs to which nitric oxide (NO) could eventually be incorporated. The presence of NO to impart vasorelaxation and antiplatelet aggregation properties, in addition to the antiarrhythmic action, could lead to useful multi-functional antiarrhythmic agents. Conformational preferences of DHBCNs were investigated by 1D and 2D NMR spectroscopy. NOESY and DQCOSY experiments suggested the prevalence of a CC conformation for the DHBCN salts, while a BC form is strongly suspected for the corresponding ketone precursors in solution.

Suggestions for Future Work

Heart disease is one of major factors for mortality across the world. Thus, there is great need for more potent, selective, and less toxic antiarrhythmic drugs. Current approaches to the treatment of most arrhythmias are somewhat emperic as the mechanism and origin of arrhythmias are complex processes and are not well understood. Until a better understanding of arrhythmias is achieved, treatment of arrhythmias with anti-arrhythmic agents possessing more than one class action may be a better approch than using an agent exhibiting a single class action only.[53,68]

As found from our earlier work, several DHBCN derivatives exhibit antiarrhythmic activity in more than one class action. An ideal drug would have slight class I and dominant class II, III, and IV features. Although, the CAST studies have



class I

96

Class II, III, and IV

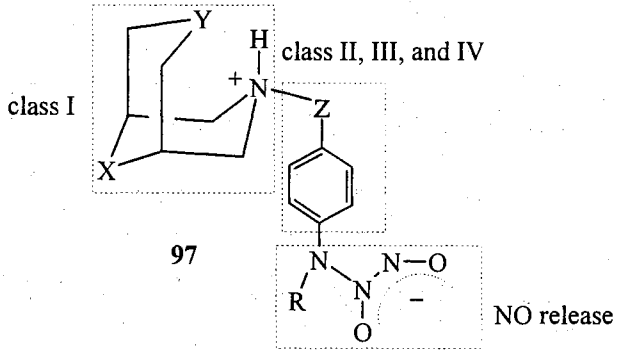
X = CH_2═C, alkyne, cyclopropyl, cyclopentyl
Y = O, S, $CH(CH_3)_2$, CH_2Ph
Z = $CH_2CH(OH)$
R = imidazole, pyrazole, NO_2, $\overset{+}{N}H_3$, NHR', SO_2R' [R' = CH_3, Ph]

showed some risk associated with class I drugs, it may still be desirable to accommodate slight class I action in an agent as found in earlier work.[53a-e] Based upon such a rationale, it is proposed that derivatives **96** would display class I, II, III, and IV action. It was realized from earlier work that the DHBCN nucleus with hydrophobic groups at the 9-

position contribute significantly to class I activity. The effects of thioketal and a methylene group at 9-position have already demonstrated good antiarrhythmic action.[53a] Incorporation of other hydrophobic groups (X = alkene, alkyne, cyclopropyl, and cyclopentyl) may lead to better agents in this family. In addition, such derivatives may impart a class III action as demonstrated by Tedisamil (**24**) and Ambasalide (**25**).

An important structural feature of most class II drugs is the presence of a hydroxyl group. It is thus speculated that Z = $CH_2CH(OH)$ may impart class II action to derivatives **96**. Class III and IV actions of DHBCN are believed to originate from the perchlorate anion and certain functional groups like NO_2, imidazole, SO_2, NH_3^+. The effects of R as a pyrazole ring on antiarrhythmic activity of DHBCNs have not been examined. Thus, derivatives with R = NO_2, imidazole, SO_2, and pyrazole are anticipated to give agents with excellent class III and IV action.

Another area of interest is the role of NO in the prevention of heart disease or arrhythmias. Incorporation of a slow and controlled NO release mechanism in a molecule, in addition to the multiple class action, may have several benefits in the



97

X = CH_2═C, alkyne, cyclopropyl, cyclopentyl

Y = O, S, $CH(CH_3)_2$, CH_2Ph

Z = $CH_2CH(OH)$

R = CH_3, $CH(CH_3)_2$, Ph

treatment of myocardial infarction. Based upon such rationale, derivatives **97** may serve as good candidates for this purpose. The rate of NO release may be modulated by varying the R group since the stability of such compounds probably depends upon the extent of orbital overlap between the amine nitrogen and the $NONO^-$ group.

EXPERIMENTAL SECTION

General Information: All ^{1}H and ^{13}C spectral data were obtained either on a Varian Unity Inova-400 MHz NMR spectrometer operating at 399.925 and 100.570 MHz, respectively, a Varian Unity Gemini 300 MHz spectrometer operating at 300.082 MHz and 75.463 MHz, respectively, or a Varian Unity Inova 600 MHz spectrometer operating at 598.724 MHz and 150.57 MHz respectively. Chemical shifts for the ^{1}H and ^{13}C NMR spectra were recorded in δ or ppm values, respectively, downfield from TMS, while the ^{77}Se NMR signals were reported in ppm downfield from sodium selenite (Na_2SeO_3) as an external standard. Most 2-D NMR experiments, including NOESY (homonuclear and heteronuclear) and DQCOSY, were recorded on Varian Unity Inova 400 MHz spectrometer. The heteronuclear NOESY (^{1}H-^{77}Se) was performed on the Varian Unity Inova 600 MHz spectrometer. The NOESY spectra were collected with a spectral width of 3827.8 Hz in both dimensions. The data were collected as an array of 2K x 400 points, which, after linear prediction and zero filling in the t_1 dimension, produced a data matrix with 2K x 4K points. A mixing time of 150 ms and a relaxation delay of 1.5 s were used. The DQCOSY data were acquired with a spectral width of 3827.8 Hz in both dimensions. The data were also collected as array of 2K x 600K points, which, after linear prediction and zero filling in the t_1 dimension, produced a data matrix with 2K x 4K points.

Melting points, which were uncorrected, were recorded on a Thomas-Hoover capillary melting point apparatus. The purity of the products was determined by Hewlett-Packard (GCD-800 series) Gas Chromatograph Mass Spectrometer (GCMS) instrument, with a electron ionization (EI) source. IR spectra were recorded on Perkin-Elmer 2000

FT-IR spectrophotometer as films or KBr pellets. High Resolution Mass Spectral (HRMS) and nominal MS analysis were performed on a VG Analytical instrument, model ZAB-2SE, by the LSIMS/FAB mode using 3-nitrobenzyl alcohol as the matrix. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, Georgia. Citations to "*in vacuo*" have reference to the use of the rotary-evaporator unless otherwise indicated.

Syntheses were performed under an atmosphere of N_2 with magnetic stirring unless otherwise specified. ACS grade solvents were used after distillation, followed by drying, for executing most reactions. All chromatographic separations were performed either via a glass column, using silica gel (Davisil, 62, 60-200 mesh) as the stationary phase or on a Chromatotron (Harrison Research, model 7924) using silica gel (pF 254 containing gypsum, EM Science) as the stationary phase. Glasswares were oven-dried and flushed with N_2 before executing all reactions.

The following reagents were obtained commercially and used without further purification: 2',2',2'-trichloroethyl chloroformate (Aldrich), benzylamine (Aldrich), hydrazine (98%, Aldrich), glacial acetic acid (Fisher Scientific), hydrochloric acid (Fisher Scientific), imidazole (Aldrich), paraformaldedyde (Aldrich), Pd/C (Aldrich), tetrahydro-4*H*-pyran-4-one (Acros), potassium hydroxide pellets (85%, Fisher Scientific), $TiCl_3$ (10 wt% or 12 wt%, Aldrich), 18-C-6 (Aldrich), potassium carbonate (Fisher Scientific), sodium carbonate (Fisher Scientific), borane methyl sulfide (10 *M*, Aldrich), sodium triacetoxyborohydride (Aldrich), *N*-benzyl-4-piperidinone (Lancaster), 4-nitrobenzoyl chloride (Aldrich), 4-nitrobenzenesulfonyl chloride (Aldrich), 4-fluorobenoyl chloride (Aldrich), 4-fluorobenzenesulfonyl chloride (Aldrich), ammonium

formate (Aldrich), perchloric acid (60%, Aldrich), 1,2-ethanedithiol (Aldrich), PTSA (Fisher), boron trifluoride etherate (Aldrich), triethylamine (Aldrich), pyridine (Fisher Scientific), 4-fluorobenzamide (Aldrich), 4-nitrobenzamide (Aldrich), acetyl chloride (Aldrich), triethylene glycol (Aldrich), and benzoyl chloride (Aldrich). The sample of *N*-benzyl-4-piperidinone was distilled under reduced pressure (bp 100-101 °C/27 mm Hg) prior to use. Best results were obtained with fresh ammonium formate and palladium on charcoal.

7-Benzyl-3-oxa-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (28). A 50-mL, Erlenmeyer flask was equipped with a magnetic stirrer, and an ice-bath. To a stirred, chilled solution of **58** (0.6 g, 2.76 mmol) in 20 mL of anhydrous ether was added $HClO_4$ (60%, 0.69 g, 4.14 mmol) dropwise over a period of 10 min. The solution was stirred for an additional 10 min to precipitate a light yellow solid. The solid was filtered (suction) and washed with copious amounts of ether. Recrystallization (ether:CH_3CN, 2:1) afforded the hydroperchlorate **28** (0.72 g, 82.6%) as a white solid, mp 188-189 °C (dec). IR (KBr) 3310 (N-H), 3035 (Ar-H), 2877, 2905 (C-H) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.79 [d, 1 H, H(9)], 1.85 [d, 1 H, H(9)], 1.95 [bs, 2 H, H(1,5)], 3.22 [d, 2 H, $H(6,8)_{ax}$], 3.40 [d, 2 H, $H(6,8)_{eq}$], 3.62 [d, 2 H, $H(2,4)_{ax}$], 3.95 [d, 2 H, $H(2,4)_{eq}$], 4.25 [s, 2 H, CH_2-benzyl], 7.45 [m, 5 H, Ar-H], 8.6 [bs, 1 H, N-H]; ^{13}C NMR (DMSO-d_6) ppm 28.25 [C(9)], 28.33 [C(1,5)], 56.03 [C(6,8)], 60.93 [C(2,4)], 71.03 [CH_2-benzyl], 128.95, 129.66, 129.69, 131.29 [Ar-C]. High resolution mass spectral (HRMS) data calcd for $C_{14}H_{20}ClNO_5$ (M^+): 218.1544 (- ClO_4^-). Found: 218.1539.

7-Benzyl-3-oxa-9,9-(1,3-dithiolan-2-yl)-7-azabicyclo[3.3.1]nonane Hydroperchlorate (29). A 50-mL, Erlenmeyer flask was equipped with a magnetic stirrer and ice-bath. To a stirred, chilled solution of amine **59** (0.100 g, 0.325 mmol) in 10 mL anhydrous ether was added $HClO_4$ (60%, 0.081 g, 0.488 mmol) dropwise over a period of 5 min. The solution was stirred for additional 10 min to form a white precipitate, which was recrystallized (CH_3OH) to give hydroperchlorate **29** (0.120 g, 87.5%) as a white solid, mp 196-196.5 °C. IR (KBr) 3153 (N-H), 3015 (Ar-H), 2962, 2886 (C-H), 1084 (Cl-O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.17 [s, 2 H, H(1,5)], 3.32 [m, 6 H, SCH_2CH_2S, CH_2-benzyl], 3.66 [d, 2 H, $H(6,8)_a$], 3.97 [d, 2 H, $H(6,8)_e$], 4.11 [d, 2 H, $H(2,4)_a$], 4.30 [d, 2 H, $H(2,4)_e$], 7.50 [m, 5 H, Ar-H], 8.85 [bs, 1 H, N-H]; ^{13}C NMR (DMSO-d_6) ppm 38.42 [C(1,5)], 41.40 [SCH_2CH_2S], 55.06 [C(6,8)], 60.13 [C(9)], 68.77 [C(2,4)], 70.29 [CH_2-benzyl], 128.76, 128.88, 129.80, 131.64 [Ar-C]. Anal. Calcd for $C_{16}H_{22}ClNO_5S_2$: C, 47.12; H, 5.39; N, 3.43. Found: C, 46.99; H, 5.38; N, 3.35.

3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (30). A 125-mL, Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. To a stirred, chilled solution of amine **66** (1.4 g, 4.57 mmol) in 25 mL of anhydrous ether was added $HClO_4$ (60%, 2.48 g, 14.86 mmol) dropwise over a period of 10 min. The solution was stirred for an additional 10 min to precipitate a light yellow solid. The solid was filtered and washed with copious amounts of ether. Recrystallization (methanol) afforded the hydroperchlorate **30** (1.64 g, 71%) as a white solid, mp 218-219 °C. IR (KBr) 3315 (N-H), 3035, 3090 (Ar-H), 2875, 2890 (C-H) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.72 [bs, 2 H, H(9)], 2.14 [bs, 1 H, H(1,5)], 2.77 [d, 2 H, $H(2,4,6,8)_{ax}$], 3.10 [d, 2 H, $H(2,4,6,8)_{eq}$], 3.57 [bs, 2 H, N-H], 3.83 [s, 2 H, CH_2-benzyl], 7.43 [m, 5 H, Ar-H]; ^{13}C NMR NMR (DMSO-

d$_6$) ppm 27.50 [C(9)], 29.70 [C(1,5)], 57.03 [C(2,4,6,8)], 60.64 [CH_2-benzyl], 128.48, 128.74, 129.91, 133.74 [Ar-C]. High resolution mass spectral (HRMS) data calcd for $C_{21}H_{27}ClN_2O_4$ (M^+): 307.2174 (- ClO_4^-). Found: 307.2173. Anal Calcd for $C_{21}H_{27}ClN_2O_4$: C, 62.00; H, 6.64; N, 6.88. Found: C, 61.95; H, 6.66; N, 6.88.

3,7-Dibenzyl-9,9-(1,3-dithiolan-2-yl)-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (31) A 50-mL, Erlenmeyer flask was equipped with a magnetic stirrer and an ice-bath. To a chilled solution of the thioketal **67** (1.03 g, 2.61 mmol) in anhydrous ether (15 mL) was added $HClO_4$ (60%, 1.31 g, 7.84 mmol) dropwise over a period of 5 min. The resulting solution was stirred for an additional 10 min at 0-5 °C to precipitate a white solid. Recrystallization (methanol, 25 mL) afforded 1.06 g (69%) of the perchlorate **31** as a white solid, mp 222-223 °C. IR (KBr) 3084 (Ar-H), 2939 (C-H), 1084 (C-S) cm^{-1}; ^{1}H NMR (DMSO-*d*$_6$) δ 2.28 [s, 2 H, H(1,5)], 3.07-3.35 [m, 12 H, $H(2,4,6,8)_{a,e}$ and SCH_2CH_2S], 3.90 [s, 4 H, CH_2-benzyl], 7.42 [m, 10 H, Ar-H], 9.80 [bs, 1 H, N-H]; ^{13}C NMR (DMSO-*d*$_6$) ppm 38.76 [SCH_2CH_2S], 40.91 [C(1,5)], 56.16 [C(2,4,6,8)], 59.75 [CH_2-benzyl], 70.08 [C(9)], 128.51, 128.69, 129.98, 133.23 [Ar-C]. Anal. Calcd for $C_{23}H_{29}ClN_2O_4S_2.0.5\ H_2O$: C, 54.66; H, 5.93; N, 5.53. Found: C, 54.82; H, 5.98; N, 5.47.

7-[4-(1*H*-Imidazol-1-yl)benzoyl]-3-oxa-7-azabicyclo[3.3.1]nonane Hydroperchlorate (32). A 25-mL, Erlenmeyer flask was equipped with a magnetic stirrer and an ice-bath. To a chilled solution of amide **62** (0.160 g, 0.53 mmol) in anhydrous ether:anhydrous THF (1:1, 10 mL) was added perchloric acid (60%, 0.135 g, 0.80 mmol) dropwise over a period of 5 min. The resulting solution was stirred vigorously at the

same temperature until a white precipitate formed. The precipitate was filtered under vaccum and washed with copious amounts of anhydrous ether and recrystallized from CH_3OH:CH_3CN (3.5:1, 10 mL) to give **32** (0.109 g, 51%) as a white solid, mp 242-242.5 °C. IR (KBr) 3150 (N-H), 3038 (Ar-H), 2875(C-H), 1625 (NC=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.61 [bs, 1 H, H(1,5)], 1.80-1.89 [m, 3 H, H(1,5), H(9)], 3.07 [d, 1 H, ring protons], 3.44 [d, 1 H, ring protons], 3.61-3.68 [m, 4 H, ring proton], 3.91 [d, 1 H, ring protons], 4.72 [d, 1 H, ring protons], 7.56 [d, 2 H, C-H imidazole, Ar-H], 7.87-7.94 [m, 3 H, Ar-H, C-H imidazole], 8.32 [s, 1 H, C-H imidazole], 9.70 [s, 1 H, N-H]; ^{13}C NMR (DMSO-d_6) ppm 28.78, 28.87 [C(1,5)], 30.62 [C(9)], 45.86, 51.47 [C(6,8)], 71.18, 71.46 [C(2,4)], 120.80, 121.10, 122.26, 127.96, 134.73, 134.85, 138.52 [Ar-C, C-H imidazole], 167.86 [NC=O]. Mass spectral (LSIMS) data calcd. for $C_{17}H_{20}ClN_3O_6$ (M^+): 298 (-ClO_4^-). Found: 298. Anal. Calcd for $C_{17}H_{20}ClN_3O_6$.1 H_2O: C, 49.10; H, 5.29; N, 10.10. Found: C, 49.54; H, 4.96; N, 10.00.

7-(4-Nitrobenzoyl)-3-oxa-7-azabicyclo[3.3.1]nonane (**33**). *Method A.* A 50-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, an addition funnel, a condenser with N_2 inlet, and two glass stoppers. A solution of amine **60** (0.234 g, 1.84 mmol) in H_2CCl_2 (5 mL) and NaOH (10%, 1.58 g, 3.96 mmol) was placed in the flask. A solution of 4-nitrobenzoyl chloride (0.393 g, 2.11 mmol) in H_2CCl_2 (7 mL) was added dropwise over a period of 5 min under N_2. The mixture was allowed to stir overnight. Addition of water (20 mL) was followed by extraction with H_2CCl_2 (3 x 10 mL). Combined extracts were dried (Na_2SO_4, 2 h), filtered, and concentrated to give a faint yellow solid. Recrystallization (ethyl acetate:hexane, 2.5:1) gave **33** (0.294 g, 58%) as a white solid, mp 197-198 °C. *Method B.* A 50-mL, three-necked, round-bottomed

flask was equipped with a magnetic stirrer, an addition funnel, a condenser with a N_2 inlet, and two glass stoppers. A solution of amine **60** (0.280 g, 2.204 mmol) in anhydrous benzene (10 mL) and pyridine (0.217 g, 2.755 mmols) was added to the flask. To this was added dropwise, a solution of 4-nitrobenzoyl chloride (0.511 g, 2.755 mmol) in anhydrous benzene (10 mL) over a period of 10 min at RT. The reaction mixture was allowed to stir an additional 12 h. A light yellow solid precipitated, and was filtered, washed with benzene, recrystallized (ethyl acetate:hexane, 1:1), and chromatographed (Chromatotron) using CH_2Cl_2:CH_3OH (30:1) to give 0.334 g (55%) **33** as a white solid, mp 198-198.5 °C. IR (KBr) 3113, 3042 (Ar-H), 2940, 2846 (C-H), 1628 (NC=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.62 [s, 1 H, $H(9_a)$], 1.72 [s, 1 H, $H(9_e)$], 1.86 [s, 1 H, H(1,5)], 1.91-2.05 [m, 2 H, H(1,5), ring protons], 3.10 [ddd, 1 H, ring protons], 3.38 [ddd, 1 H, ring protons], 3.67-3.84 [m, 3 H, ring protons], 4.14 [d, 1 H, ring protons], 7.56 [m, 2 H, Ar-H], 8.28 [d, 2 H, Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 29.44, 29.59 [C(1,5)], 31.51 [C(9)], 46.62, 51.95 [C(6,8)], 71.68, 71.96 [C(2,4)], 123.87, 127.58, 143.47, 147.92 [Ar-C], 168.53 [NC=O]. Mass spectral (LSIMS) data calcd for $C_{14}H_{16}N_2O_4$ (M^+): 276. Found: 277 ($M^+ + 1$). This compound was used directly to prepare **34**.

7-(4-Aminobenzoyl)-3-oxa-7-azabicyclo[3.3.1]nonane (34). *Method A*. A 50-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, heating mantle, a condenser with a N_2 inlet, and two glass stoppers. The system was initially flushed with N_2 for a period of 10 min and palladium-on-carbon (10%, 0.040 g, 30 mg of catalyst/mmol of the amine) was added to the flask in one portion, and the system was flushed with N_2 again. Dry and deoxygenated methanol (5 mL) was slowly poured over the catalyst. To the stirred solution were added amide **33** (0.250 g, 0.90 mmol) and

anhydrous ammonium formate (0.23 g, 3.80 mmol), and the resulting mixture was boiled under N_2 for 1 h. Cooling the mixture to RT and filtering through a celite pad was followed by concentration of the resulting solution to give an off white solid. The solid was recrystallized from approximately 10 mL of ethyl acetate:hexane (3.5:1) to give **34** (0.212 g, 95.4%) as a white solid, mp 224-225.5 °C. *Method B*. A 50-mL, Erlenmeyer flask was equipped with a magnetic stirrer, and an ice-bath. A solution of amide **33** (0.200 g, 0.724 mmol) in CH_3CO_2H:H_2O (1:1, 8 mL) was placed in the flask and stirred vigorously until the solution became homogenous. To this was added $TiCl_3$ (10%, 7.82 g, 5.07 mmol) in one portion, and the resulting solution was stirred at RT for 1 h. The solution was chilled at 0-5 °C and basified with NaOH pellets (pH = 12). Extraction with $HCCl_3$ (4 x 10 mL) was followed by washing with H_2O (20 mL) amd brine (20 mL). The organic layer was dried ($MgSO_4$, 1 h), filtered, and concentrated *in vacuo* to give 0.130 g (72%) of the crude product as a white solid. Recrystallization (ethyl acetate) gave 0.110 g (61.7%) of **34** as a white solid, mp 225-226 °C. IR (KBr) 3466, 3344 (N-H), 3034 (Ar-H), 2933, 2846 (C-H), 1635 (NC=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.90 [m, 2 H, $H(9)_{a,e}$], 1.26 [bs, 2 H, H(1,5)], 1.63-2.05 [m, 4 H, ring protons], 3.12 [d, 1 H, ring protons], 3.73-4.05 [m, 4 H, ring protons and N-H], 6.65 [d, 2 H, Ar-H], 7.23 [d, 2 H, Ar-H]; ^{13}C NMR (DMSO-d_6) ppm 29.70 [C(1,5)], 31.52 [C(9)], 71.81 [C(2,4,6,8)], 114.33, 126.76, 128.62, 147.35 [Ar-C], 171.35 [NC=O]. High resolution mass spectral (HRMS) data calcd for $C_{14}H_{19}N_2O_2$ ($M^+ + 1$): 247.1446. Found: 247.1456.

7-[(4-*N*-Benzoyl)benzoyl]-3-oxa-7-azabicyclo[3.3.1]nonane (35). A 10-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser with a N_2 inlet, and two glass stoppers. A solution of the amide **34** (0.036 g, 0.146 mmol) in

anhydrous benzene (1 mL) was placed in the flask, followed by pyridine (0.023 g, 0.168 mmol), and the mixture was flushed with N_2 and stirred at RT. To this was added a solution of benzoyl chloride (0.023 g, 0.168 mmol) in anhydrous benzene (1 mL) dropwise over a period of 5 min. The resulting solution was stirred for an additional 2 h. The product was filtered, washed with benzene, and recrystallized (ethyl acetate) to give 0.040 g (78%) of **35** as a white solid, mp 93-94 °C. IR (KBr) 3358 (N-H), 3035 (Ar-H), 2805, 2885 (C-H), 1685 (NC=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.56 [bs, 1 H, H(1,5)], 1.77 [bs, 1 H, H(1,5)], 1.88 [d, 1 H, $H(9)_a$], 1.94 [d, 1 H, $H(9)_e$], 3.02 [d, 1 H, $H(6)_a$], 3.32 [d, 1 H, $H(6)_e$], 3.65-3.89 [m, 4 H, $H(4,8)_{a,e}$], 4.03 [d, 1 H, $H(2)_a$], 4.87 [d, 1 H, $H(2)_e$], 7.23-7.98 [m, 9 H, Ar-H], 9.18 [s, 1 H, N-H]; ^{13}C NMR ($DCCl_3$) ppm 29.54 [C(1,5)], 31.42 [C(9)], 46.52, 52.14 [C(6,8)], 71.56, 71.85 [C(2,4)], 120.83, 127.20, 127.47, 128.22, 128.41, 132.44, 134.58, 139.01 [Ar-C], 166.18, 170.73 [NC=O]. Mass spectral data (LSIMS) calcd for $C_{21}H_{22}N_2O_3$ (M^+): 350. Found: 351 ($M^+ + 1$). This compound was used directly to prepare **51**.

7-(4-Nitrobenzenesulfonyl)-3-oxa-7-azabicyclo[3.3.1]nonane (**36**). A 50-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser with a N_2 inlet, and two glass stoppers. A solution of amine **60** (0.320 g, 2.51 mmol) in H_2CCl_2 (5 mL) and NaOH (10%, 2.01 g, 5.03 mmol) was placed in the flask. A solution of 4-nitrobenzenesulfonyl chloride (0.690 g, 3.14 mmol) in H_2CCl_2 (10 mL) was added dropwise over a period of 10 min under N_2. The reaction mixture was allowed to stir overnight. Addition of water (20 mL) was followed by extraction with H_2CCl_2 (3 x 10 mL). Combined extracts were dried ($MgSO_4$, 2 h), filtered, and concentrated *in vacuo* to give a yellow solid. Recrystallization (ethyl acetate:hexane, 3.5:1) gave **36** (0.455 g,

58%) as a yellow solid, mp 177.5-178.5 °C. IR (KBr) 3113, (Ar-H), 2926, 2846 (C-H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.45 [d, 2 H, H(9)], 1.73 [bs, 2 H, H(1,5)], 2.70 [d, 2 H, $H(6,8)_a$], 3.58 [d, 2 H, $H(6,8)_e$], 3.72-3.79 [m, 4 H, $H(2,4)_{a,e}$], 7.94-7.99 [d, 2 H, Ar-H], 8.38-8.43 [d, 2 H, ring protons]; ^{13}C NMR ($DCCl_3$) ppm 28.11 [C(9)], 28.72 [C(1,5)], 49.44 [C(6,8)], 70.62 [C(2,4)], 124.63, 128.93, 141.86, 149.94 [Ar-C]. Mass spectral (LSIMS) data calcd for $C_{13}H_{16}N_2O_5S$ (M^+): 312. Found: 313 ($M^+ + 1$). Anal. Calcd for $C_{13}H_{16}N_2O_5S$: C, 50.00; H, 5.12; N, 8.97. Found: C, 50.04; H, 5.16; N, 8.96.

7-(4-Aminobenzenesulfonyl)-3-oxa-7-azabicyclo[3.3.1]nonane (37). To a 25-mL, Erlenmeyer flask, equipped with a magnetic stirrer, was added a solution of sulfonamide **36** (0.140 g, 0.448 mmol) in 8 mL of CH_3CO_2H:H_2O (1:1). The solution was stirred vigorously at RT until the solution became homogeneous (~1 h). To this solution, was added $TiCl_3$ (12%, 4.84 g, 3.14 mmols) in one portion, and the resulting solution was stirred at RT for 1.5 h. Upon cooling at 0-5 °C (ice-bath), a 20% NaOH solution was added slowly until a dark blue color persisted (pH = 12). Extraction ($HCCl_3$, 4 x 15 mL) was followed by washing of the organic layer with H_2O (15 mL) and brine (15 mL). The organic layer was dried ($MgSO_4$, 2 h), filtered, and concentrated *in vacuo* to give a light yellow oil. Crystallization of the oil was induced by addition of ethyl acetate followed by chilling at -10 °C overnight to give 0.100 g (79%) of **37** as a white solid, mp 183-183.5 °C. IR (KBr) 3373, 3380 (N-H), 3040, (Ar-H), 2977, 2908 (C-H), 1161 (S=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.87 [d, 1 H, H(9)], 1.95 [d, 2 H, H(1,5), H(9)], 2.18 [s, 1 H, H(1,5)], 2.38 [d, 1 H, ring protons], 2.79 [d, 2 H, ring protons], 3.18 [m, 2 H, ring protons], 3.48 [d, 1 H, ring proton], 3.94 [bs, 2 H, N-H], 5.03 [d, 1 H, ring protons], 7.64 [d, 2 H, Ar-H], 8.28 [d, 2 H, ring protons]; ^{13}C NMR ($DCCl_3$) ppm 26.35, 26.74 [C(1,5)], 31.66 [C(9)],

31.72, 32.19 [C(6,8)], 46.28, 52.07 [C(2,4)], 123.47, 123.83, 127.51, 143.41 [Ar-C]. Mass spectral (LSIMS) data calcd for $C_{13}H_{18}N_2O_3S$ (M^+): 282. Found: 283 ($M^+ + 1$). Anal. Calcd for $C_{13}H_{18}N_2O_3S$: C, 55.31; H, 6.38; N, 9.92. Found: C, 55.26; H, 6.40; N, 10.00.

7-[4-(1*H*-Imidazol-1-yl)benzoyl]-3-benzyl-3,7-diazabicyclo[3.3.1]nonane (38). A 25-mL, five-necked, jacketed flask was equipped with a magnetic stirrer, heating mantle, a condenser with a N_2 inlet, a lower take-off condenser, and three glass stoppers. A solution of amide **69** (0.300 g, 1.33 mmol) in DMSO (7 mL) was added to the flask followed by imidazole (0.09 g, 1.33 mmol), dried and powdered K_2CO_3 (0.36 g, 2.66 mmol), and 18-C-6 (60 mg) in one portion. The system was flushed with N_2 and then boiled at 110 °C for 48 h via the use of boiling toluene in the outer jacket. Cooling the solution to RT was followed by the addition of chilled H_2O (10 mL). Combined extracts (H_2CCl_2, 4 x 10 mL) of the suspension were washed with H_2O (15 mL) and brine (15 mL) and then dried ($MgSO_4$, 2 h). Filtration and concentration gave a light yellow oil. This oil was chromatographed (Chromatotron) over silica gel with hexane:ethyl acetate:methanol (5:2:0.5) to give **38** (0.215 g, 38.5%) as a faint yellow oil. IR (film) 3110 (Ar-H), 2910, 2800 (C-H), 1620 (NC=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.68 [d, 2 H, H(9)], 1.81 [bs, 2 H, H(1,5)], 2.45 [d, 2 H, ring protons], 2.57 [d, 2 H, ring protons], 2.77 [d, 2 H, ring protons], 3.09 [d, 2 H, ring protons], 3.59 [s, 2 H, CH_2-benzyl], 7.22 [s, 1 H, C-H imidazole], 7.32 [s, 1 H, C-H imidazole], 7.41-7.54 [m, 5 H, Ar-H], 7.89 [s, 1 H, imidazole]; ^{13}C NMR ($DCCl_3$) ppm 29.03 [C(1,5)], 32.26 [C(9)], 46.72 [C(2)], 52.15, 52.61, 54.38 [C(4,6,8)], 112.57, 113.21, 113.91, 114.04, 114.54, 117.06 [Ar-C], 118.07 [C-H imidazole], 119.06 [C-H imidazole], 135.44 [C-H imidazole], 168.80 [NC=O].

High resolution mass spectral (HRMS) data calcd for $C_{24}H_{26}N_4O$ (M^+): 386.4980. Found: 386.4974.

3-Benzyl-7-(4-nitrobenzoyl)-3,7-diazabicyclo[3.3.1]nonane (**39**). A 250-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser with N_2 inlet, and two glass stoppers. A solution of amine **68** (4.19 g, 19.39 mmol) in H_2CCl_2 (25 mL) and NaOH (10%, 23.29 g, 58.19 mmol) were placed in the flask and flushed with N_2. A solution of 4-nitrobenzoyl chloride (4.49 g, 24.24 mmol) in H_2CCl_2 (20 mL) was added dropwise over a period of 10 min under N_2. The mixture was allowed to stir overnight. Addition of water (30 mL) was followed by extraction with H_2CCl_2 (3 x 15 mL). Combined extracts were dried ($MgSO_4$, 4 h), filtered, and concentrated *in vacuo* to give a light yellow oil which solidified at RT after 48 h to form a light yellow-colored solid. Recrystallization (ethyl acetate:hexane, 1:2) gave **39** (6.50 g, 91.8%) as a light yellow solid, mp 103-104 °C. IR (KBr) 3390 (N-H), 3055, 3090 (Ar-H), 2850, 2810 (C-H), 1630 (NC=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.32 [m, 2 H, H(9)], 1.78 [bs, 2 H, H(1,5)], 2.31 [d, 1 H, ring protons], 2.78 [d, 1 H, ring protons], 3.15 [bs, 1 H, ring protons], 3.40 [dd, 2 H, ring protons], 3.78 [d, 2 H, ring protons], 3.96 [d, 1 H, ring protons], 6.87 [Ar-H], 7.45 [Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 27.64 [C(1,5)], 31.08 [C(9)], 48.86 [C(6,8)], 55.43 [C(2,4)], 111.09, 113.13, 114.09, 114.21, 118.55, 132.56, 145.70, 161.04 [Ar-C], 170.06 [NC=O]. Mass spectral (LSIMS) data calcd for $C_{21}H_{23}N_3O_3$ (M^+): 365. Found: 366 ($M^+ + 1$). This compound was used directly to prepare **40**.

3-Benzyl-7-(4-aminobenzoyl)-3,7-diazabicyclo[3.3.1]nonane (**40**). A solution of amide **39** (6.50 g, 18.87 mmol) in 70 mL of CH_3CO_2H:H_2O (1:1). The solution was

stirred vigorously at RT until the solution became homogeneous. To this solution was added $TiCl_3$ (12%, 170.02 g, 132.26 mmols) in one portion, and the resulting solution was stirred at RT for 0.5 h. Upon cooling at 0-5 °C (ice-bath), a 20% NaOH solution was added slowly until a dark blue color persisted (pH = 12). Extraction ($HCCl_3$, 4 x 80 mL) was followed by washing of the organic layer with H_2O (70 mL) and brine (70 mL). The organic layer was dried ($MgSO_4$, 2 h), filtered, and concentrated *in vacuo* to give a white solid. Recrystallization (ethyl acetate) gave **40** (3.08 g, 48.7%) as a white solid, mp 205-206 °C. IR (KBr) 3390 (N-H), 3055, 3090 (Ar-H), 2850, 2810 (C-H), 1630 (NC=O) cm^{-1} ; ^1H NMR ($DCCl_3$) δ 1.72 [m, 2 H, H(9)], 1.95 [bs, 2 H, H(1,5)], 2.20 [bs, 1 H, ring protons], 2.85 [bs, 1 H, ring protons], 3.07 [bs, 1 H, ring protons], 3.36 [m, 2 H, ring protons], 3.86 [m, 4 H, ring protons and N-H], 4.71 [d, 1 H, ring protons], 6.57 [Ar-H], 7.30 [Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 28.97 [C(1,5)], 32.16 [C(9)], 46.59 [C(6,8)], 54.65 [C(2,4)], 112.56, 113.13, 114.09, 115.78, 128.45, 133.64, 134.90, 160.04 [Ar-C], 168.06 [NC=O]. Mass spectral data (LSIMS) calcd for $C_{21}H_{25}N_3O$ (M^+): 335. Found: 336 ($M^+ + 1$). This compound was used directly to prepare **41**.

3-Benzyl-7-[4-(dimethylsulfonyl)amino]benzoyl-3,7-diazabicyclo[3.3.1]nonane (41). A 25-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser with a N_2 inlet, an addition funnel, and one glass stopper. A solution of the amide **40** (0.150 g, 0.44 mmol) in H_2CCl_2 (3 mL) was placed in the flask, followed by triethylamine (0.090 g, 0.89 mmol), and the system was flushed with N_2. To this solution was added a solution of methanesulfonyl chloride (0.107 g, 0.94 mmol) in H_2CCl_2 (3 mL) dropwise via an addition funnel at RT over a period of 5 min. The reaction mixture was stirred for an additional 12 h. Addition of H_2O (3 mL) was

followed by extraction with H_2CCl_2 (3 x 3 mL). Combined extracts were dried ($MgSO_4$, 1 h), filtered, and concentrated *in vacuo* to give 0.120 g (56%) of **41** as a gummy solid. The proton and carbon spectra appeared complex, and the signals could not be interpreted well. The IR spectrum did not show any bands in the region for a primary amine and thus suggested the formation of the desired product. Consequently, **41** was directly used without further purification to prepare **70**.

3-Benzyl-7-(4-nitrobenzenesulfonyl)-3,7-diazabicyclo[3.3.1]nonane (**42**). In a standard setup were placed amine **68** (1.137 g, 5.26 mmol) and NaOH (10%, 6.32 g, 15.79 mmol) in H_2CCl_2 (15 mL). A solution of 4-nitrobenzenesulfonyl chloride (1.34 g, 6.05 mmol) in H_2CCl_2 (15 mL) was added dropwise over a period of 10 min under N_2. The mixture was then allowed to stir overnight. Addition of water (30 mL) was followed by extraction with H_2CCl_2 (3 x 15 mL). Combined extracts were dried ($MgSO_4$, 2 h), filtered, and concentrated to give a yellow solid. Recrystallization (ethyl acetate:hexane, 1:1) gave **42** (1.35 g, 87%) as a yellow solid, mp 151.5-152.5 °C. IR (KBr) 3090, 3005 (Ar-H), 2920, 2880, 2770 (C-H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.25 [bs, 2 H, H(1,5)], 1.57 [m, 2 H, H(9)], 1.96 [d, 2 H, ring protons], 2.29 [d, 2 H, ring protons], 2.92 [m, 2 H, ring protons], 3.42 [s, 2 H, CH_2-benzyl], 3.71 [d, 2 H, ring protons], 7.23 [m, 5 H, Ar-H], 7.95 [d, 2 H, Ar-H], 8.35 [d, 2 H, ring protons]; ^{13}C NMR ($DCCl_3$) ppm 28.46 [C(9)], 29.86 [C(1,5)], 49.45, 57.77, 63.05, 64.96 [C(2,4,6,8)], 124.113, 126.86, 128.14, 128.39, 128.75, 138.60, 142.94, 149.78 [Ar-C]. Mass spectral (LSIMS) data calcd for $C_{20}H_{23}N_3O_4S$ (M^+): 401. Found: 402 ($M^+ + 1$).

3-Benzyl-7-(4-aminobenzenesulfonyl)-3,7-diazabicyclo[3.3.1]nonane (43). To a 50-mL, Erlenmeyer flask, equipped with a magnetic stirrer, was added a solution of sulfonamide **42** (0.395 g, 9.85 mmol) in 8 mL of CH_3CO_2H:H_2O (1:1). The solution was stirred vigorously at RT until the solution became homogeneous (~30 min). To this solution was added $TiCl_3$ (12%, 9.65 g, 8.01 mmols) in one portion, and the resulting solution was stirred at RT for 0.5 h. Upon cooling at 0-5 °C (ice-bath), a 20% NaOH solution was added slowly until a dark blue color persisted (pH = 12). Extraction ($HCCl_3$, 4 x 10 mL) was followed by washing of the organic layer with H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$, 2 h), filtered, and concentrated *in vacuo* to give a white solid. Recrystallization (ethyl acetate:hexane, 2:1) gave **43** (0.195 g, 53%) as a white solid, mp 170-171 °C. IR (KBr) 3474, 3380 (N-H), 3070 (Ar-H), 2911, 2767 (C-H), 1040 (S=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.37 [d, 2 H, H(9)], 1.91 [bs, 2 H, H(1,5)], 2.18 [d, 2 H, $H(2,4)_{ax}$], 2.71 [m, 4 H, $H(2,4)_{eq}$ and $H(6,8)_{ax}$], 3.35 [m, 4 H, $H(6,8)_{eq}$ and CH_2-benzyl], 6.68 [d, 2 H, Ar-H], 7.28 [m, 7 H, Ar-H]; ^{13}C NMR (DMSO-d_6) 28.01 [C(1,5)], 29.95 [C(9)], 49.50 [C(6,8)], 58.01 [C(2,4)], 62.25 [CH_2-benzyl], 112.22, 121.09, 126.13, 127.32, 128.91, 130.12, 139.32, 154.15 [Ar-C]. Mass spectral (LSIMS) data calcd for $C_{20}H_{25}N_3O_2S$ (M^+): 371. Found: 372 ($M^+ + 1$). Anal. Calcd for $C_{20}H_{25}N_3O_2S$: C, 64.69; H, 6.73; N, 11.32. Found: C, 64.46; H, 6.75; N, 11.40.

Attempted Preparation of 7-[4-(Amino)benzyl]-3-oxa-7-azabicyclo[3.3.1]nonane (49). A 25-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, heating mantle, a condenser with a N_2 inlet, a rubber septum stopper, and one glass stopper. A heterogenous mixture of the amide **34** (0.050 g, 0.203 mmol) in

anhydrous THF (5 mL) was introduced in the flask and stirred at RT. To this solution was added borane dimethyl sulfide (10 *M*, 0.308 g, 4.06 mmol) dropwise via a syringe. The reaction mixture was boiled for 4 h. The flask was allowed to cool to RT, and 6 *N* HCl (0.203 mmol) was added dropwise to decompose the borane-amine complex. *Caution*: 6 *N* HCl should be added very slowly and cautiously as the reaction is highly exothermic and liberates H_2 gas. The reaction mixture was stirred at RT for 10 min and 50% (excess, pH = 12) was added dropwise to neutralize the acid. The THF layer was separated, dried (Na_2SO_4, 2 h), and concentrated *in vacuo* to give 0.020 g of the product as a light yellow-colored oil. GCMS, IR, and NMR analyses indicated the presence of starting material only. This procedure was also performed using 1,4-dioxane as the solvent, but only starting material was recovered. An alternative methodology using LAH was attempted for this conversion only to recover the starting material.

7-[4-(Amino)benzyl]-3-isopropyl-3,7-diazabicyclo[3.3.1]nonane (52). To a 25-mL, Erlenmeyer flask, equipped with a magnetic stirrer, was added a solution of amine **85** (0.270 g, 0.891 mmol) in 5 mL of CH_3CO_2H:H_2O (1:1). To this solution was added was added $TiCl_3$ (12%, 4.84 g, 3.14 mmol) in one portion, and the resulting solution was stirred at RT for 1.5 h. Upon cooling at 0-5 °C (ice-bath), a 20% NaOH solution was added slowly until a dark blue color persisted (pH = 12). Extraction ($HCCl_3$, 4 x 10 mL) was followed by washing of the organic layer with H_2O (15 mL) and brine (15 mL). The organic layer was dried ($MgSO_4$, 1 h), filtered, and concentrated *in vacuo* to give 0.243 g (50%) of **52** as a light yellow oil. IR (film) 3366 (N-H), 3033 (Ar-H), 2969, 2926 (C-H) cm^{-1}; ^1H NMR (D_3COD) δ 1.10-1.18 [m, 6 H, CH_3], 1.56 [d, 1 H, $H(9)_a$], 1.63 [d, 1 H, $H(9)_{eq}$], 1.98 [bs, 2 H, H(1,5)], 2.41 [dd, 2 H, $H(2,4)_{ax}$], 2.72-2.89 [m, 9 H, $H(2,4)_{eq}$,

$H(6,8)_{ax,eq}$, CH-isopropyl, NH_2], 3.37 [CH_2-benzyl], 6.59-6.70 [m, 4 H, Ar-H]; ^{13}C NMR (D_3COD) ppm 15.47 [C(1,5)], 18.18 [C(9)], 30.05, 30.32, 53.94, 56.33, 58.84, 63.85, 66.84 [CH_3, CH-isopropyl, C(2,4,6,8), CH_2-benzyl], 115.38, 117.33, 120.13, 129.90, 139.98, 148.68 [Ar-C]. Mass spectral data (LSIMS) calcd for $C_{17}H_{27}N_3$ (M^+): 273. Found: 274 ($M^+ + 1$). This was used directly to prepare **53**.

7-[4-(*N*-Benzylamino)benzyl]-3-isopropyl-3,7-diazabicyclo[3.3.1]nonane (53). A 25-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser with a N_2 inlet, and two glass stoppers. A solution of amine **52** (0.060 g, 0.216 mmol) in 1,2-dichloroethane (4 mL) was added to the flask. To this was added benzaldehyde (0.022 g, 0.216 mmol) and sodium triacetoxyborohydride (0.065 g, 0.307 mmol) in one portion. The reaction mixture was stirred for 4 h and was then quenched by adding aqueous saturated sodium bicarbonate. The product was extracted (H_2CCl_2, 3 x 5 mL), dried ($MgSO_4$, 1 h), and concentrated *in vacuo* to give 0.064 g (83%) of **53** as a light yellow oil. IR (film) 3397 (N-H), 3038 (Ar-H), 2970, 2924, 2793 (C-H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.03 [d, 6 H, CH_3], 1.49 [d, 2 H, $H(9)_{ax,eq}$], 1.90 [bs, 2 H, H(1,5)], 2.34-2.74 [m, $H(2,40_{ax,eq}$, $H(6,8)_{ax}$, CH-isopropyl], 3.36 [CH_2-benzyl], 3.71 [CH_2-benzyl], 6.48-6.51 [m, 2 H, Ar-H], 7.06-7.47 [m, 7 H, Ar-H], 8.47 [s, 1 H, N-H]; ^{13}C NMR ($DCCl_3$) ppm 18.19 [C(9)], 29.08 [CH_3], 29.28 [C(1,5)], 48.42, 52.55, 54.17, 57.73, 62.94 [C(2,4,6,8), CH-isopropyl, CH_2-benzyl], 111.06, 118.20, 127.54, 128.53, 128.66, 128.69, 128.80, 148.11 [Ar-C]. High resolution mass spectral (HRMS) data calcd for $C_{24}H_{33}N_3$ (M^+): 363.5472. Found: 363.5465.

7-[4-(*N*-Ethylamino)benzyl]-3-isopropyl-3,7-diazabicyclo[3.3.1]nonane (54). A 25-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, heating

mantle, a condenser with a N_2 inlet, a rubber septum stopper, and one glass stopper. A heterogeneous solution of the amide **86** (0.855 g, 2.59 mmol) in anhydrous toluene (8 mL) was added to the flask, and the solution was chilled to 0-5 °C (ice-bath). To this was added borane dimethyl sulfide (10 *M*, 0.98 g, 13.00 mmol) dropwise via a syringe. The reaction mixture was stirred at 0-5 °C for 15 min and then boiled for 8 h. The flask was allowed to cool to RT and Na_2CO_3 (10%, 5 mL) was added, and the solution was stirred at RT for 30 min. The toluene layer was separated, dried ($MgSO_4$, 2 h), and concentrated *in vacuo* to give 0.070 g (9%) of **54** as a light yellow oil. IR (film) 3388 (N-H), 3035 (Ar-H), 2922, 2871 (C-H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.21-1.29 [m, 6 H, CH_3], 1.71-1.85 [m, 2 H, $H(9)_{ax,eq}$], 2.11 [bs, 2 H, H(1,5)], 2.56 [dd, 2 H, ring protons], 2.82-2.96 [m, 7 H, ring protons, and CH-isopropyl], 3.11 [m, 4 H, CH_2-benzyl, and $NHCH_2CH_3$], 3.40 [bs, 1 H, N-H], 6.51-6.54 [m, 2 H, Ar-H], 6.96 [d, 2 H, Ar-H]. ^{13}C NMR ($DCCl_3$) ppm 14.83 [CH_3], 15.99 [CH_3], 20.27 [C(9)], 28.15 [C(1,5)], 32.18 [CH-isopropyl], 56.42 [C(2,4,6,8)], 60.30 [CH_2-benzyl], 61.28 [$NHCH_2CH_3$]. This compound was extremely sensitive to moisture and air oxidation. The compound changed color from light yellow oil to green oil within 12 h of storage under N_2 at -10 °C. The ^1H, ^{13}C NMR, and mass spectral data indicated that the product had decomposed to complex and unidentifyable products.

7-[4-(*N*-Ethylamino)phenylacetyl]-3-isopropyl-3,7-diazabicyclo[3.3.1]nonane (55). A 25-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, heating mantle, a condenser with a N_2 inlet, a rubber septum stopper, and one glass stopper. A heterogeneous solution of the amide **87** (0.545 g, 1.58 mmol) in anhydrous toluene (5 mL) was added to the flask, and the solution was chilled to 0-5 °C (ice-bath).

To this was added borane dimethyl sulfide (10 *M*, 0.72 g, 9.53 mmol) dropwise via a syringe. The reaction mixture was stirred at 0-5 °C for 15 min and then boiled for 12 h. The flask was allowed to cool to RT and Na_2CO_3 (10%, 4 mL) was added, and the solution was stirred at RT for 30 min. The toluene layer was separated, dried ($MgSO_4$, 1 h), and concentrated *in vacuo* to give 0.040 g (8%) of **55** as a light yellow oil. IR (film) 3395 (N-H), 2966, 2875 (C-H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.02-1.25 [m, 9 H, CH_3], 1.67-1.89 [m, 2 H, $H(9)_{a,e}$], 2.07 [bs, 2 H, H(1,5)], 2.46 [d, 2 H, ring protons], 2.67-3.24 [m, 14 H, ring protons, $NHCH_2CH_3$, NCH_2CH_2-Ar, N-H, and CH-isopropyl], 6.51 [d, 2 H, Ar-H], 6.91-6.98 [m, 2 H, Ar-H]. ^{13}C NMR ($DCCl_3$) ppm 14.73 [CH_3], 16.05, 16.23 [CH_3], 27.17, 27.60 [C(1,5)], 28.22 [C(9)], 32.26 [CH-isopropyl], 56.52, 60.00, 60.39, 61.37, 62.88, 64.36 [C(2,4,6,8), CH_2-CH_2, $NHCH_2CH_3$], 113.20, 128.47, 129.56, 129.76 [Ar-C].

7-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (**57**) A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, heating mantle, an addition funnel, and two glass stoppers. A mixture of benzylamine (3.21 g, 29.96 mmol), HCl (37%, 1.48 g, 14.98 mmol), glacial acetic acid (2.7 g, 44.94 mmol), and paraformaldehyde (7.2 g, 239.68 mmol) in deoxygenated methanol (25 mL) was stirred at reflux for 15 min under N_2. A solution of tetrahydro-4*H*-pyranone (**56**, 3.0 g, 29.96 mmol) in glacial acetic acid (2.7 g, 44.94 mmol) in 25 mL methanol was added dropwise over a period of 0.5 h, which was followed by a period of boiling for an additional 12 h. After cooling to RT, the solution was concentrated *in vacuo* to give an orange color oil which was redissolved in H_2O (75 mL), and the extracts (ether, 2 x 50 mL) thereof were discarded. The aqueous layer was chilled (5 °C) in an ice bath and made basic (pH = 12) with NaOH pellets. Extraction (ether, 3 x 50 mL) gave a solution which was dried

(Na_2SO_4, 4 h), filtered, and concentrated to give a viscous, reddish color oil. Vaccum distillation of this oil (130-140 °C/0.01 mm Hg) gave 3.55 g (51.4%) of **57** as a clear oil which solidified after 72 h at -10 °C, mp 37-38 °C IR (KBr) 3065 (Ar-H), 2870, 2795 (C-H), 1735 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 2.53 [bs, 2 H, H(1,5)], 2.93 [dd, 2 H, $H(6,8)_a$], 3.12 [dd, 2 H, $H(6,8)_e$], 3.56 [s, 2 H, CH_2-benzyl], 3.89 [dd, 2 H, $H(2,4)_a$], 4.09 [d, 2 H, $H(2,4)_e$], 7.33 [Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 49.42 [C(1,5)], 57.57 [C(6,8)], 61.15 [CH_2-benzyl], 73.48 [C(2,4)], 127.00, 128.14, 128.47, 137.84 [Ar-C], 211.86 [C=O]. GC-MS data calcd for $C_{14}H_{17}NO_2$ (M^+): 231. Found: 231. This compound was used directly to prepare **58**

7-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonane (**58**). A 50-mL, five-necked, jacketed flask was equipped with a magnetic stirrer, heating mantle, a lower take off condenser, a condenser with a N_2 inlet. To a solution of ketone **57** (3.55 g, 15.36 mmol) in triethylene glycol (20 mL) was added KOH pellets (85%, 10.09 g, 153.6 mmol), and hydrazine (95%, 2.58 g, 76.8 mmol). The stirred mixture was boiled at 140-145 °C for 4 h under N_2 using xylenes in the outer jacket. Cooling the solution to RT (1 h) was followed by the addition of chilled water (20 mL). Extraction (ether, 3 x 30 mL) was followed by washing the combined extracts with 10% NaOH (25 mL) and saturated NaCl (25 mL) and then drying (Na_2SO_4, 1 h). Filtration and concentration of the solution gave a light yellow oil **57** (3.16 g, 95%). IR (film) 3060, 3030 (Ar-H), 2918, 2819 (C-H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.54 [m, 1 H, $H(9_a)$], 1.70 [bs, 2 H, H(1,5)], 1.77 [m, 1 H, $H(9_e)$], 2.31 [dd, 2 H, $H(6,8)_a$], 2.94 [d, 2 H, $H(6,8)_e$], 3.50 [s, 2 H, CH_2-benzyl], 3.77 [m, 2 H, $H(2,4)_a$], 3.90 [d, 2 H, $H(2,4)_e$], 7.36 [m, 5 H, Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 30.30

[C(9)], 30.35 [C(1,5)], 57.73 [C(6,8)], 61.78 [C(2,4)], 63.31 [CH_2-benzyl], 126.57, 127.97, 128.78, 138.59 [Ar-C]. GC-MS data calcd for $C_{14}H_{19}NO$ (M^+): 217. Found: 217. This compound was used directly to prepare **28**.

7-Benzyl-3-oxa-9,9-(1,3-dithiolan-2-yl)-7-azabicyclo[3.3.1]nonane (59). A 50-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser with a N_2 inlet, one rubber septum stopper, and one glass stopper. A solution of ketone **57** (1.40 g, 6.06 mmol) in methylene chloride (15 mL) was placed in the flask, and the system was flushed with N_2. Then, 1,2-ethanedithiol (0.71 g, 7.57 mmol) was added, followed by 2.22 mL of boron trifluoride etherate in one portion. The solution was stirred overnight at room temperature, and then 20 mL of 5% sodium hydroxide was added. The organic layer was separated, washed with water and with brine, and then dried ($MgSO_4$, 1 h). Concentration *in vacuo* gave a white solid. The solid was recrystallized (hexane:ethyl acetate, 3:1) to give 1.52 g (82%) of **59** as a white solid, mp 79.5-80.5 °C. IR (KBr) 3039 (Ar-H), 2872, 2793 (C-H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.89 [bs, 2 H, H(1,5)], 2.87 [d, 2 H, $H(6,8)_{ax}$], 2.95 [d, 2 H, $H(6,8)_{eq}$], 3.22 [m, 4 H, S-CH_2], 3.53 [s, 2 H, CH_2-benzyl], 3.98 [d, 2 H, $H(2,4)_{ax}$], 4.15 [d, 2 H, ring protons], 7.30 [Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 38.12, 38.40 [S-CH_2], 44.03 [C(9)], 56.63 [C(1,5)], 62.09 [C(6,8)], 70.52 [CH_2-benzyl], 71.79 [C(2,4)], 126.76, 128.14, 128.65, 138.58 [Ar-C]. Anal. Calcd for $C_{16}H_{21}NOS_2$: C, 62.54; H, 6.84; N, 4.56. Found: C, 62.35; H, 6.91; N, 4.49.

3-Oxa-7-azabicyclo[3.3.1]nonane (60). A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a condenser with a N_2 inlet,

and two glass stoppers. The system was initially flushed with a N_2 for a period of 15 min. Palladium-on-carbon (10%, 0.436 g, 30 mg of catalyst/mmol of the amine) was added in one portion, and the system was again flushed with N_2. Dry and deoxygenated methanol (30 mL) was slowly poured over the catalyst. To the stirred solution were added amine **58** (3.16 g, 14.58 mmol) and anhydrous ammonium formate (3.67 g, 58.24 mmol) in one portion, and the resulting mixture was boiled under N_2 for 1 h. Cooling the mixture to RT and filtering through a celite pad was followed by concentration of the resulting solution to give a light yellow oil. The oil was then dissolved in water (30 mL) and made basic (pH = 12) using a 10% NaOH solution. Combined extracts ($HCCl_3$, 4 x 30 mL) of the aqueous solution were dried (Na_2SO_4, 1 h), filtered, and concentrated to give a faint yellow oil **60** (1.38 g, 75%). IR (film) 3431 (N-H), 2933, 2868 (C-H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.48 [bs, 2 H, H(1,5)], 1.94 [m, 2 H, H(9)], 2.88 [bs, 1 H, N-H], 3.05 [dd, 2 H, $H(6,8)_a$], 3.16 [d, 2 H, $H(6,8)_e$], 3.87 [dd, 2 H, $H(2,4)_a$], 4.03 [d, 2 H, $H(2,4)_e$]; ^{13}C NMR ($DCCl_3$) ppm 29.74 [C(9)], 31.65 [C(1,5)], 51.33 [C(6,8)], 72.88 [C(2,4)]. Mass spectral (LSIMS) data calcd for $C_7H_{13}NO$ (M^+): 127. Found: 128 ($M^+ + 1$). The oil was used directly to prepare **61**.

7-(4-Fluorobenzoyl)-3-oxa-7-azabicyclo[3.3.1]nonane (61). A 50-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser with a N_2 inlet, and two glass stoppers. A solution of amine **60** (0.300 g, 2.36 mmol) in H_2CCl_2 (7 mL) and NaOH (10%, 2.36 g, 5.90 mmol) were placed in the flask. A solution of 4-fluorobenzoyl chloride (0.56 g, 3.54 mmol) in H_2CCl_2 (8 mL) was added dropwise over a period of 5 min under N_2. The mixture was allowed to stir an additional 6 h. Addition

of water (15 mL) was followed by extraction with H_2CCl_2 (3 x 10 mL). Combined extracts were dried (Na_2SO_4, 2 h), filtered, and concentrated *in vacuo* to give a white solid. Recrystallization (ethyl acetate:hexane, 2:1) gave **61** (0.456 g, 77.5%) as a white solid, mp 115-115.5 °C. IR (KBr) 3069 (Ar-H), 2954, 2916, 2832 (C-H) 1618 (NC=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.52 [bs, 2 H, H(1,5)], 1.90 [m, 4 H, H(9) and ring protons], 3.03 [d, 1 H, ring protons], 3.26 [d, 1 H, ring protons], 3.75 [m, 2 H, ring protons], 4.07 [d, 1 H, ring protons], 4.86 [d, 1 H, ring protons], 7.25 [m, 2 H, Ar-H], 8.14 [d, 2 H, Ar-H]; ^{13}C NMR NMR ($DCCl_3$) ppm 29.78, 29.92 [C(1,5)], 31.77 [C(9)], 46.89, 52.38 [C(6,8)], 71.95, 72.21 [C(2,4)], 115.61, 115.83, 116.40, 116.62, 129.08, 133.49 [Ar-C], 170.28 [NC=O]. Mass spectral (LSIMS) data calcd for $C_{14}H_{16}FNO_2$ (M^+): 249. Found: 250 ($M^+ + 1$). Anal. Calcd for $C_{14}H_{16}FNO_2$: C, 67.46; H, 6.42; N, 5.62. Found: C, 67.31; H, 6.45; N, 5.67.

7-[4-(1*H*-Imidazol-1-yl)benzoyl]-3-oxa-7-azabicyclo[3.3.1]nonane (62). A 20-mL, five-necked, jacketed flask, was equipped with a magnetic stirrer, heating mantle, a lower take off condenser with a N_2 inlet, a condenser, and three glass stoppers. To a solution of the amide **61** (0.450 g, 1.80 mmol) in DMSO (8 mL) was added imidazole (0.184 g, 2.70 mmol), K_2CO_3 (anhydrous, 0.561 g, 4.06 mmol), and 18-C-6 (100 mg). The stirred mixture was heated at 110 °C for 48 h under N_2 via the use of boiling toluene in the outer jacket. Cooling the solution to RT was followed by the addition of chilled H_2O (10 mL). Combined extracts (H_2CCl_2, 4 x 8 mL) of the suspension were washed with H_2O (10 mL) and brine (10 mL) and dried ($MgSO_4$, 2 h). Filtration and concentration *in vacuo* gave the product as a light yellow color oil. The oil was chromatographed (Chromatotron)

over silica gel using the solvent system hexane:ethyl acetate:methanol (3:3:1) to give **62** (0.200 g, 38%) as a clear, viscous oil. IR (film) 3108 (Ar-H), 2965, 2901, 2796 (C-H), 1628 (NC=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.60 [bs, 1 H, H(9)], 1.82 [bs, 1 H, H(9)], 1.90 [dd, 1 H, ring protons], 1.97 [dd, 1 H, ring protons], 2.25 [bs, 2 H, H(1,5)], 3.07 [d, 1 H, ring protons], 3.42 [d, 1 H, ring protons], 3.88 [m, 2 H, ring protons], 4.13 [d, 1 H, ring protons], 4.96 [d, 1 H, ring protons], 7.18 [s, 1 H, C-H imidazole], 7.25 [d, 2 H, Ar-H], 7.39 [d, 1 H, C-H imidazole], 7.41 [d, 2 H, Ar-H], 7.85 [d, 1 H, C-H imidazole]; ^{13}C NMR ($DCCl_3$) ppm 28.75 [C(9)], 30.03, 30.76 [C(9)], 48.76, 52.85, 53.44, 55.08 [C(2,4,6,8)], 114.32 [Ar-C], 120.06 [C-H imidazole], 121.76 [C-H imidazole], 130.97 [Ar-C], 139.56 [C-H imidazole], 166.23 [NC=O]. GC-MS (EI) data calcd for $C_{17}H_{19}N_3O_2$ (M^+): 297. Found: 297. This compound was used directly to prepare **32**.

7-(4-Fluorobenzenesulfonyl)-3-oxa-7-azabicyclo[3.3.1]nonane (63). A three-necked, 50-mL, round-bottomed flask was equipped with a magnetic stirrer, an addition funnel, a condenser with a N_2 inlet and two glass stoppers. A solution of the secondary amine **60** (0.237 g, 1.866 mmol) in H_2CCl_2 (7 mL) was added to the flask, followed by NaOH (10%, 1.86 g, 4.66 mmol) in one portion, and the resulting mixture was stirred at RT and flushed with N_2. To this was added dropwise, a solution of 4-fluorobenzenesulfonyl chloride (0.417 g, 2.14 mmol) in H_2CCl_2 (5 mL) via an addition funnel over a period of 5 min. The reaction mixture was stirred for an additional 6 h at RT. Addition of H_2O (10 mL) was followed by extraction with H_2CCl_2 (3 x 5 mL). The organic layer was washed with brine (10 mL), dried ($MgSO_4$, 1 h), and concentrated *in vacuo* to give 0.240 g (45%) **63** as a white solid, mp 137-139 °C. IR (KBr) 3108, 3063 (Ar-H), 2928, 2845 (C-H), 1167 (Ar-F), 1032, 1070 (S-O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.50 [d, 1 H, $H(9)_{ax}$], 1.73 [bs, 2

H, H(1,5)], 1.79 [d, 1 H, $H(9)_{eq}$], 2.75 [d, 2 H, $H(6,8)_{ax}$], 3.66 [d, 2 H, $H(6,8)_{eq}$], 3.72 [d, 2 H, $H(2,4)_{ax}$], 3.83 [d, 2 H, $H(2,4)_{eq}$], 7.15 [d, 2 H, Ar-H], 7.74 [q, 2 H, Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 28.61 [C(9)], 29.20 [C(1,5)], 49.37 [C(6,8)], 70.87 [C(2,4)], 115.76, 130.01, 132.50, 163.50 [Ar-C]. Mass spectral data (LSIMS) calcd for $C_{13}H_{16}FNO_3S$ (M^+): 285. Found: 286 ($M^+ + 1$).

3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**65**). A 500-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, heating mantle, a condenser with a N_2 inlet, an addition funnel, and two glass stoppers. A mixture of benzylamine (10.71 g, 100.0 mmol), HCl (37%, 4.93 g, 50.0 mmol), glacial acetic acid (6.0 g, 100 mmol), and paraformaldehyde (6.31 g, 210.0 mmol) in deoxygenated methanol (100 mL) was stirred at reflux for 15 min under N_2. A solution of *N*-benzyl-4-piperidinone (**64**, (18.93 g, 100.0 mmol) in methanol (100 mL) and glacial acetic acid (6.01 g, 100.0 mmol) was added dropwise over a period of 1.5 h, which was followed by a period of boiling for an additional 24 h. After the initial heating (10 h), more paraformaldehyde (6.31 g, 210.0 mmol) was added in one portion to the reaction mixture after which boiling was continued for an additional 14 h. After cooling to RT, concentration of the solution *in vacuo* gave an orange oil which was redissolved in H_2O (150 mL), and the extracts (ether, 2 x 100 mL) thereof were discarded. The aqueous layer was chilled (5 °C) in an ice bath and made basic (pH = 11) with NaOH pellets. Extraction (ether, 3 x 75 mL) gave a solution which was dried (Na_2SO_4, 4 h), filtered, and concentrated in *vacuo* to give a viscous reddish oil. This oil was digested with hexanes:pentane (2:1, 2 x 200 mL, 20 min), and the supernatent extracts were concentrated *in vacuo* to give a light yellow oil. Crystallization of the oil was induced by dissolving the oil in hot pentane (600 mL) and

then chilling (-10 °C) the solution gave 14.66 g (45.8%) of a white, crystalline solid **65**, mp 83-84 °C (Lit[51] mp 70-71 °C). IR (KBr) 3035 (Ar-H), 2955, 2980 (C-H), 1720 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 2.54 [bs, 2 H, H(1,5)], 2.80 [dd, 4 H, $H(2,4,6,8)_{ax}$], 3.01 [dd, 4 H, $H(2,4,6,8)_{eq}$], 3.54 [s, 4 H, CH_2-benzyl], 7.30 [m, 10 H, Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 46.63 [C(1,5)], 58.00 [CH_2-benzyl], 61.11 [C(2,4,6,8)], 127.15, 128.28, 128.79, 138.27 [Ar-C], 215.00 [C=O]. GC-MS (EI) data calcd for $C_{21}H_{24}N_2O$ (M^+): 320. Found: 320. This compound was used directly to prepare **66**.

3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]nonane (**66**). A 100-mL, jacketed flask was equipped with a magnetic stirrer, a heating mantle, a condenser, a lower take-off condenser with a N_2 inlet, and three glass stoppers. To a solution of ketone **65** (2.43 g, 7.59 mmol) in triethylene glycol (30 mL) was added KOH pellets (85%, 4.26 g, 75.99 mmol), and hydrazine (98%, 1.21 g, 37.96 mmol), and then the apparatus was flushed with N_2. The mixture was heated at 140-150 °C for 4 h under N_2 via the use of boiling tetralin (bp 207 °C) in the outer jacket. Cooling the solution to RT was followed by the addition of chilled water (30 mL). Combined extracts (ether, 3 x 40 mL) of the suspension were washed with NaOH (10%, 40 mL), brine (50mL), dried ($MgSO_4$, 2 h), filtered, and concentrated *in vacuo* to give 2.17 g (93.78%) of **66** as a faint yellow-colored oil. IR (film) 3075, 3032 (Ar-H), 2918, 2797, 2762 (C-H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.55 [bs, 2 H, H(9)], 1.89 [bs, 2 H, H(1,5)], 2.35 [dd, 4 H, $H(2,4,6,8)_{ax}$], 2.83 [d, 4 H, $H(2,4,6,8)_{eq}$], 3.50 [s, 4 H, CH_2-benzyl], 7.42 [m, 10 H, Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 29.59 [C(9)], 30.85 [C(1,5)], 57.75 [CH_2-benzyl], 63.17 [C(2,4,6,8)], 126.73, 128.14, 129.06, 139.28 [Ar-C]. GC-MS (EI) data calcd for $C_{21}H_{26}N_2$ (M^+): 306. Found: 306. This oil was used directly to prepare **30**.

3,7-Dibenzyl-9,9-(1,3-dithiolan-2-yl)-3,7-diazabicyclo[3.3.1]nonane (67). *Method A.* A 100-mL, single necked round-bottomed flask was equipped with a magnetic stirrer, a Dean-Stark trap, a condenser with a N_2 inlet, and a heating mantle. A solution of ketone **65** (2.50 g, 7.81 mmol) in anhydrous benzene (50 mL) was placed in the flask. To this was added 1,2-ethanedithiol (7.35 g, 78.12 mmol) and PTSA (3.36 g, 19.5 mmol) in one portion, and the resulting solution was boiled for 48 h. The solvent (benzene) was then removed through the Dean-Stark trap, and the resulting oil was dissolved in water (20 mL) and transferred to a separatory funnel. The aqueous layer was extracted (ether, 3 x 20 mL), the extracts being discarded. Basification (pH~12) was achieved using 10% NaOH followed by extraction (ether, 4 x 15 mL) and washing with NaOH (1 *N*, 20 mL) and brine (25 mL). After drying ($MgSO_4$, 1 h) the solution, evaporation *in vacuo* afforded a light yellow oil, which was digested in hexanes (30 mL) for 15 min. The supernatent extracts were collected and chilled at -10 °C overnight to give 1.45 g (47%) of **67** as a white solid, mp 101-102 °C. *Method B.* A 50-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser with a N_2 inlet, a rubber septum stopper, and one glass stopper. A solution of ketone **65** (1.50 g, 4.68 mmol) in dry CH_2Cl_2 (15 mL) was placed in the flask. To this was added 1,2-ethanedithiol (0.55 g, 5.85 mmol) in one portion, followed by boron trifluoride etherate (1.98 g, 14.06 mmol) dropwise via a syringe at RT. The reaction mixture was stirred for an additional 12 h, and NaOH (5%, 10 mL) was added. The organic layer was separated and washed with H_2O (10 mL), dried ($MgSO_4$, 1 h), and concentrated *in vacuo* to give a white solid. Recrystallization (hexanes) gave 1.45 g (79%) of **67** as a white solid, mp 98-98.5 °C. IR (KBr) 3024 (Ar-H), 2951, 2915, 2709 (C-H), 1150, 1100, 1059 (C-S) cm^{-1};

^{1}H NMR ($DCCl_3$) δ 2.12 [bs, 2 H, H(1,5)], 2.82 [m, 8 H, $H(2,4,6,8)_{a,e}$], 3.15 [s, 4 H, SCH_2CH_2S], 3.52 [s, 4 H, CH_2-benzyl], 7.31 [m, 10 H, Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 38.08 [C(1,5)], 43.61 [SCH_2CH_2S], 56.69 [C(2,4,6,8)], 62.10 [CH_2-benzyl], 71.96 [C(9)], 126.73, 128.11, 128.85, 139.17 [Ar-C]. This compound was used directly to prepare **31**.

3-Benzyl-3,7-diazabicyclo[3.3.1]nonane (68). A 50-mL, three-necked, round bottomed-flask was equipped with a magnetic stirrer, a condenser with a N_2 inlet, and two glass stoppers. Palladium-on-carbon (10%, 0.120 g, 30 mg of catalyst/mmol of the amine) was added in one portion, and the system was flushed with N_2 for 15 min. Dry and deoxygenated methanol (8 mL) was slowly poured over the catalyst. To the stirred solution were added amine **66**, (1.20 g, 3.94 mmol) and anhydrous ammonium formate (0.74 g, 11.84 mmol) in one portion, and the resulting mixture was boiled under N_2 for 1 h. Cooling the mixture to RT and filtering through a celite pad was followed by concentration of the resulting solution to give a light yellow oil. The oil was then dissolved in water (25 mL) and made basic (pH = 11) using 10% NaOH solution. Combined extracts ($HCCl_3$, 4 x 10 mL) of the aqueous solution were dried (Na_2SO_4, 2 h), filtered, and concentrated to give a light yellow color oil **68** (0.78 g, 92%). IR (film) 3323 (N-H), 3060 (Ar-H), 2875, 2790 (C-H) cm^{-1}. GC-MS data calcd for $C_{14}H_{20}N_2$ (M^+): 216. Found: 216. Due to the hygroscopic nature of this oil, it was used directly used to prepare **69**.

3-Benzyl-7-(4-fluorobenzoyl)-3,7-diazabicyclo[3.3.1]nonane (69) A 50-mL, three-necked, round bottomed flask was equipped with a magnetic stirrer, a condenser with a N_2 inlet, an addition funnel, and two glass stoppers. A solution of secondary amine **68**

(0.283 g, 1.310 mmol) in H_2CCl_2 (5 mL) and NaOH (10%, 1.31 g, 3.27 mmol) was placed in the flask and stirred. A solution of 4-fluorobenzoyl chloride (0.228 g, 1.44 mmol) in H_2CCl_2 (5 mL) was added dropwise over a period of 5 min under N_2. The mixture was allowed to stir overnight at RT. Addition of H_2O (10 mL) was followed by extraction with H_2CCl_2 (3 x 10 mL). Combined extracts were dried ($MgSO_4$, 2 h), filtered, and concentrated to give a white solid. Recrystallization (hexane:ethyl acetate, 2.5:1) gave 0.31 g (81.67%) of **69** as a white solid, mp 203-204 °C. IR (KBr) 3070 (Ar-H), 2933, 2868 (C-H), 1628 (NC=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.60-1.80 [m, 2 H, H(9)], 1.86 [d, 2 H, H(1,5)], 2.99 [d, 2 H, $H(2,4)_a$], 3.26 [dd, 2 H, $H(6,8)_a$], 3.84 [d, 2 H, $H(2,4)_e$], 4.67 [d, 2 H, $H(6,8)_e$], 7.00-7.41 [m, 9 H, Ar-H]; ^{13}C NMR (DMSO-d_6) ppm 27.93 [C(9)], 31.43 [C(1,5)], 46.06, 52.61, 76.68 [ring carbons], 115.48, 115.69, 128.27, 129.08, 129.33, 129.42, 132.14, 132.18 [Ar-C], 164.38 [NC=O]. Mass spectral data (LSIMS) calcd for $C_{21}H_{23}FN_2O$ (M^+): 338. Found: 339 ($M^+ + 1$).

3-Benzyl-7-[4-(dimethylsulfonyl)amino]benzoyl-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (70). A 25-mL, Erlenmeyer flask was equipped with a magnetic stirrer and an ice-bath. To a chilled (5 °C, ice-bath) solution of amide **41** (0.120 g, 0.244 mmol) in anhydrous ether (5 mL) was added perchloric acid (60%, 0.061 g, 0.366 mmol) dropwise over a period of 2 min. The mixture was allowed to stir for an additional 10 min at 0-5 °C. A white precipitate formed and was filtered and washed with cold ether. Recrystallization (CH_3OH) gave 0.085 g (59%) of **70** as a white solid, mp 236-237 °C. IR (KBr) 3096 (Ar-H), 2937, 2879 (C-H), 1619 (NC=O) 1095 (Cl-O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.13 [bs, 2 H, H(1,5)], 1.74 [dd, 2 H, $H(9)_{ax,eq}$], 3.17-3.71 [m, 12 H, $H(6,8)_{ax,eq}$, CH_3, CH_2-benzyl], 4.10-4.36 [m, 4 H, $H(2,4)_{ax,eq}$], 7.26-7.65 [m, 9 H, Ar-H],

8.23 [bs, 1 H, N-H]; ^{13}C NMR (DMSO-d_6) ppm 26.45 [C(9)], 27.77 [C(1,5)], 43.04 [C(2,4,6,8)], 61.19 [CH_2-benzyl], 127.84, 129.15, 129.64, 129.86, 130.95, 131.01, 134.53, 137.90 [Ar-C], 171.66 [NC=O]. High resolution mass spectral (HRMS) data calcd for $C_{23}H_{30}ClN_3O_9$ (- ClO_4^-) (M^+): 492.1627. Found: 492.1637.

3-Benzyl-7-(2',2',2'-trichloroethoxycarbonyl)-9,9-(1,3-dithiolan-2-yl)-3,7-diazabicyclo[3.3.1]nonane (71). A three-necked, 50-mL, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a rubber septum stopper, a condenser with a N_2 inlet and one glass stopper. A solution of the tertiary amine **67** (1.100 g, 2.770 mmol) in anhydrous benzene (10 mL) was added to the flask, and the system was flushed with N_2. To this solution was added dropwise, 2',2',2'-trichloroethyl chloroformate (0.617 g, 3.19 mmol) via a syringe over a period of 5 min. The reaction mixture was stirred for an additional 10 min at RT and then was boiled for 48 h. Cooling the solution to RT resulted in the formation of a tan color solid, which was filtered under vaccum and recrystallized (absolute ethanol) to give 1.05 g (79%) of **71** as a white solid, mp 207-210 °C. 3070 (Ar-H), 2940, 2868 (C-H), 1715 (C=O) cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 2.88 [bs, 2 H, H(1,5)], 3.28-3.82 [m, 10 H, $H(2,4)_{ax,eq}$, CH_2-benzyl, SCH_2CH_2S], 4.28, 4.44 [4 H, $H(6,8)_{ax,eq}$], 4.71 [s, 2 H, $C(O)OCH_2CCl_3$], 7.29-7.64 [m, 5 H, Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 39.09, 39.36 [C(1,5)], 40.79 [SCH_2CH_2S], 47.07, 53.26, 53.96 [C(2,4,6,8)], 62.44 [CH_2-benzyl], 67.95 [C(9)], 75.49 [$C(O)OCH_2CCl_3$], 127.47, 129.15, 130.25, 132.45 [Ar-C], 154.70 [NC=O]. Mass spectral data (LSIMS) calcd for $C_{19}H_{23}Cl_3N_2O_2S_2$ (M^+): 481. Found: 481. This compound was used directly to prepare **72**.

7-Aza-3-benzyl-9,9-(dithiolan-2-yl)-3,7-diazabicyclo[3.3.1]nonane (72). A 15-mL, jacketed flask was equipped with a magnetic stirrer, a heating mantle, a condenser, a lower take-off condenser with a N_2 inlet, and three glass stoppers. To a solution of carbamate **71** (0.145 g, 0.301 mmol) in triethylene glycol (1.5 mL) was added KOH pellets (85%, 0.25 g, 3.011 mmol), and hydrazine (98%, 0.049 g, 1.505 mmol), and then the apparatus was flushed with N_2. The mixture was heated at 140-150 °C for 4 h under N_2 via the use of boiling xylenes in the outer jacket. Cooling the solution to RT was followed by the addition of chilled water (2 mL). Combined extracts ($HCCl_3$, 3 x 2 mL) of the suspension were washed with NaOH (10%, 3 mL), brine (3 mL), dried ($MgSO_4$, 2 h), filtered, and concentrated *in vacuo* to give 0.095 g (99%) of **72** as a light yellow oil. IR (film) 3435 (N-H), 3073, 3028 (Ar-H), 2930, 2877 (C-H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.58-1.88 [m, 3 H, H(1,5), ring proton], 2.10-2.30 [m, 2 H, ring protons], 2.70 [bs, 1 H, N-H], 2.83-3.35 [m, 4 H, ring protons], 3.58-3.75 [m, 7 H, ring proton, C*H*$_2$-benzyl, SC*H*$_2$C*H*$_2$S], 7.25 [m, 5 H, Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 28.83, 28.92 [C(1,5)], 48.18 [SCH_2CH_2S], 53.35, 58.25, 58.98, 61.64 [C(2,4,6,8)], 63.64 [CH_2-benzyl], 70.49 [C(9)], 126.93, 128.05, 128.79, 138.90 [Ar-C]. This oil was used directly to prepare **73**.

4-*N*-Acetylbenzamide (75a). A 250-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser with a N_2 inlet, an addition funnel, and two glass stoppers. A heterogenous mixture of the benzamide **74** (5.0 g, 36.72 mmol) in 30 mL anhydrous benzene was placed in the flask, followed by pyridine (3.60 g, 45.90 mmol) in one portion. To this was added a solution of acetyl chloride (3.60 g, 45.90 mmol) in anhydrous benzene (10 mL) dropwise over a period of 10 min, and the reaction mixture was stirred at RT for 12 h. The product was filtered, washed with benzene and

recrystallized (H_2O:C_2H_5OH, 1:1) to give 5.10 g (78%) of **75a** as a light yellow solid, mp 264.5-266 °C. IR (KBr) 3372, 3314, 3175 (N-H), 1667, 1623 (NC=O) cm^{-1}; ^1H NMR (DMSO-d_6) d 2.05 [s, 3 H, CH_3], 3.42 [bs, 2 H, $_2$HNC(O)] 7.22 [bs, 1 H, 2° N-H], 7.79 [d, 2 H, Ar-H], 7.82 [d, 2 H, Ar-H], 10.15 [bs, 1 H, 2° N-H]; ^{13}C NMR (DMSO-d_6) ppm 24.12 [CH_3], 117.97, 128.34, 128.52, 141.91 [Ar-C], 167.40, 168.68 [NC=O]. This compound was used directly to prepare **76a**.

4-*N*-Ethylbenzylamine (76a). A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, heating mantle, a condenser with a N_2 inlet, a rubber septum stopper, and one glass stopper. A heterogeneous mixture of the amide **75a** (2.50 g, 14.04 mmol) in anhydrous toluene (20 mL) was added to the flask, and the solution was chilled to 0-5 °C (ice-bath). To this was added borane dimethyl sulfide (10 *M*, 6.40 g, 84.20 mmol) dropwise via a syringe. The reaction mixture was stirred at 0-5 °C for 15 min and then boiled for 8 h. The flask was allowed to cool to RT, and Na_2CO_3 (10%, 15 mL) was added dropwise. The solution was stirred at RT for an additional 30 min. The toluene layer was separated, dried ($MgSO_4$, 1 h), and concentrated *in vacuo* to give 1.96 g (93%) of **76a** as a light yellow-colored oil. IR (film) 3330 (N-H), 3030 (Ar-H), 2890, 2925 (C-H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.17 [t, 3 H, CH_3], 1.60 [bs, 2 H, NH], 3.08 [d, 2 H, CH_2], 3.64 [q, 2 H, CH_2], 4.01 [m, 2 H, Ar-H], 7.01 [m, 2 H, Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 14.41 [CH_3], 38.02 [CH_2], 52.49 [CH_2], 112.63, 112.69, 128.06, 129.46 [Ar-C]. This was used directly to prepare **77**.

4-*N*-Benzoylbenzamide (75b). A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser with a N_2 inlet, an addition funnel, and two glass stoppers. A heterogenous mixture of the benzamide **74** (2.50 g, 18.36 mmol) in 20

mL anhydrous benzene was placed in the flask, followed by pyridine (1.81 g, 22.95 mmol) in one portion. To this was added a solution of benzoyl chloride (3.22 g, 22.95 mmol) in anhydrous benzene (10 mL) dropwise over a period of 10 min, and the reaction mixture was stirred at RT for 12 h. The product was filtered, washed with benzene and recrystallized (H_2O:C_2H_5OH, 1:1) to give 3.40 g (77%) of **75b** as a white solid, mp > 295 °C. IR (KBr) 3365, 3320, 3189 (N-H), 1660, 1635 (NC=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.36 [s, 2 H, $H_2NC(O)$], 7.28 [s, 1 H, 2° N-H] 7.53 [m, 2 H, Ar-H], 7.86 [m, 2 H, Ar-H], 10.44 [bs, 1 H, 2° N-H]; ^{13}C NMR (DMSO-d_6) ppm 119.52, 127.92, 128.43, 128.62, 129.34, 131.96, 134.94, 142.07 [Ar-C], 166.11, 167.72 [NC=O]. This compound was used directly to prepare **76b**.

4-*N*-Benzylbenzylamine (76b). A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, heating mantle, a condenser with a N_2 inlet, a rubber septum stopper, and one glass stopper. A heterogeneous mixture of amide **75b** (2.26 g, 9.41 mmol) in anhydrous toluene (20 mL) was added to the flask, and the solution was chilled to 0-5 °C (ice-bath). To this was added borane dimethyl sulfide (10 *M*, 2.50 g, 32.95 mmol) dropwise via a syringe. The reaction mixture was stirred at 0-5 °C for 15 min and then boiled for 8 h. The flask was allowed to cool to RT, and Na_2CO_3 (10%, 15 mL) was added dropwise. The solution was stirred at RT for an additional 30 min. The toluene layer was separated, dried ($MgSO_4$, 1 h), and concentrated *in vacuo* to give 1.37 g (68.5%) of **76b** as a light yellow-colored oil. IR (film) 3321 (N-H), 3030 (Ar-H), 2890, 2925 (C-H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 3.62 [s, 2 H, CH_2], 3.84 [s, 2 H, NH_2], 4.27 [s, 2 H, CH_2], 4.47 [s, 2 H, N-H], 6.58 [d, 2 H, Ar-H], 7.06 [d, 2 H, Ar-H], 7.28-7.36 [m, 5 H, Ar-

H]; ^{13}C NMR ($DCCl_3$) ppm 14.41 [CH_3], 38.02 [CH_2], 52.49 [CH_2], 112.63, 112.69, 128.06, 129.46 [Ar-C].

Attempted Preparation of 7-[4-(*N*-Ethyl)benzyl]-3-benzyl-3,7-diazabicyclo[3.3.1]-nonan-9-one (77). A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, heating mantle, a condenser with a N_2 inlet, an addition funnel, and two glass stoppers. A mixture of amine **76a** (1.06 g, 7.10 mmol), HCl (37%, 0.70 g, 7.10 mmol), glacial acetic acid (0.42 g, 7.10 mmol), and paraformaldehyde (0.53 g, 17.76 mmol) in deoxygenated methanol (15 mL) was stirred at reflux for 15 min under N_2. A solution of *N*-benzyl-4-piperidinone (**64**, 1.34 g, 7.10 mmol) in 10 mL of methanol and glacial acetic acid (0.42 g, 7.10 mmol) was added dropwise over a period of 10 min, which was followed by a period of boiling for an additional 24 h. After cooling to RT, concentration of the solution *in vacuo* gave an orange oil which was redissolved in H_2O (15 mL), and the extracts (ether, 2 x 10 mL) thereof were discarded. The aqueous layer was chilled (5 ^{o}C) in an ice bath and made basic (pH = 12) with NaOH pellets. Extraction (ether, 3 x 10 mL) gave a solution which was dried ($MgSO_4$, 1 h), filtered, and concentrated in *vacuo* to give a viscous, reddish oil. This oil was digested in hexanes (20 mL, 20 min), and the supernatent extracts were concentrated *in vacuo* to give a light yellow oil. The oil was chromatographed (column) using silica gel as the stationary phase and hexanes:ethyl acetate (3:1) as mobile phase to give a light yellow oil. The GCMS, IR, and NMR analyses of this oil indicated the presence of only starting materials.

4-Nitrobenzylamine (79). A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, heating mantle, a condenser with a N_2 inlet, a rubber

septum stopper, and one glass stopper. A heterogeneous mixture of the amide **78** (4.15 g, 24.97 mmol) in anhydrous THF (25 mL) was added to the flask. To this solution was added borane dimethyl sulfide (10 *M*, 3.79 g, 49.95 mmol) dropwise via a syringe over a period of 5 min. The reaction mixture was boiled for 3 h. The flask was allowed to cool to RT, and 6 *N* HCl (24.97 mmol) was added dropwise to decompose the borane-amine complex. *Caution*: 6 *N* HCl should be added very slowly and cautiously as the reaction is highly exothermic and liberates H_2 gas. The reaction mixture was stirred at RT for 5 min, and 50% (excess, pH = 12) was added dropwise to neutralize the acid. The organic layer (THF) was separated, dried (Na_2SO_4, 2 h), and concentrated *in vacuo* to give 2.50 g (66%) of **79** as a yellowish, orange-colored oil. No spectral data is provided as this compound is now commercially available compound from Aldrich Chemical Company, Milwaukee, WI. This compound was used directly without further purification to pepare **80**.

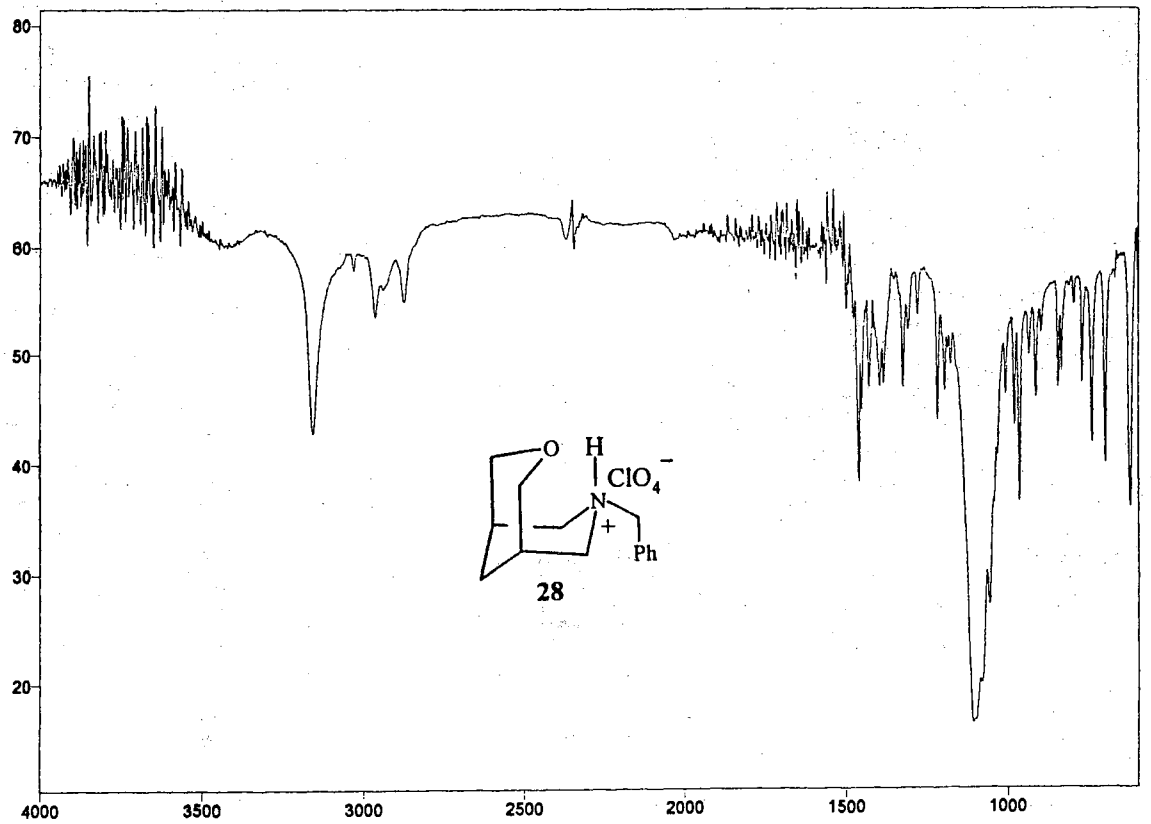
Attempted Preparation of 7-[4-Nitrobenzyl]-3-benzyl-3,7-diazabicyclo[3.3.1]-nonan-9-one (80). A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, heating mantle, a condenser with a N_2 inlet, an addition funnel, and two glass stoppers. A mixture of amine **79** (2.50 g, 16.43 mmol), HCl (37%, 0.810 g, 8.21 mmol), glacial acetic acid (0.98 g, 16.43 mmol), and paraformaldehyde (2.96 g, 98.59 mmol) in deoxygenated methanol (20 mL) was stirred at reflux for 15 min under N_2. A solution of *N*-benzyl-4-piperidinone (**64**, 3.10 g, 16.43 mmol) in 15 mL of methanol, and glacial acetic acid (0.98 g, 16.43 mmol) was added dropwise over a period of 10 min, which was followed by a period of boiling for an additional 24 h. After cooling to RT, concentration of the solution *in vacuo* gave an orange oil which was redissolved in H_2O

(20 mL), and the extracts (ether, 2 x 15 mL) thereof were discarded. The aqueous layer was chilled (5 °C) in an ice bath and made basic (pH = 12) with NaOH pellets. Extraction $HCCl_3$ (3 x 10 mL) gave a solution, which was dried (Na_2SO_4, 1 h), filtered, and concentrated in *vacuo* to give a viscous reddish oil. This oil was digested in hexanes (2 x 20 mL, 20 min), and the supernatent extracts were concentrated *in vacuo* to give a light yellow oil. The oil was chromatographed (column) using silica gel as the stationary phase and hexanes:ethyl acetate (3:1) as mobile phase to give a light yellow oil. The GCMS, IR, and NMR analyses of this oil indicated the presence of starting materials and other complex byproducts.

Attempted Preparation of 7-[4-(*N*-Ethyl)benzyl]-3-thia-3,7-diazabicyclo[3.3.1]-nonan-9-one (84). A 50-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, heating mantle, a condenser with a N_2 inlet, an addition funnel, and two glass stoppers. A mixture of amine **76** (0.60 g, 3.99 mmol), HCl (37%, 0.19 g, 2.0 mmol), glacial acetic acid (0.47 g, 7.99 mmol), and paraformaldehyde (0.83 g, 27.90 mmol) in deoxygenated methanol (15 mL) was stirred and flushed for 15 min under N_2. Tetrahydrothiopyran-4-one (**83**, 0.46 g, 3.99 mmol) was added in one portion, which was followed by a period of boiling for an additional 24 h. After cooling to RT, concentration of the solution *in vacuo* gave an orange oil which was redissolved in H_2O (20 mL), and the extracts (ether, 2 x 10 mL) thereof were discarded. The aqueous layer was chilled (5 °C) in an ice bath and made basic (pH = 12) with NaOH pellets. Extraction $HCCl_3$ (3 x 10 mL) gave a solution, which was dried (Na_2SO_4, 2 h), filtered, and concentrated *in vacuo* to give a viscous reddish oil. This oil was digested in hexanes (2 x 15 mL, 20 min), and the supernatent extracts were concentrated *in vacuo* to give a light yellow oil.

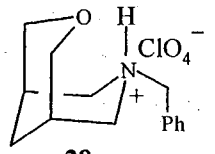
The oil was chromatographed (column) using silica gel as the stationary phase and hexanes:ethyl acetate (3:1) as elutant to give a light yellow oil. GCMS, IR, and NMR analyses of this oil proved difficult to analyze due to complex, unidentifiable peaks.

Plate I



IR Spectrum of **28**

Plate II

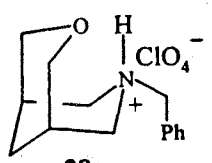


28

^{1}H NMR Spectrum of **28**

Plate III

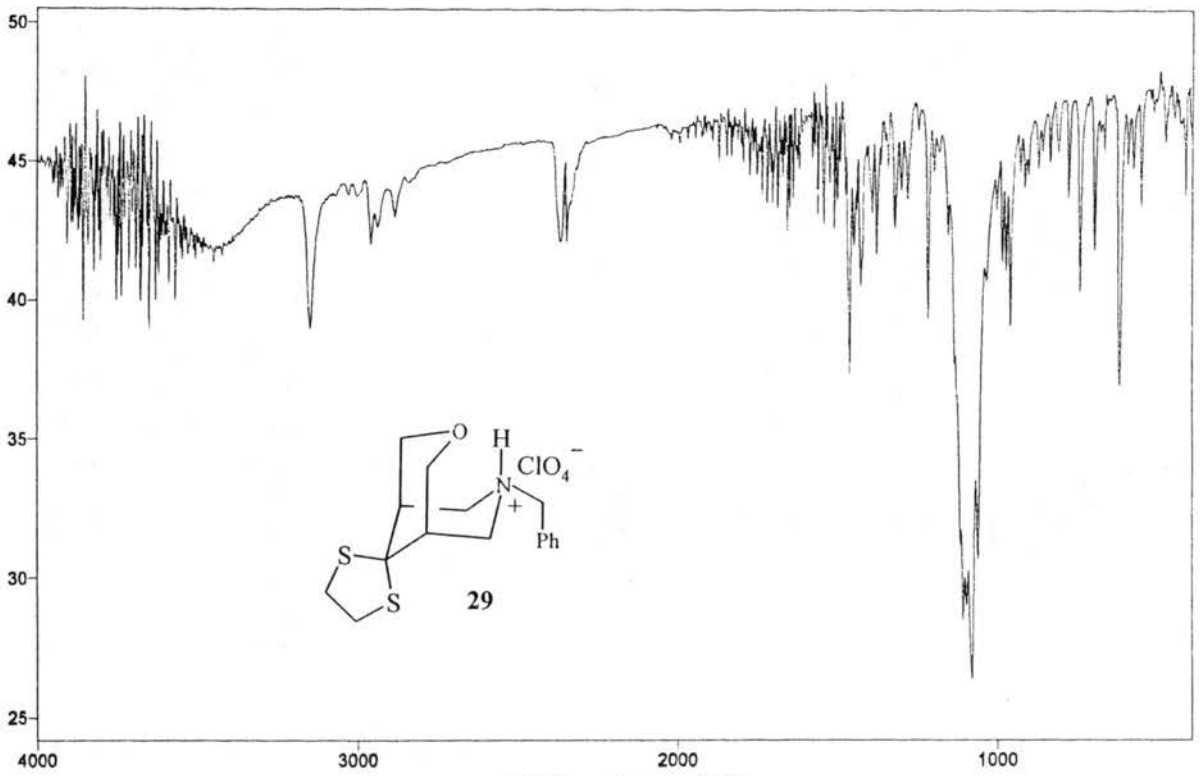
```
GAMMA-H2 TEST
USE 1 WATT DECOUPLING

expl  s2pul

      SAMPLE                    DEC. & VT
date       Nov 13 97    dn              H1
solvent         DMSO    dof              0
file             exp    dm             nny
    ACQUISITION         dmm              w
sfrq         100.574    dmf           9158
tn               C13    dpwr            40
at             1.983          PROCESSING
np             55744    lb            0.50
sw          24140.0     fn           65536
fb             13000    math            1
bs                32
pw               4.9    werr
pw               4.9    wexp           wft
tpwr              51    wbs            wft
d1             1.000    wnt
tof            1711.4         DISPLAY
nt               1024    sp          -887.6
ct                832    wp         24140.0
alock               n    vs             147
gain               44    sc               0
      FLAGS              wc             200
il                  n    hzmm        120.70
in                  n    is          500.00
dp                  y    rfl         4880.0
hs                 nn    rfp         3972.4
                         th               28
                         ins         100.000
                         nm    ph
```



28

^{13}C NMR Spectrum of **28**

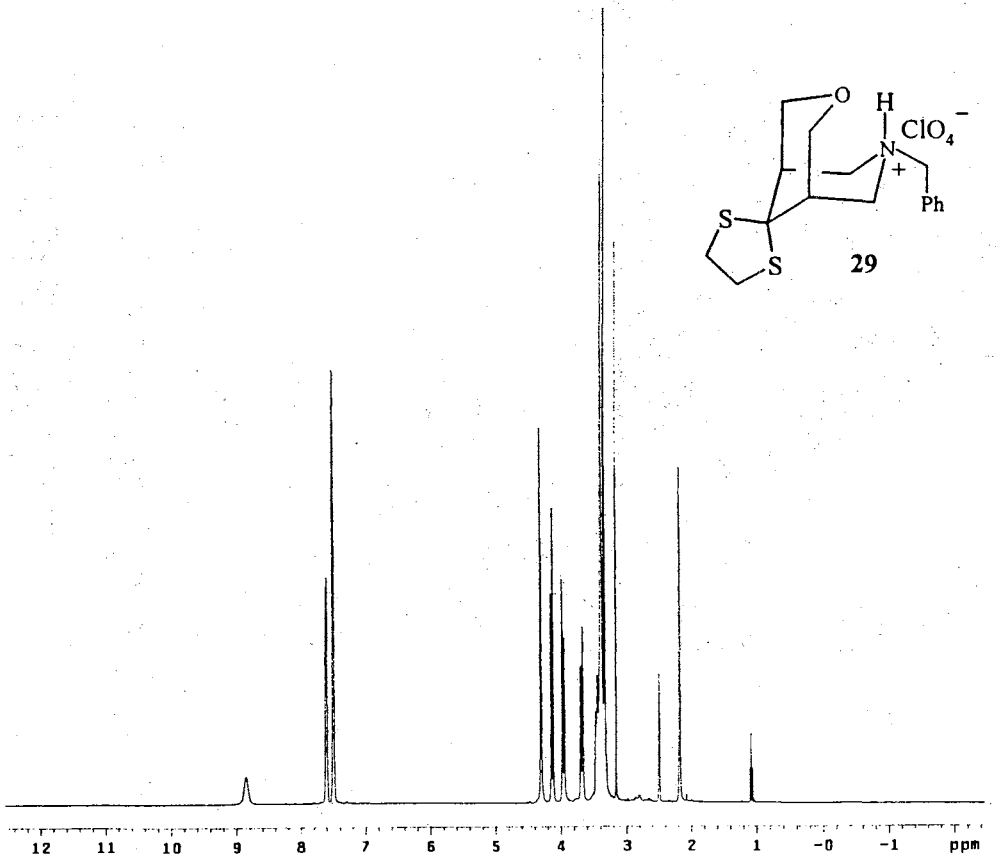
Plate IV



29

IR Spectrum of **29**

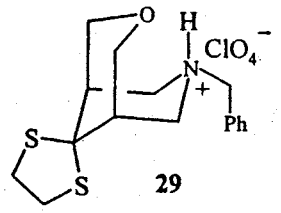
Plate V



29

^{1}H NMR Spectrum of **29**

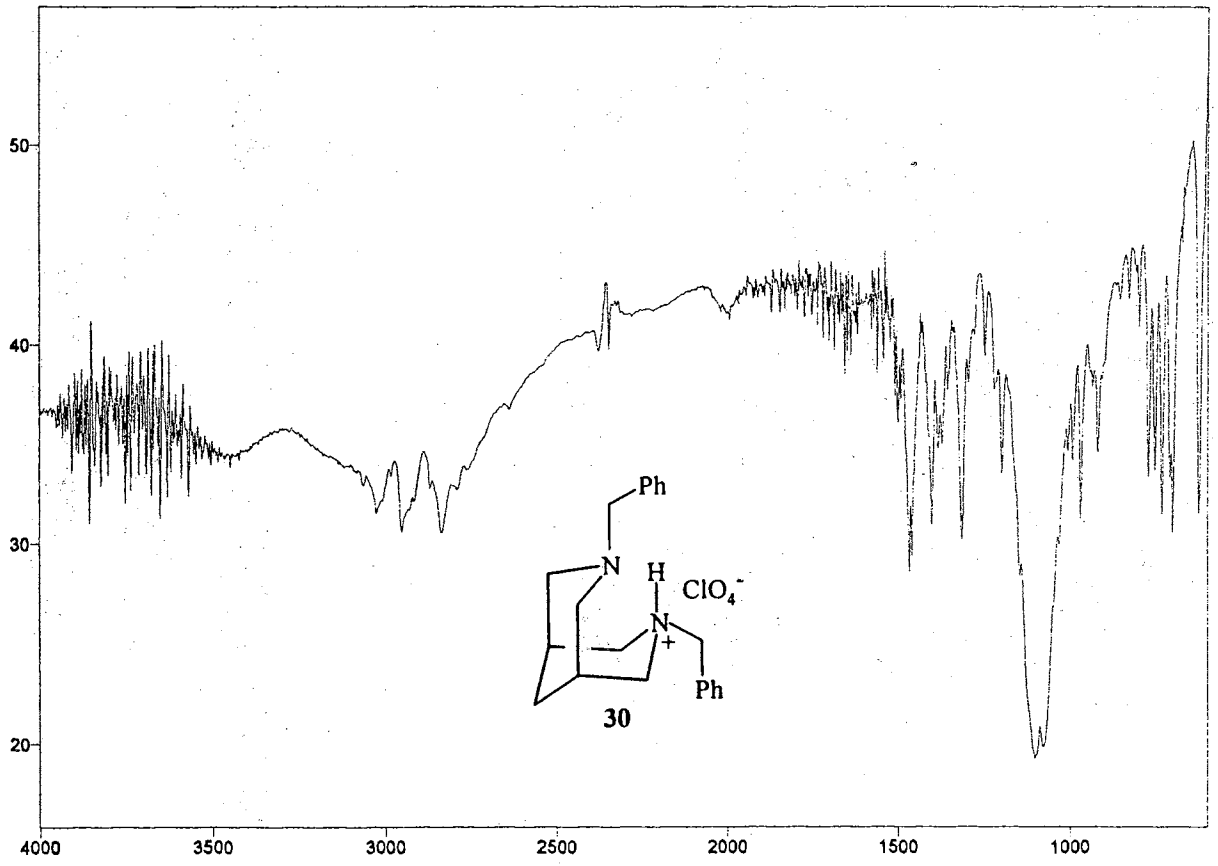
Plate VI



29

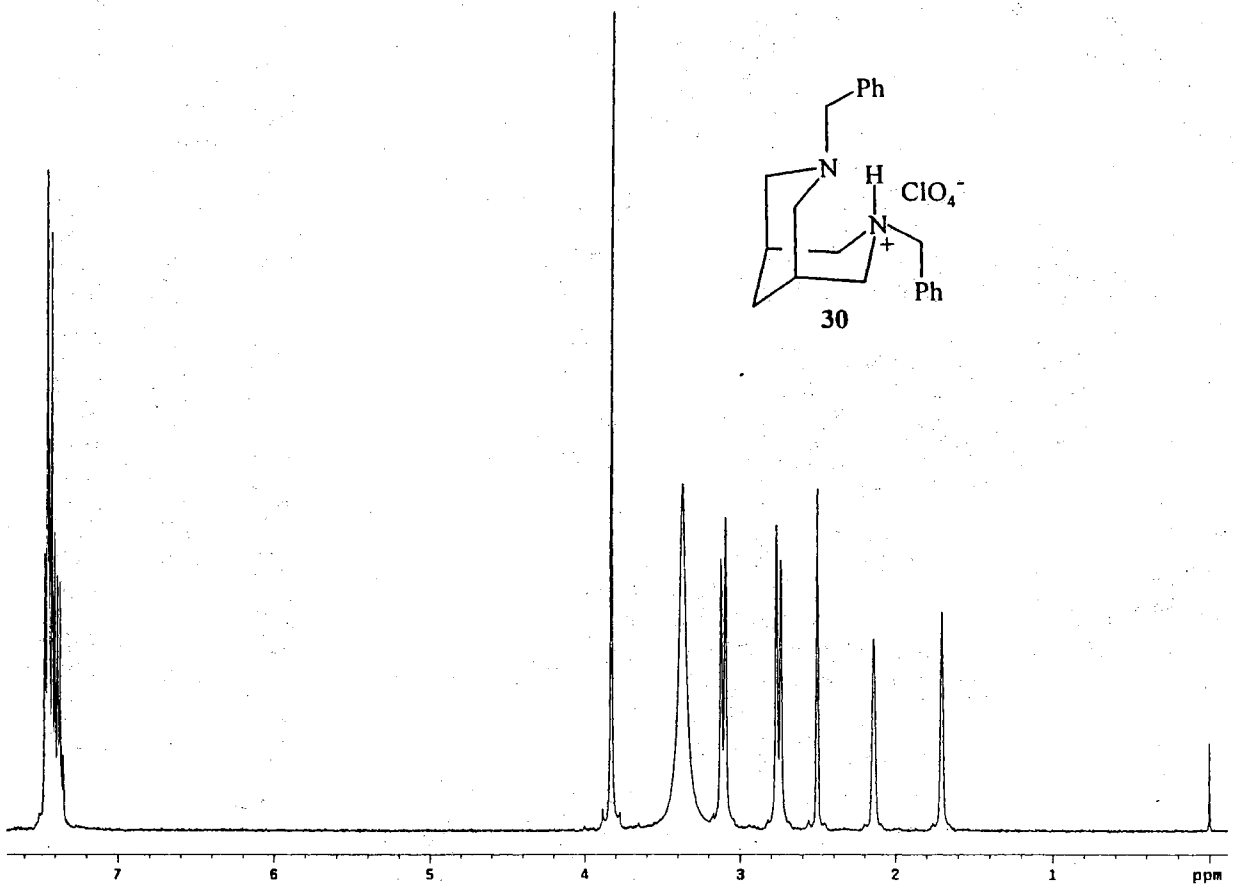
^{13}C NMR Spectrum of **29**

Plate VII



IR Spectrum of **30**

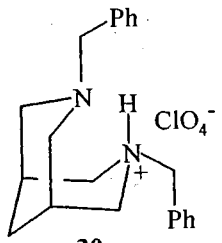
Plate VIII



30

^{1}H NMR Spectrum of **30**

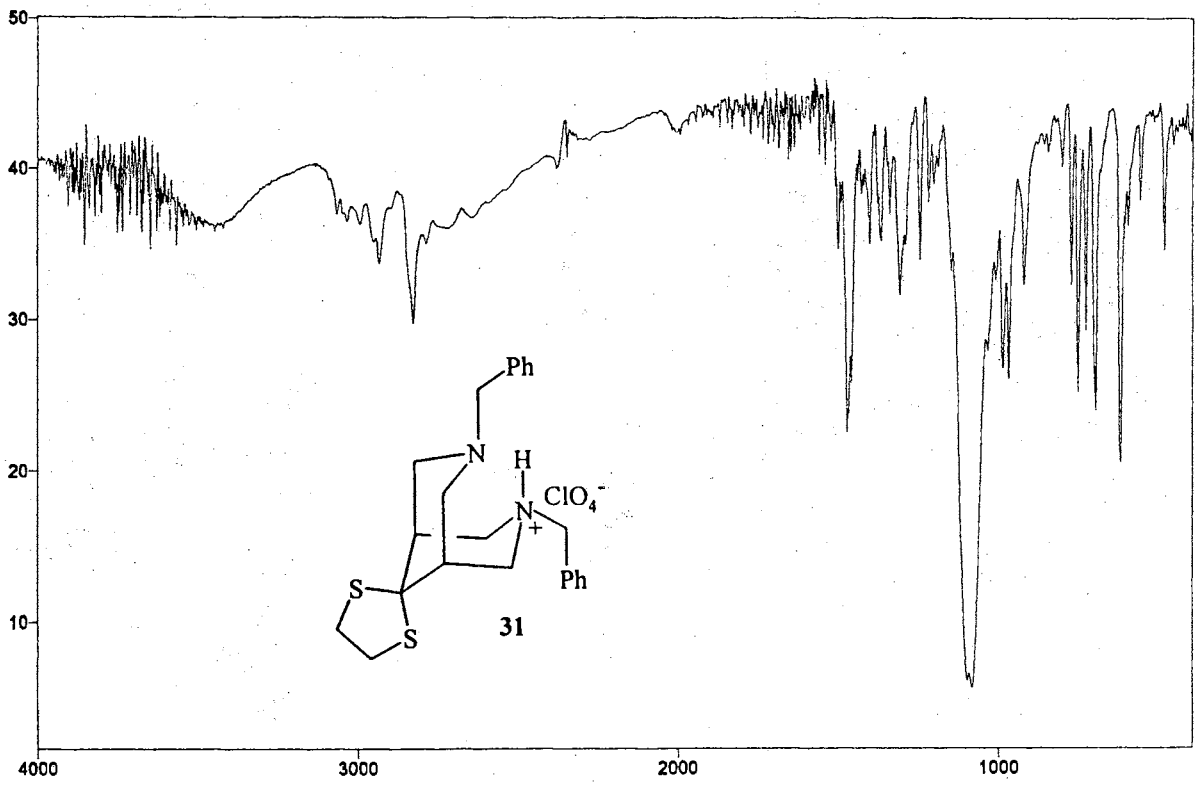
Plate IX



30

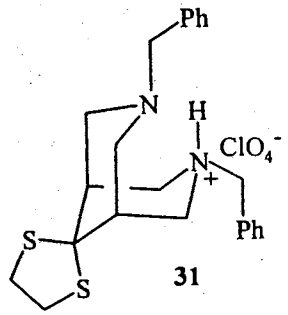
^{13}C NMR Spectrum of **30**

Plate X



IR Spectrum of **31**

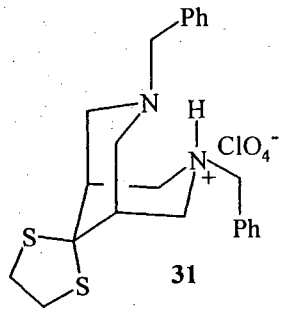
Plate XI



31

^{1}H NMR Spectrum of **31**

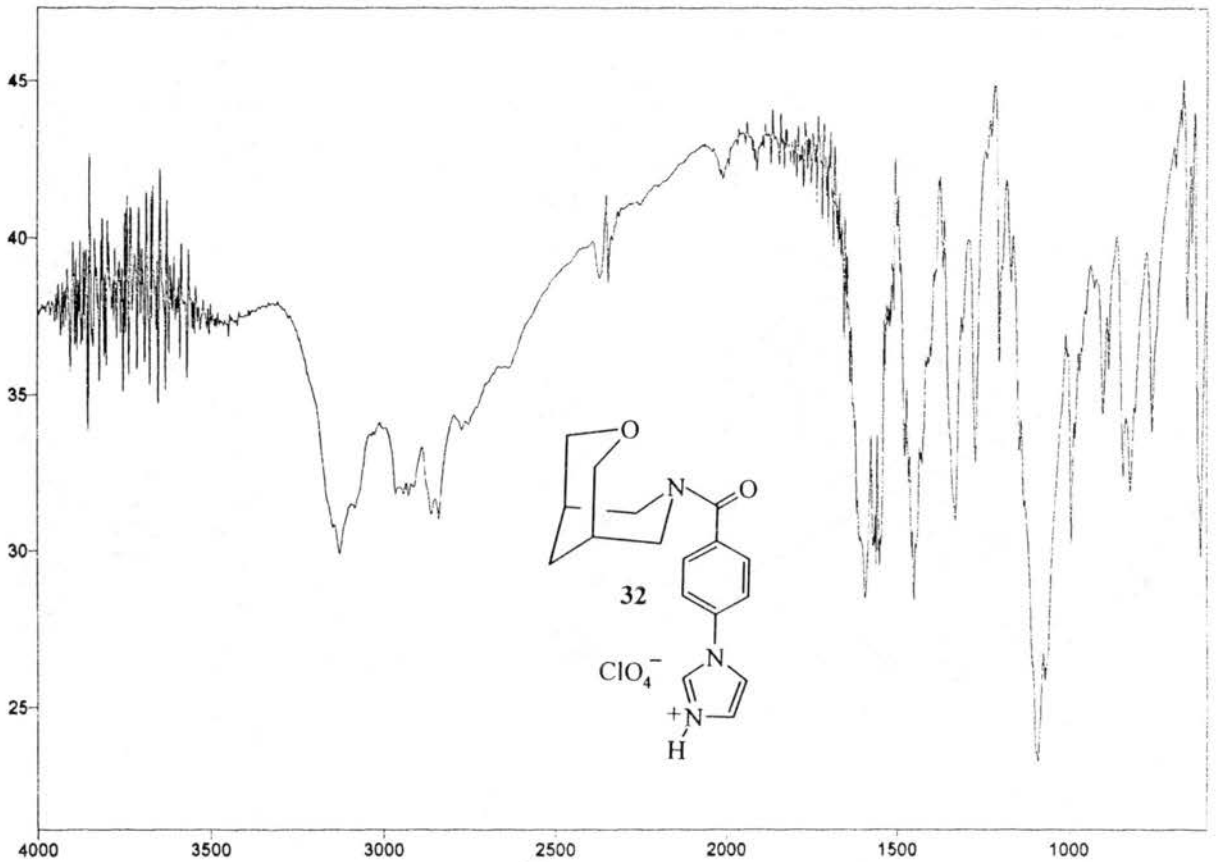
Plate XII



31

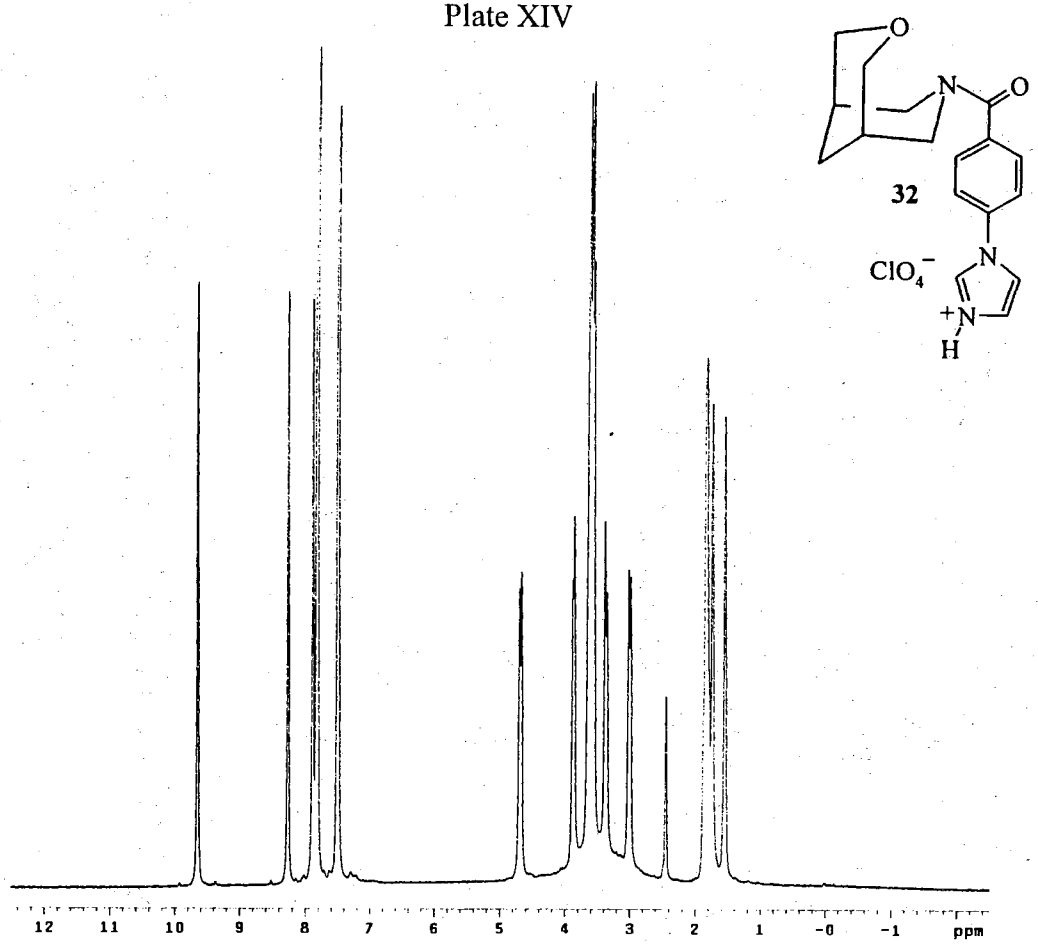
^{13}C NMR Spectrum of **31**

Plate XIII



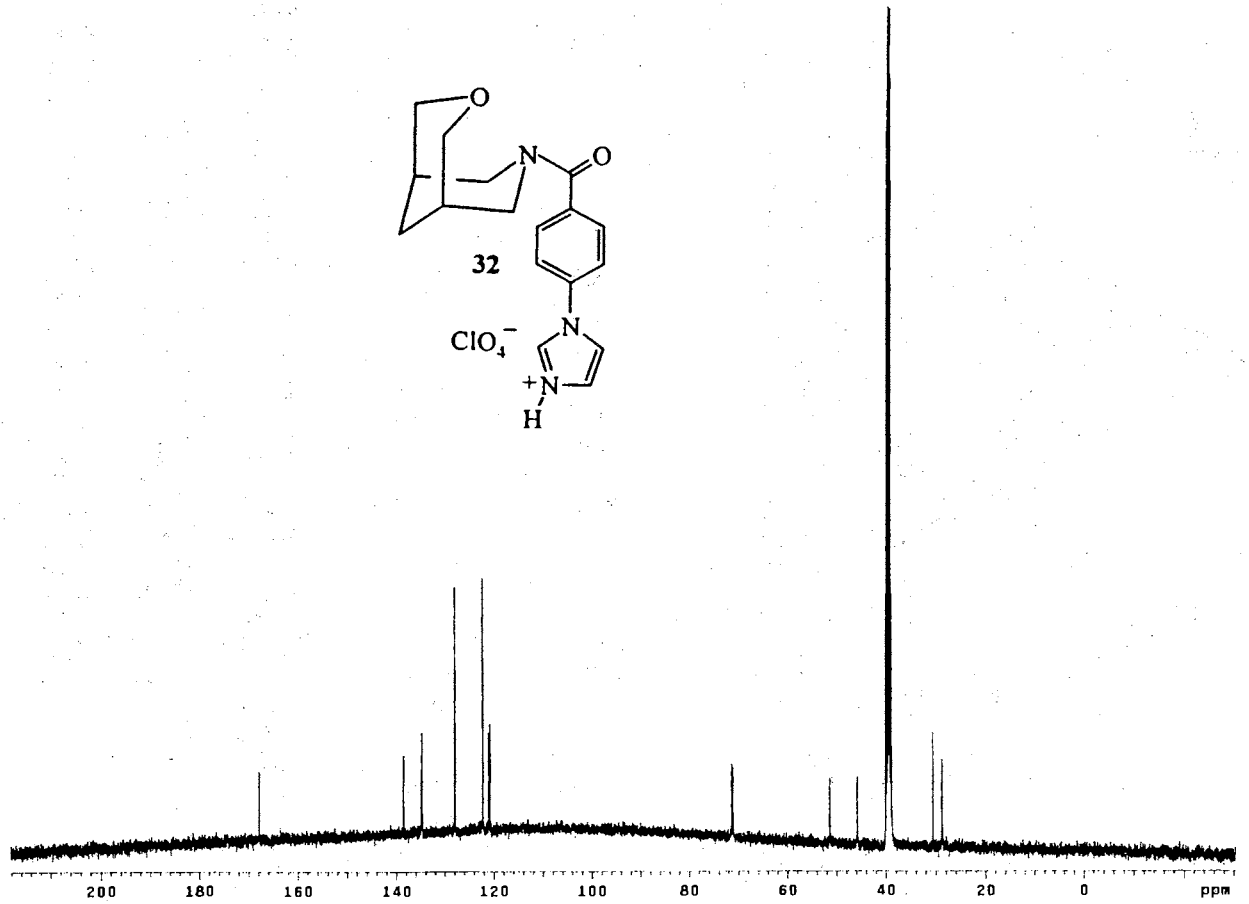
IR Spectrum of **32**

Plate XIV



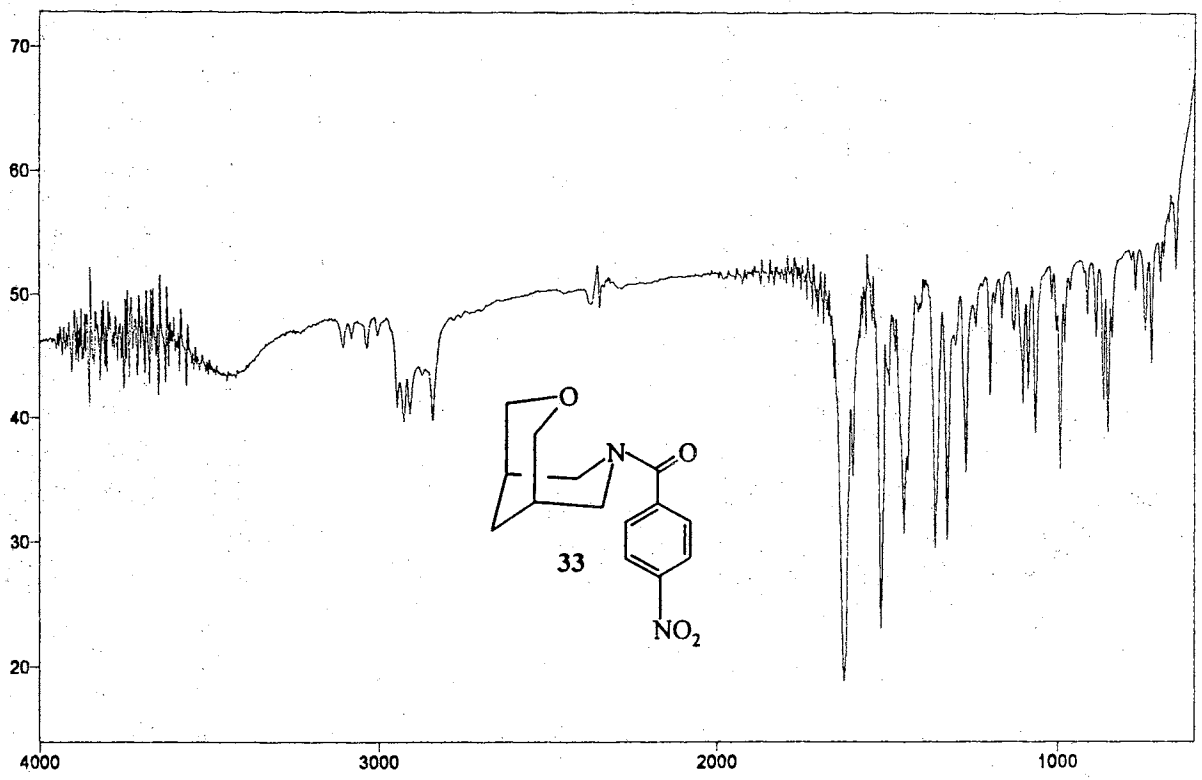
^{1}H NMR Spectrum of **32**.

Plate XV



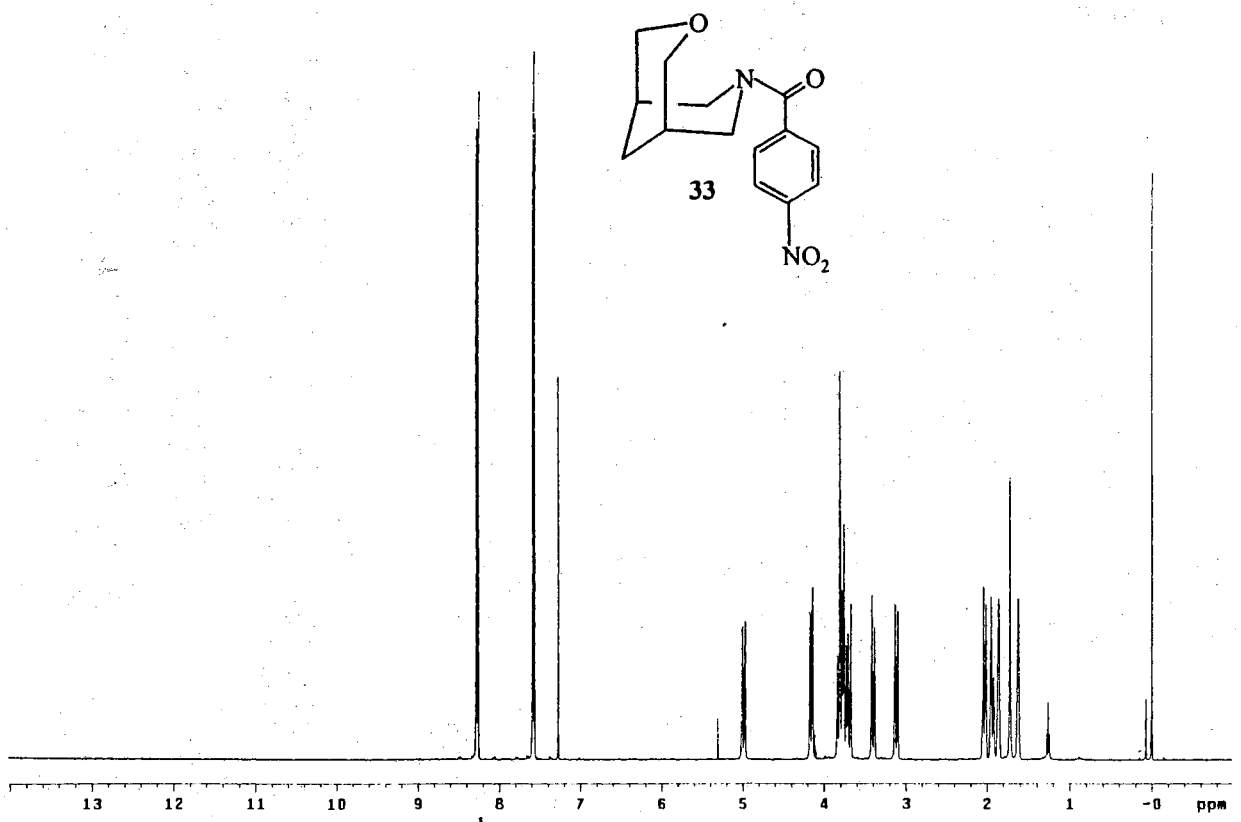
^{13}C NMR Spectrum of **32**

Plate XVI



IR Spectrum of **33**

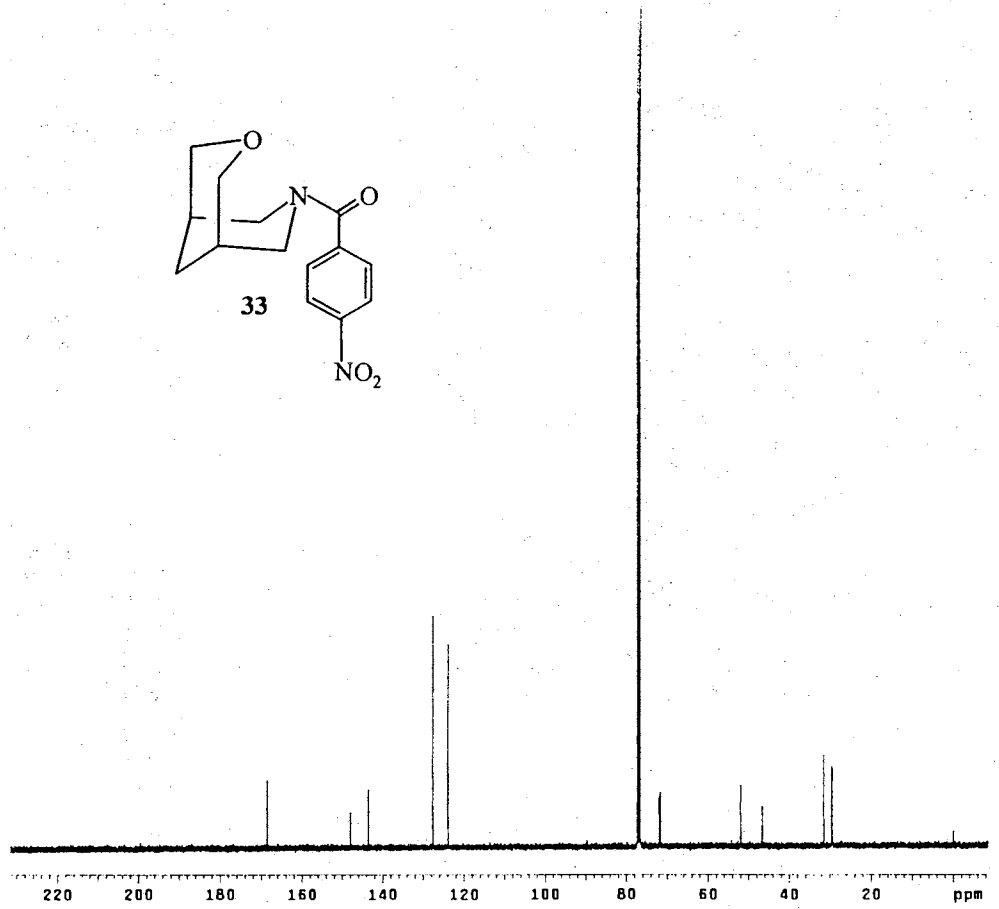
Plate XVII



33

^{1}H NMR Spectrum of **33**

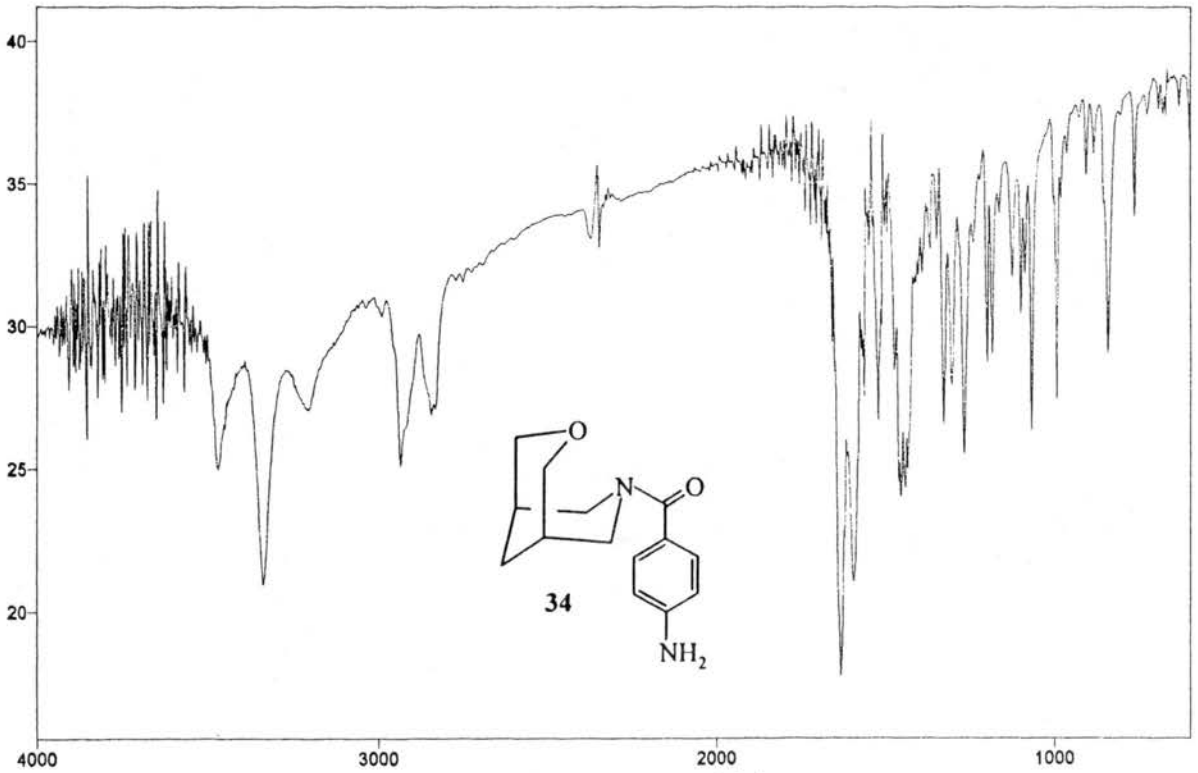
Plate XVIII



33

^{13}C NMR Spectrum of **33**

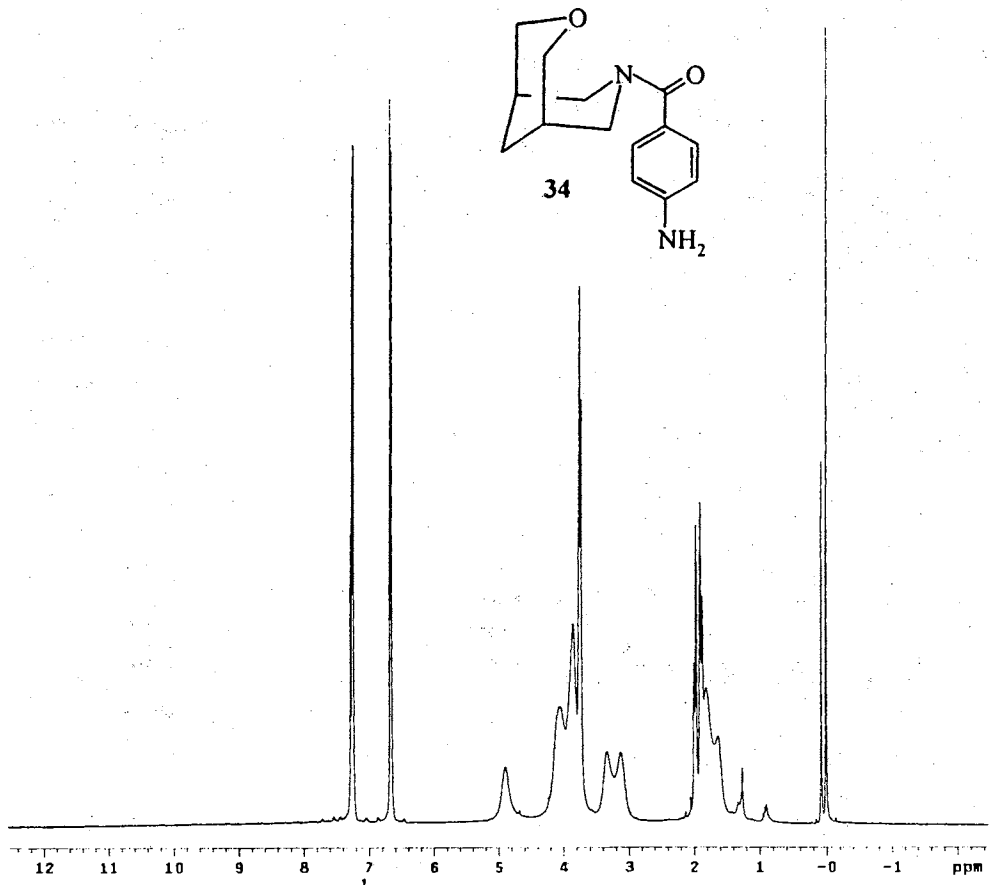
Plate XIX



34

IR Spectrum of **34**

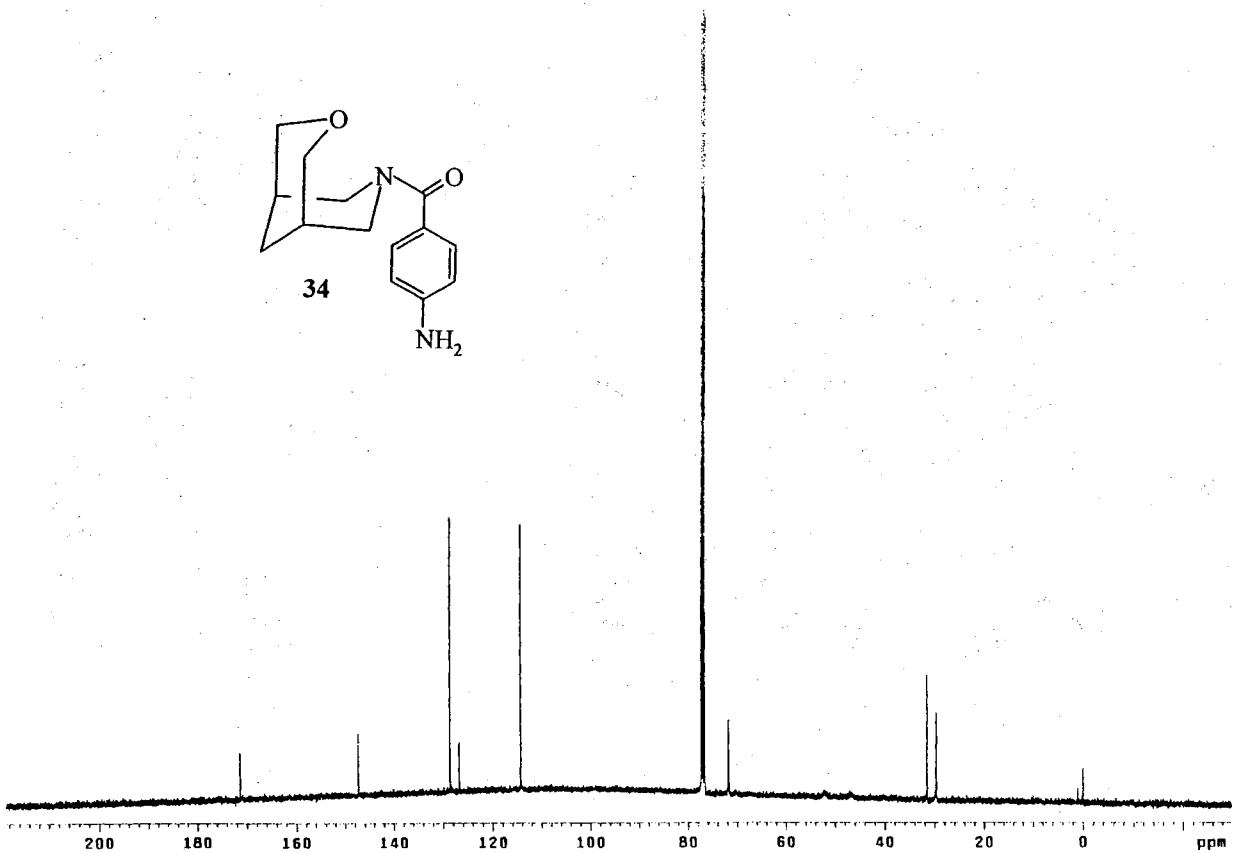
Plate XX



34

^{1}H NMR Spectrum of **34**

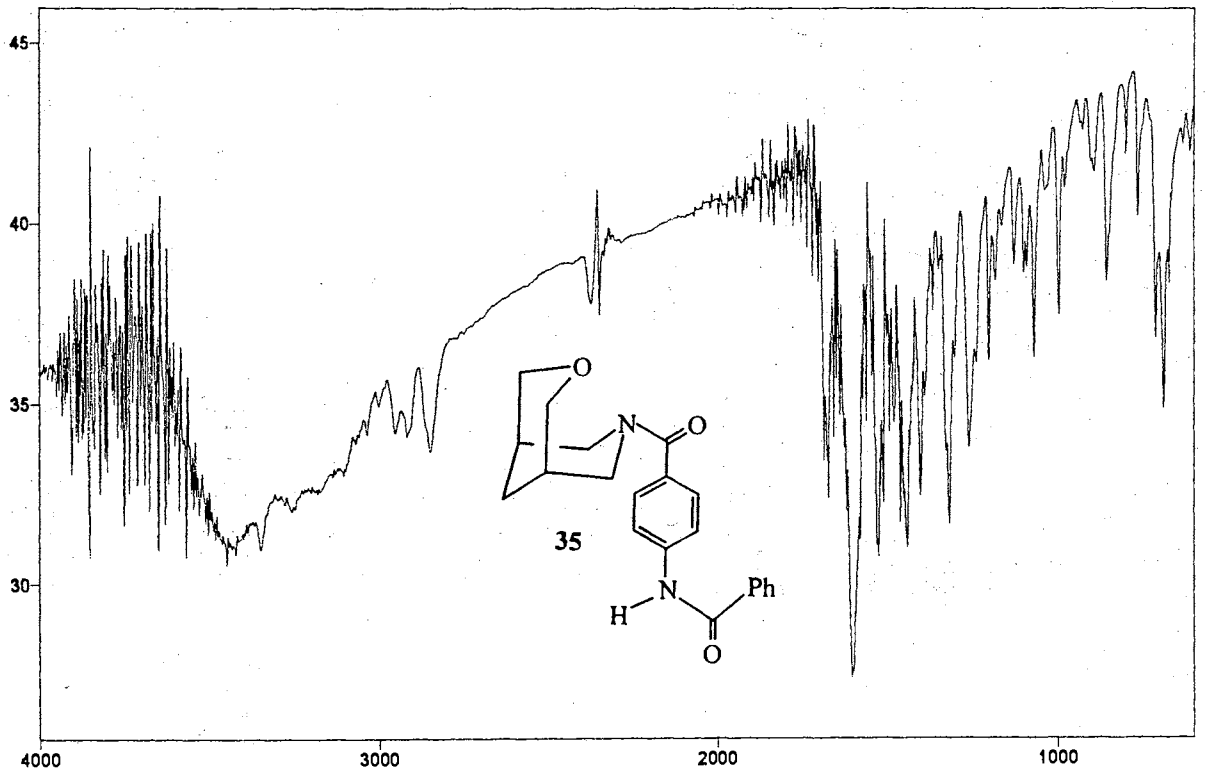
Plate XXI



34

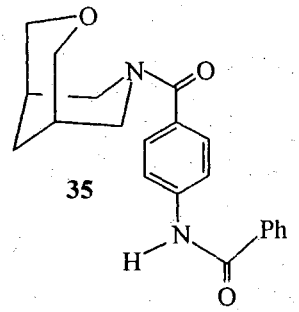
^{13}C NMR Spectrum of **34**

Plate XXII



IR Spectrum of **35**

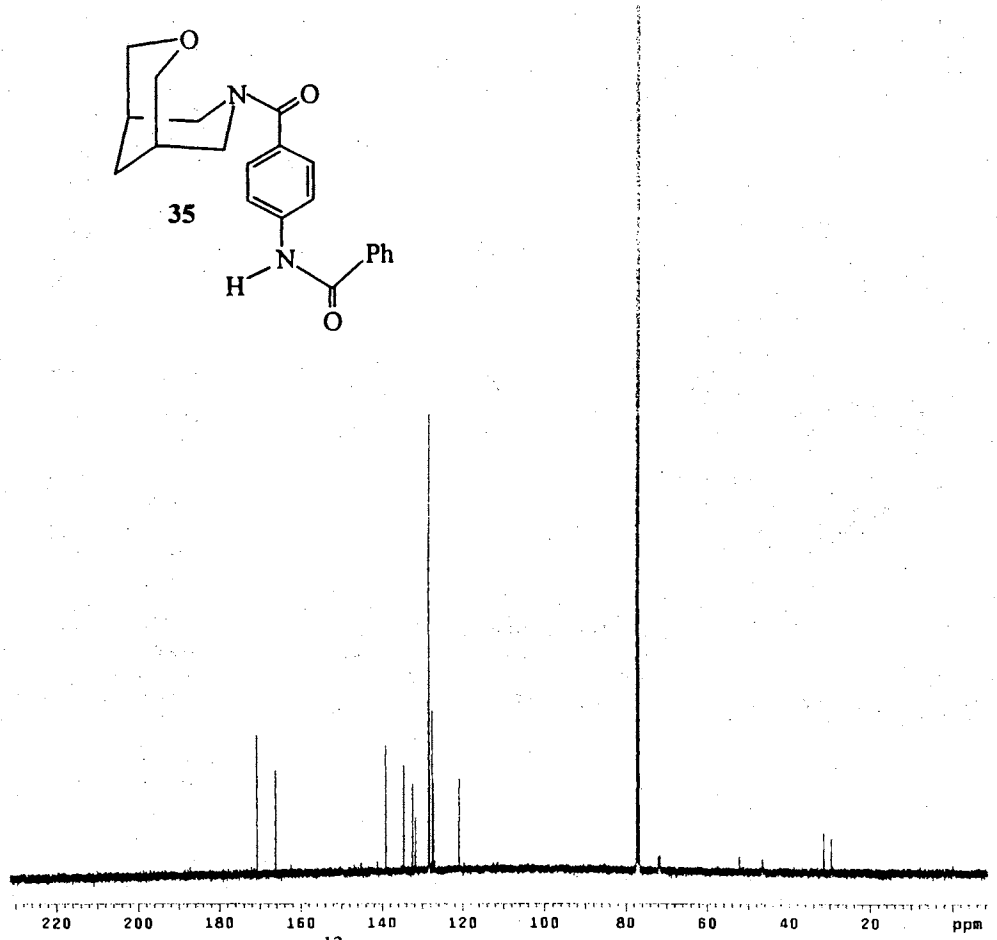
Plate XXIII



35

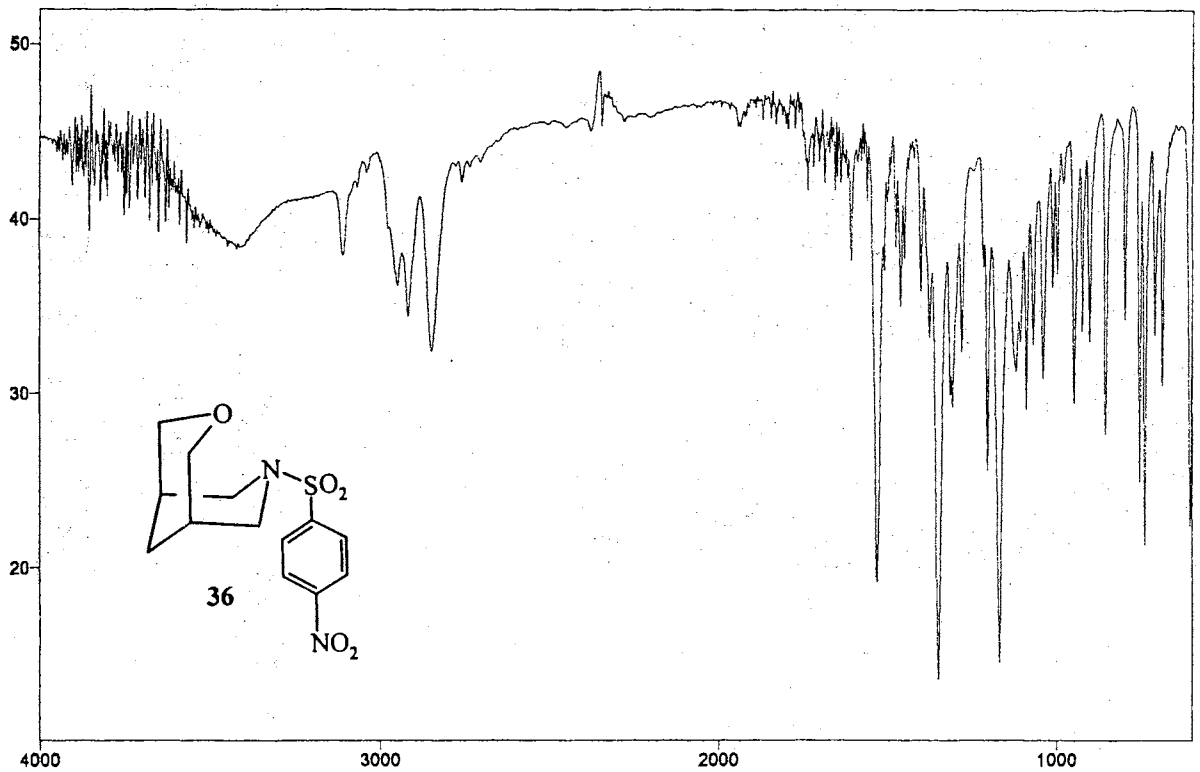
^{1}H NMR Spectrum of **35**

Plate XXIV



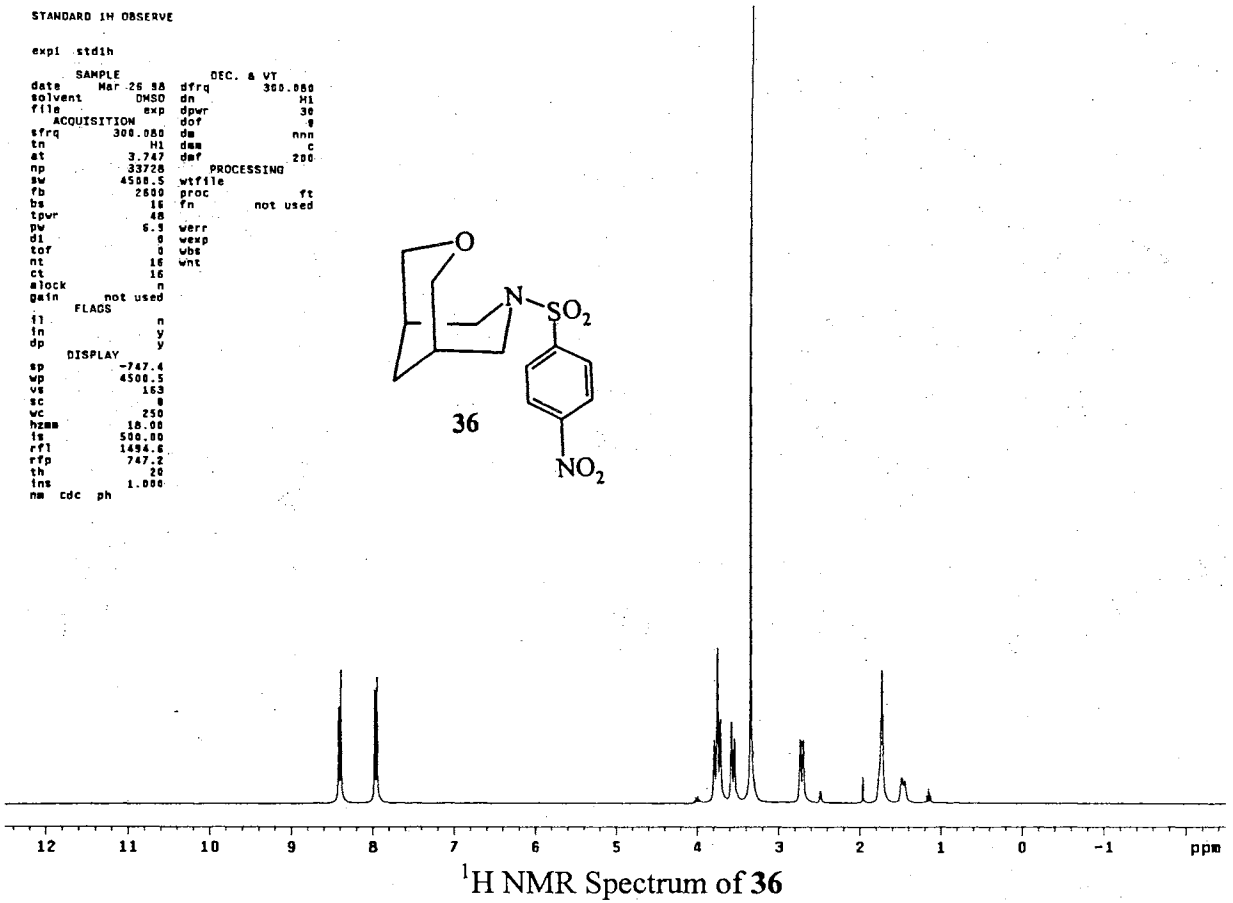
^{13}C NMR Spectrum of **35**

Plate XXV



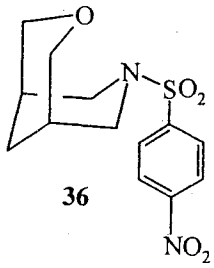
IR Spectrum of **36**

Plate XXVI



^{1}H NMR Spectrum of **36**

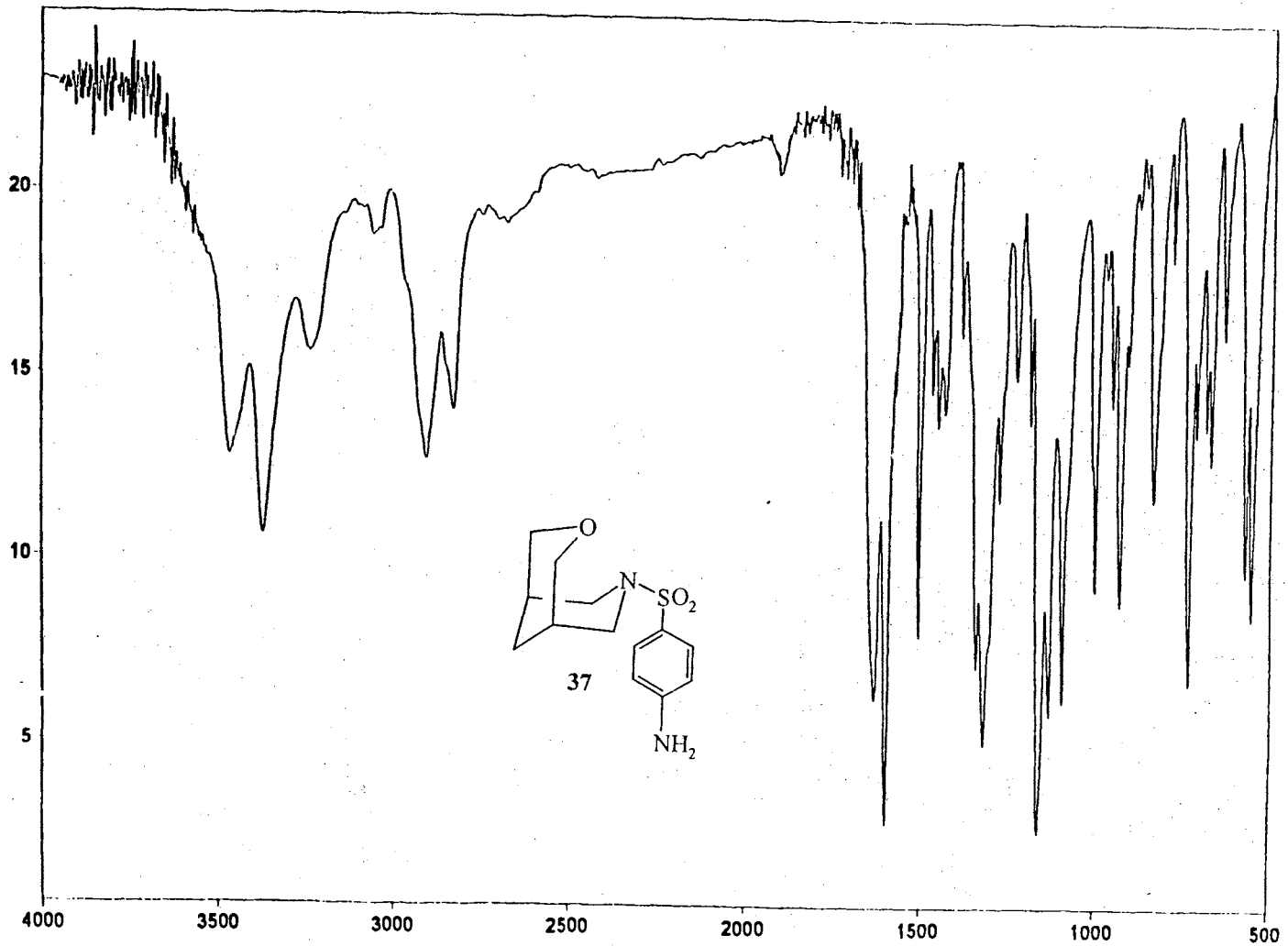
Plate XXVII



36

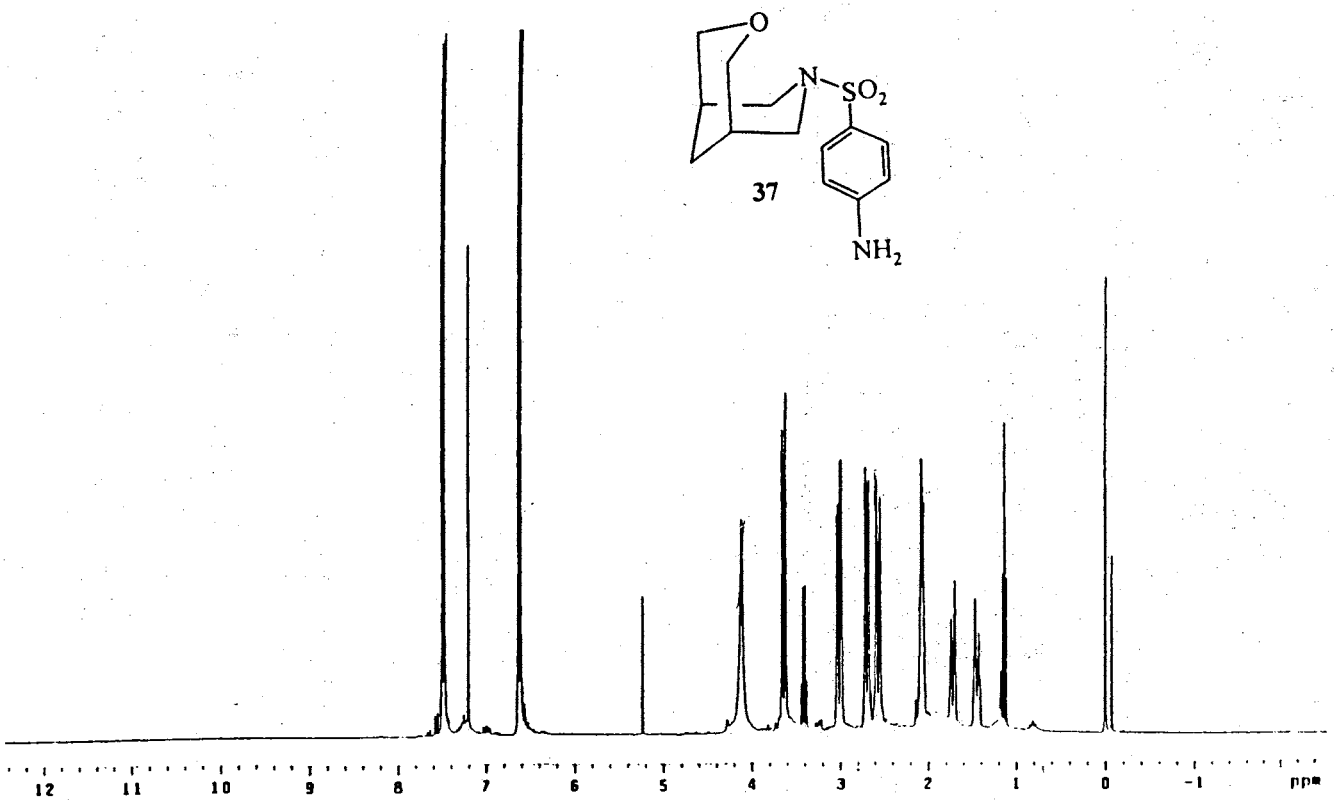
^{13}C NMR Spectrum of **36**

Plate XXVIII



IR Spectrum of **37**

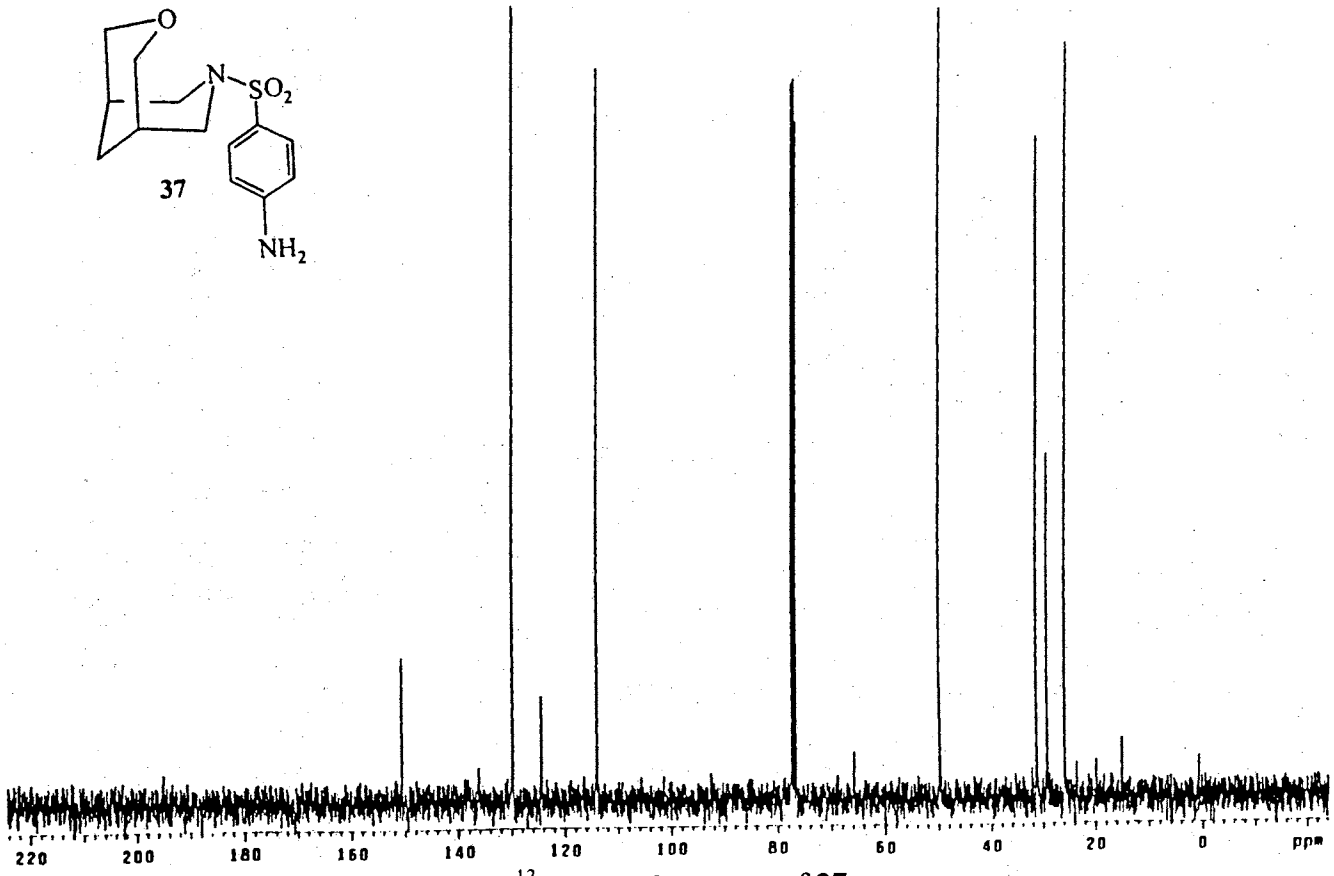
Plate XXIX



37

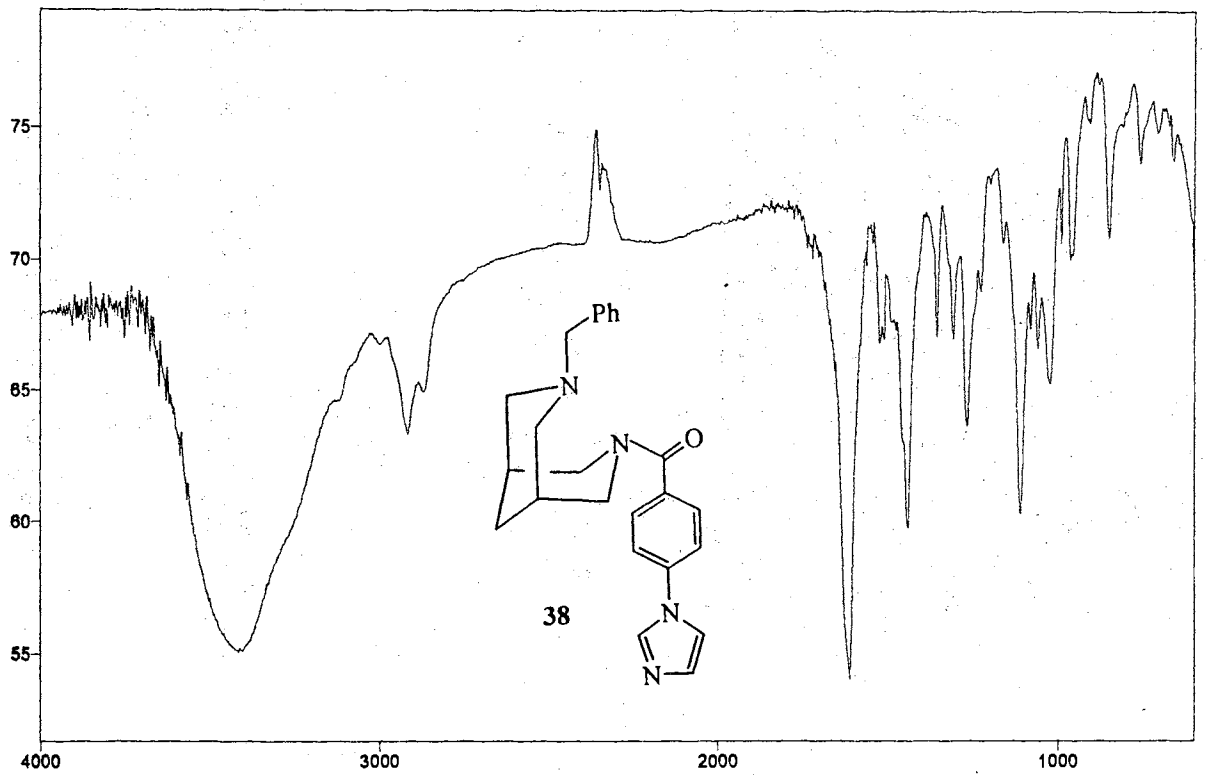
^{1}H NMR Spectrum of **37**

Plate XXX



^{13}C NMR Spectrum of **37**

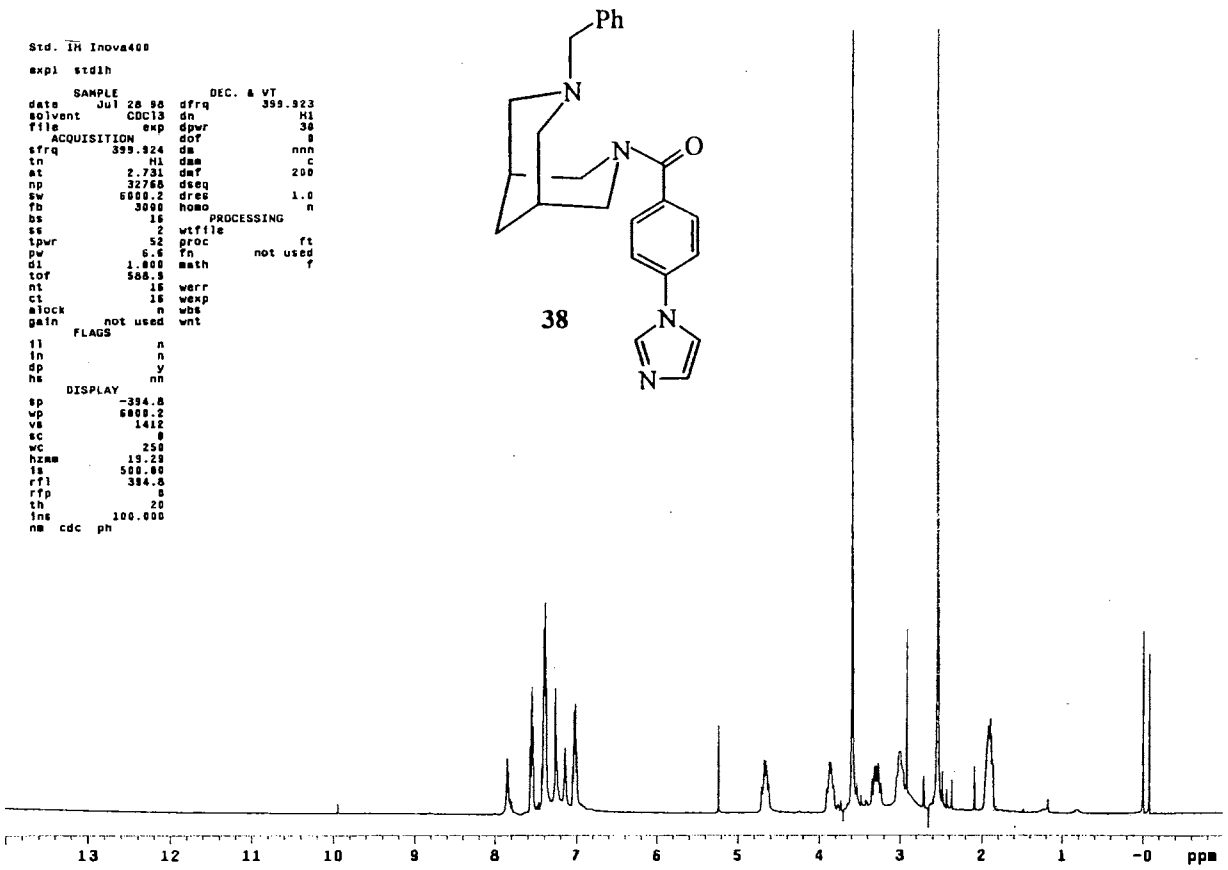
Plate XXXI



38

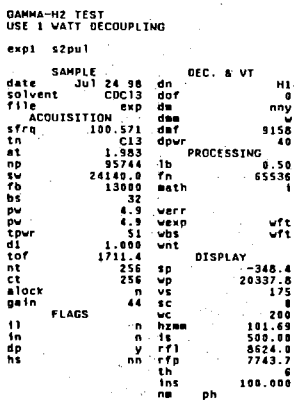
IR Spectrum of **38**

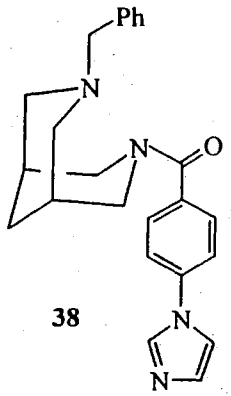
Plate XXXII



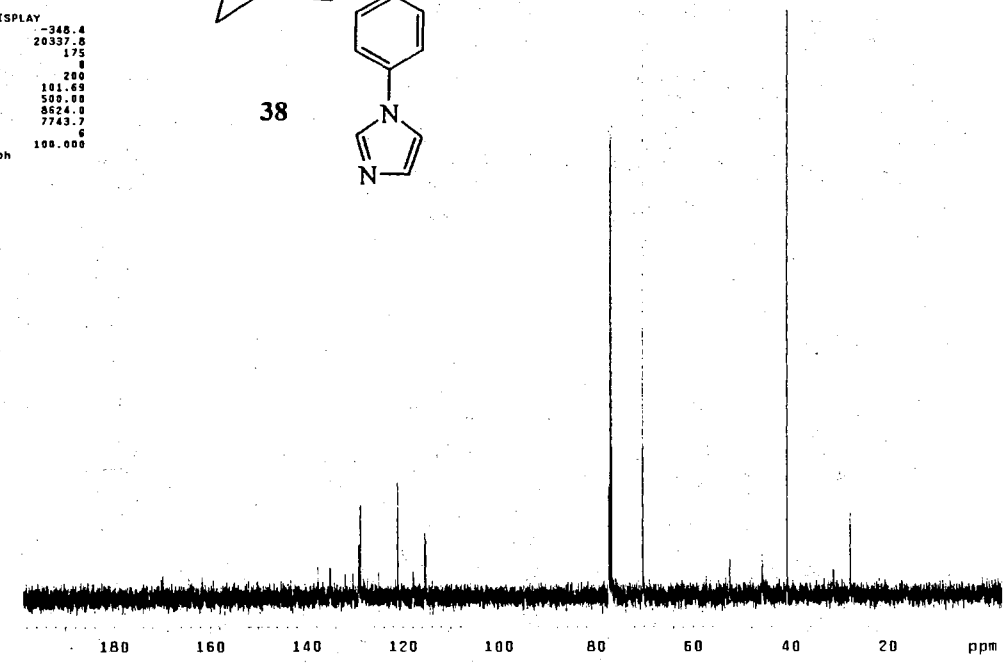
^{1}H NMR spectrum of **38**

Plate XXXIII



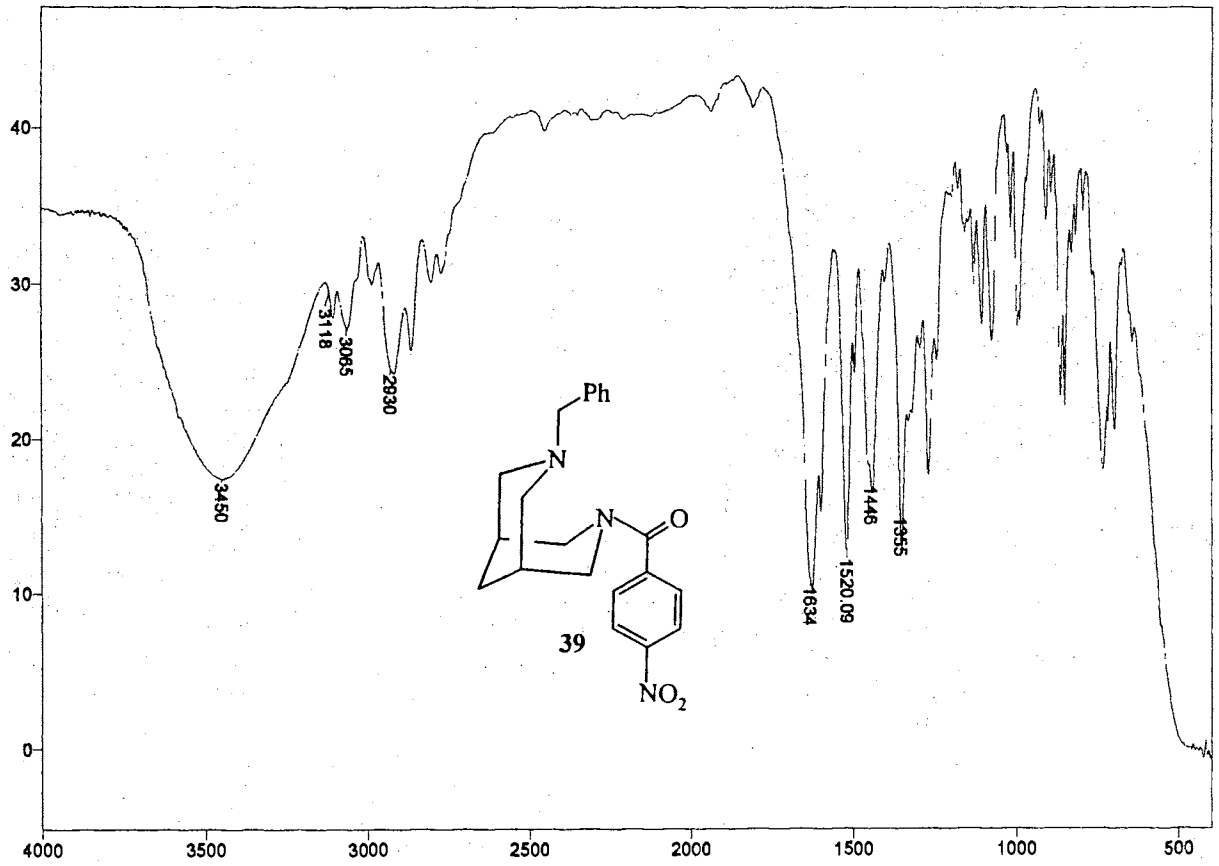


38



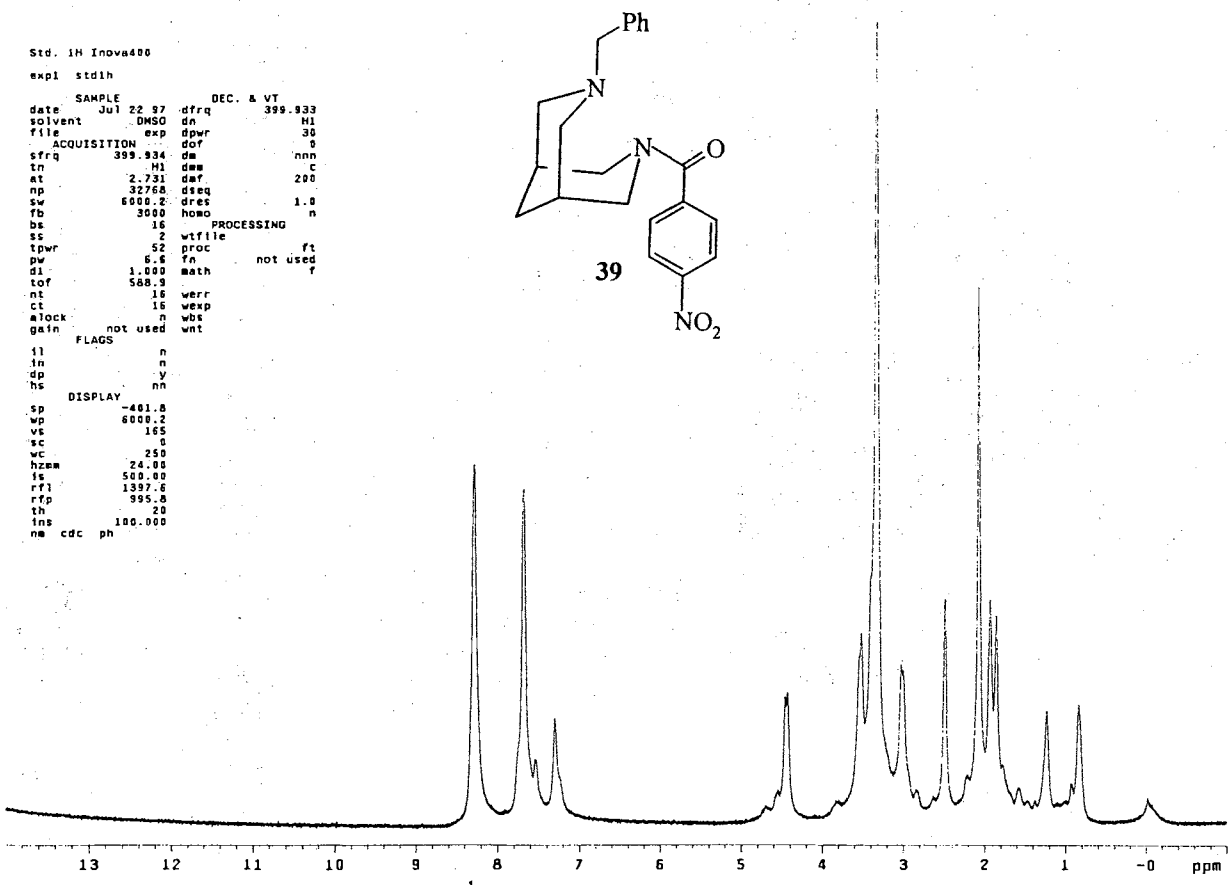
^{13}C NMR Spectrum of **38**

Plate XXXIV



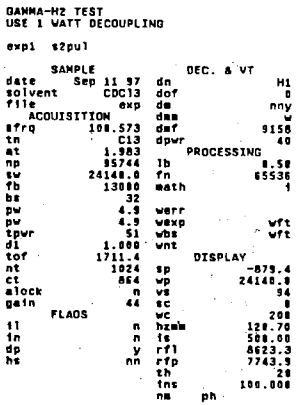
IR Spectrum of **39**

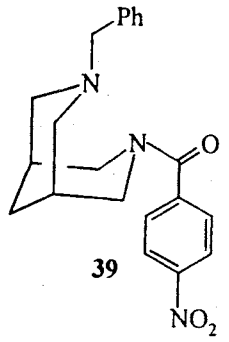
Plate XXXV



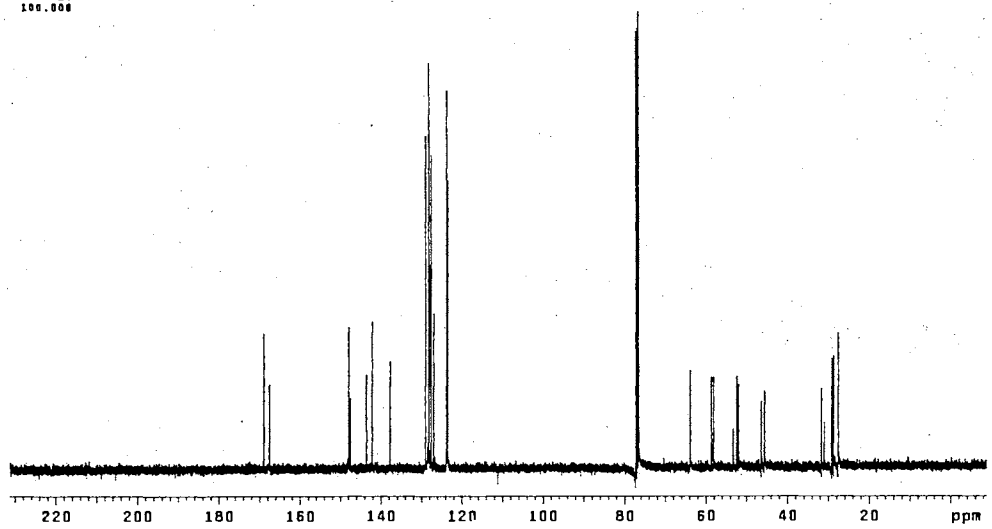
^{1}H NMR Spectrum of **39**

Plate XXXVI



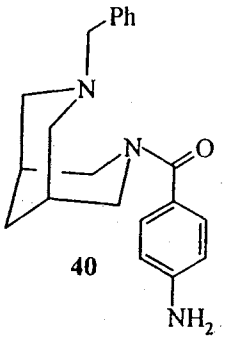


39

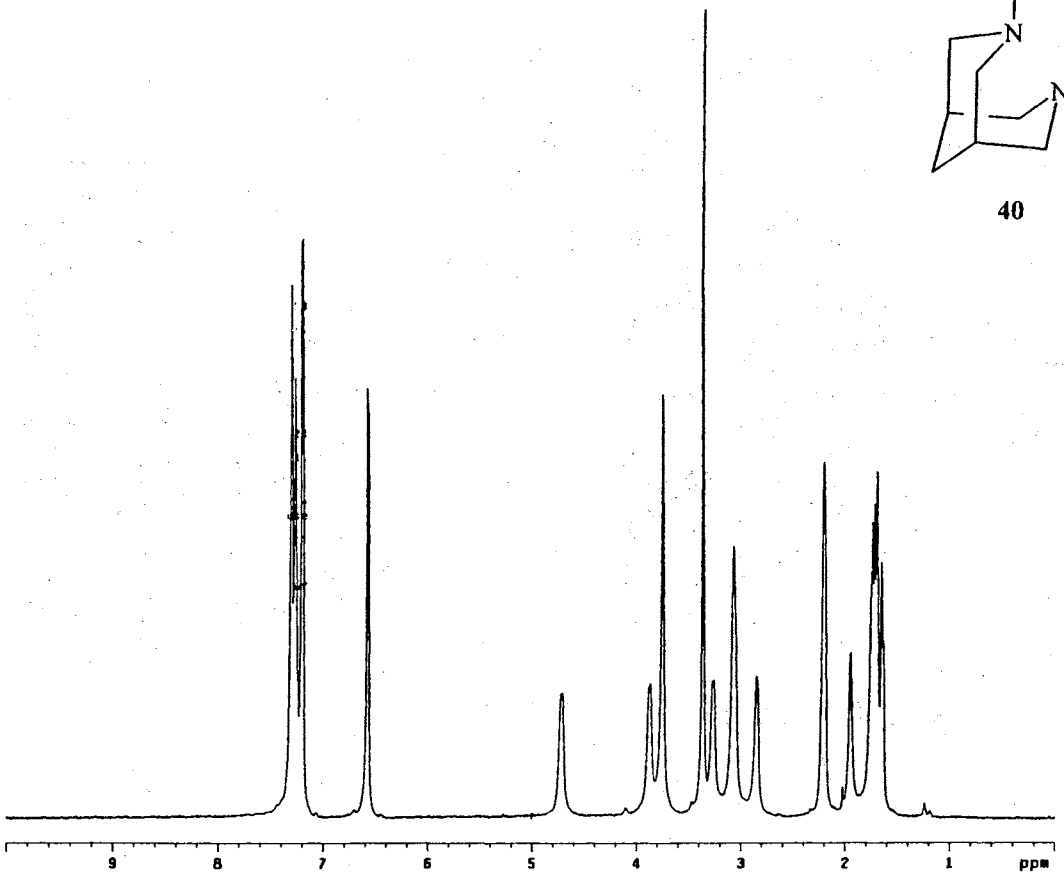


^{13}C NMR Spectrum of **39**

Plate XXXVII

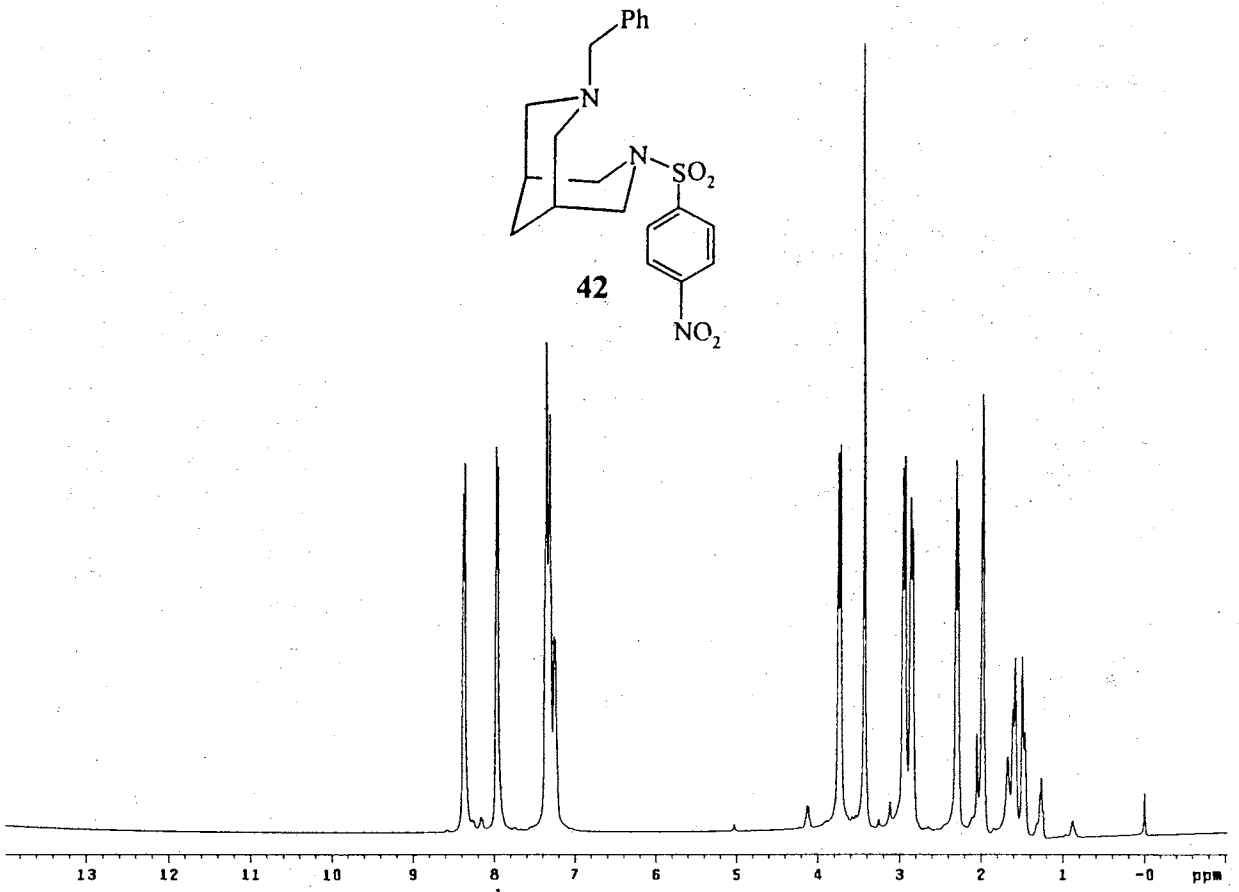


40



^{1}H NMR Spectrum of **40**

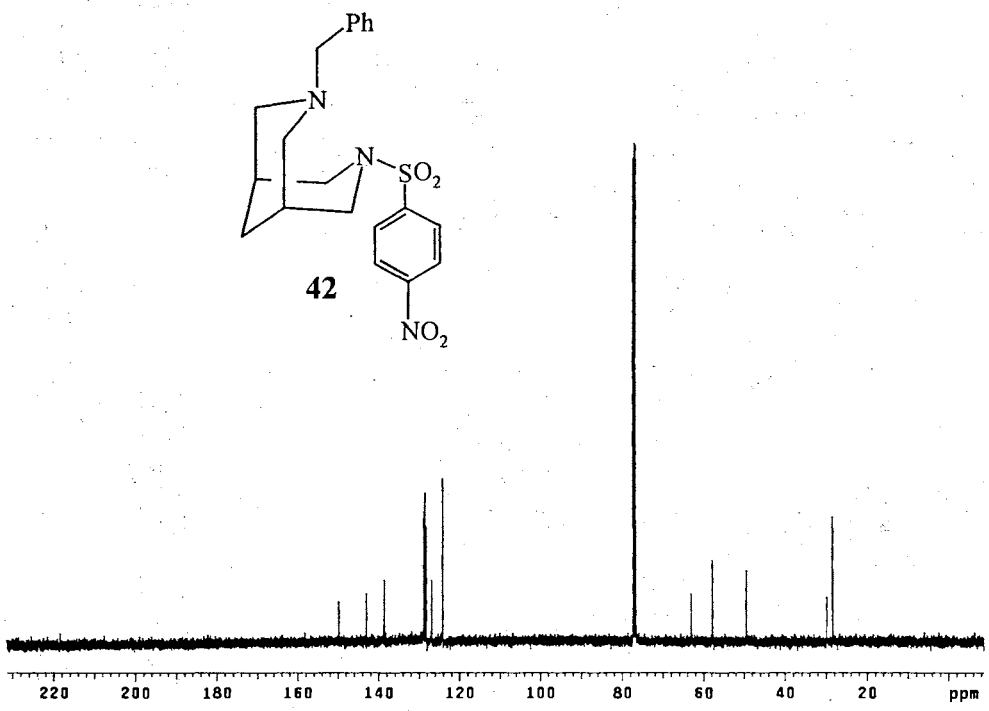
Plate XXXVIII



42

^{1}H NMR Spectrum of **42**

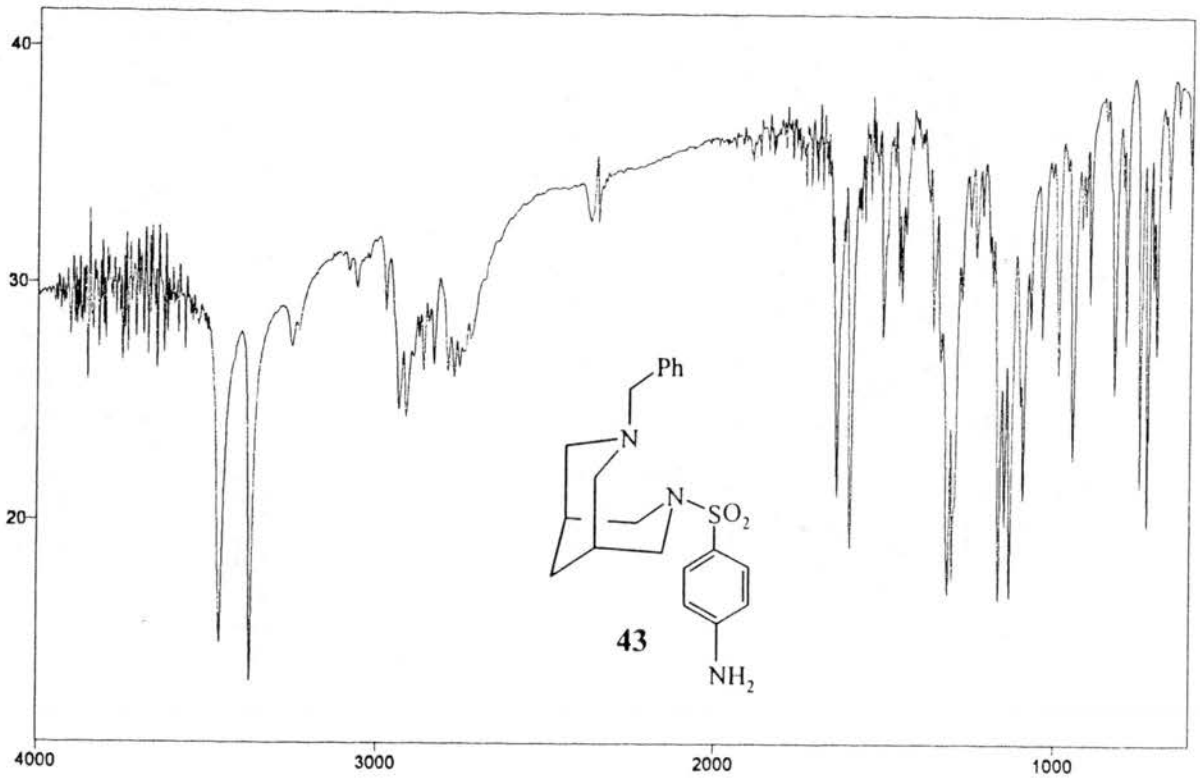
Plate XXXIX



42

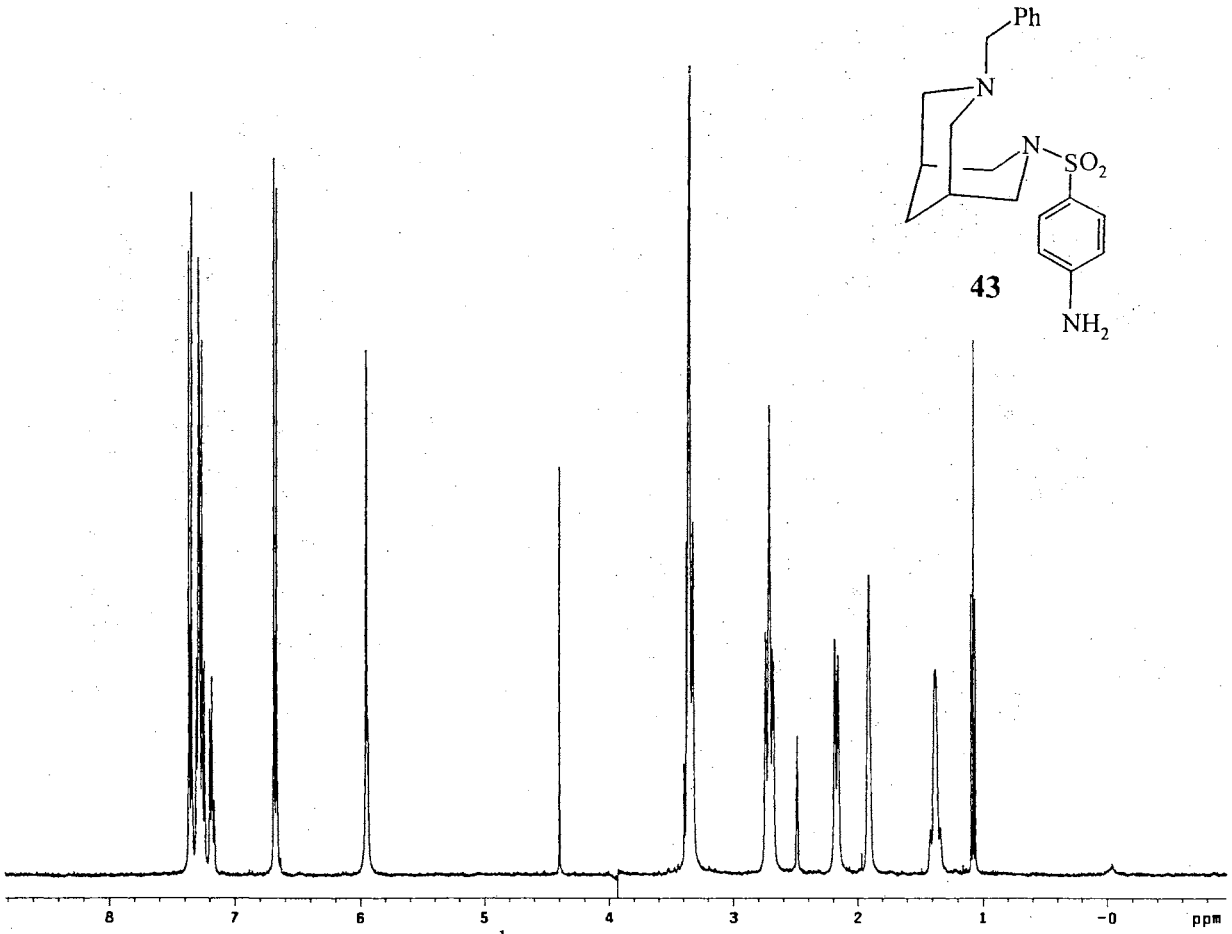
^{13}C NMR Spectrum of **42**

Plate XL



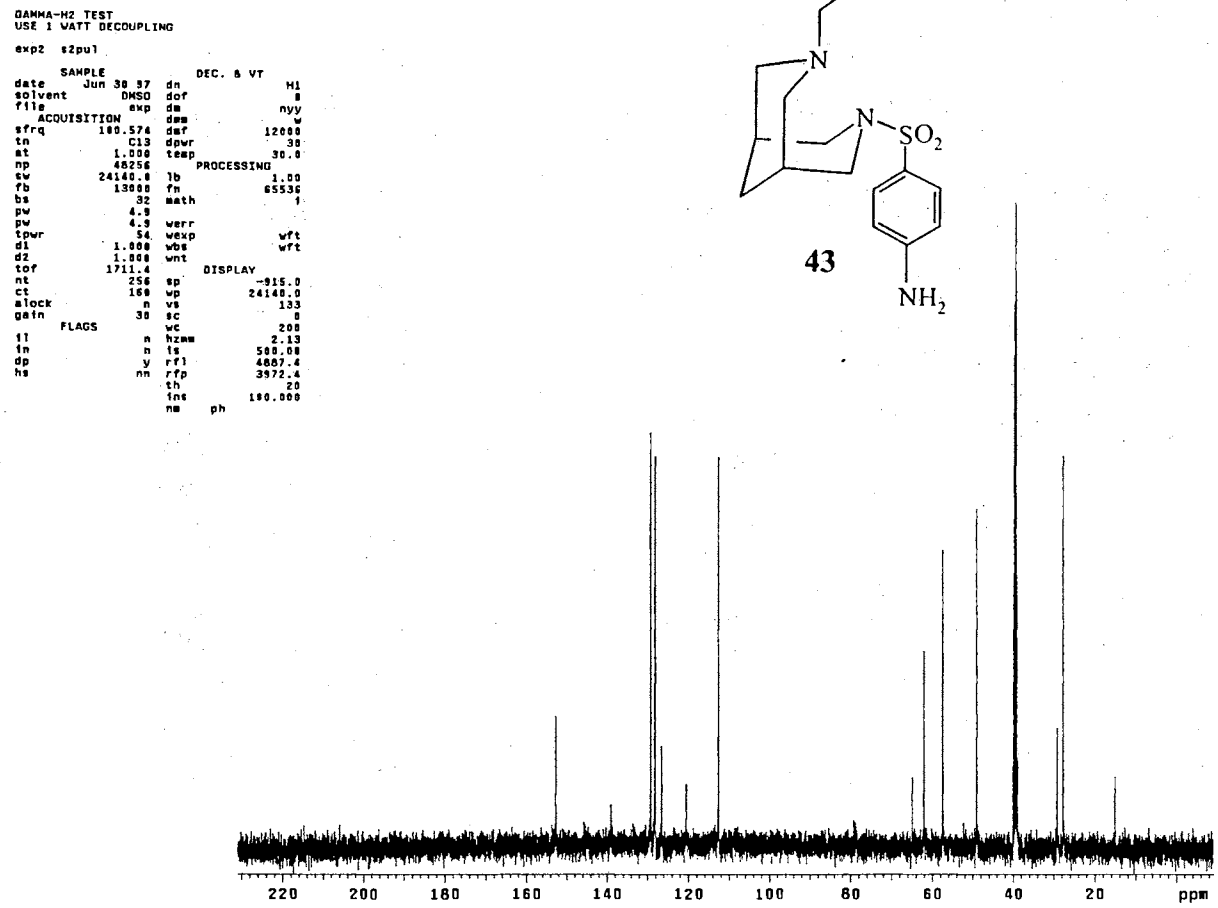
IR Spectrum of **43**

Plate XLI



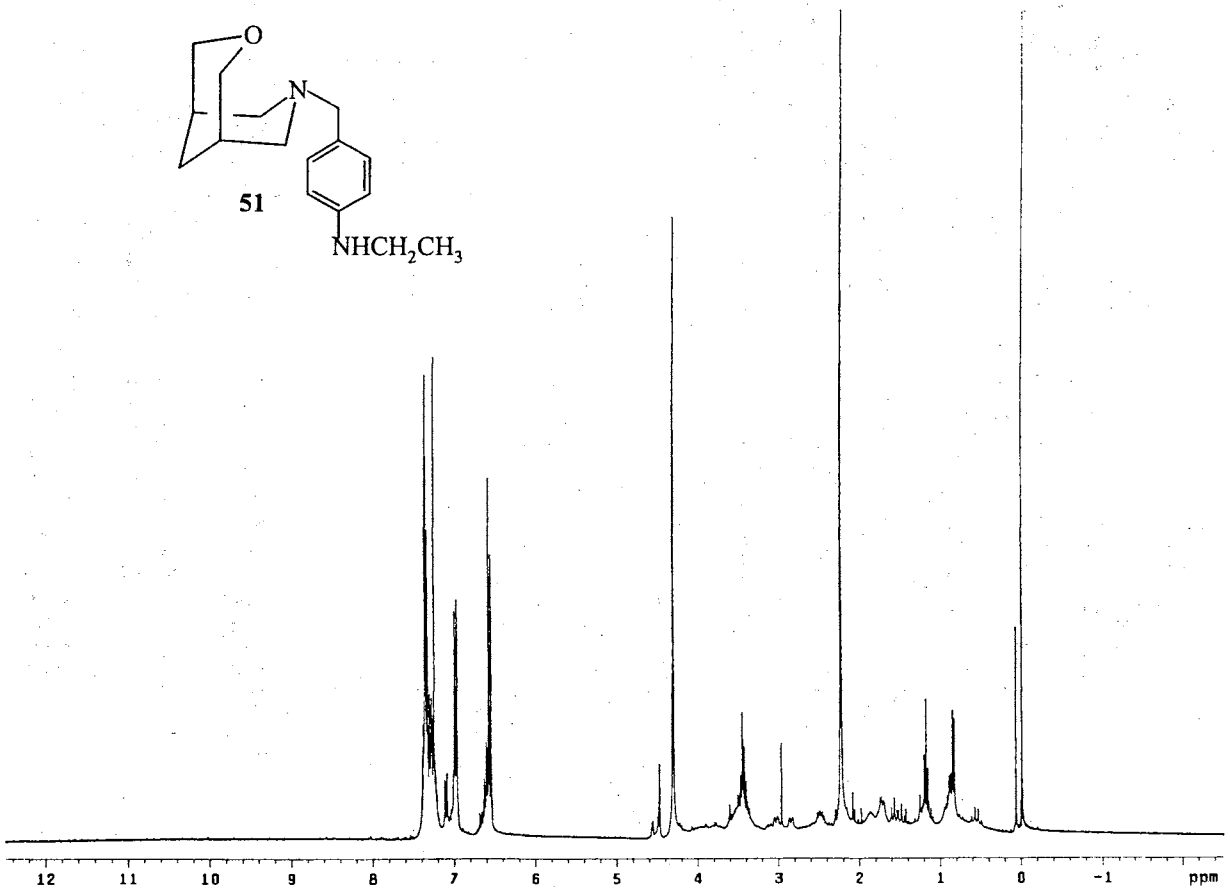
^{1}H NMR Spectrum of **43**

Plate XLII



^{13}C NMR Spectrum of **43**

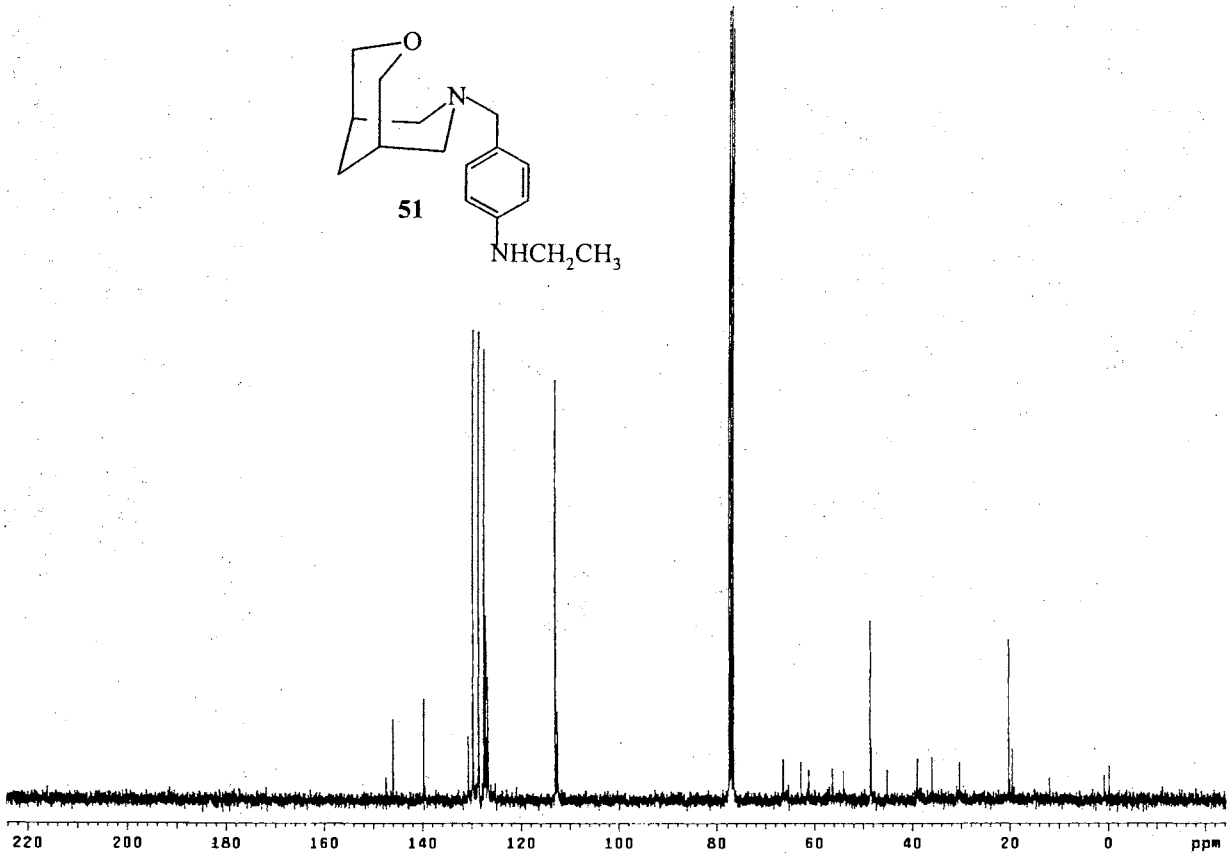
Plate XLIII



51

^{1}H NMR Spectrum of **51**

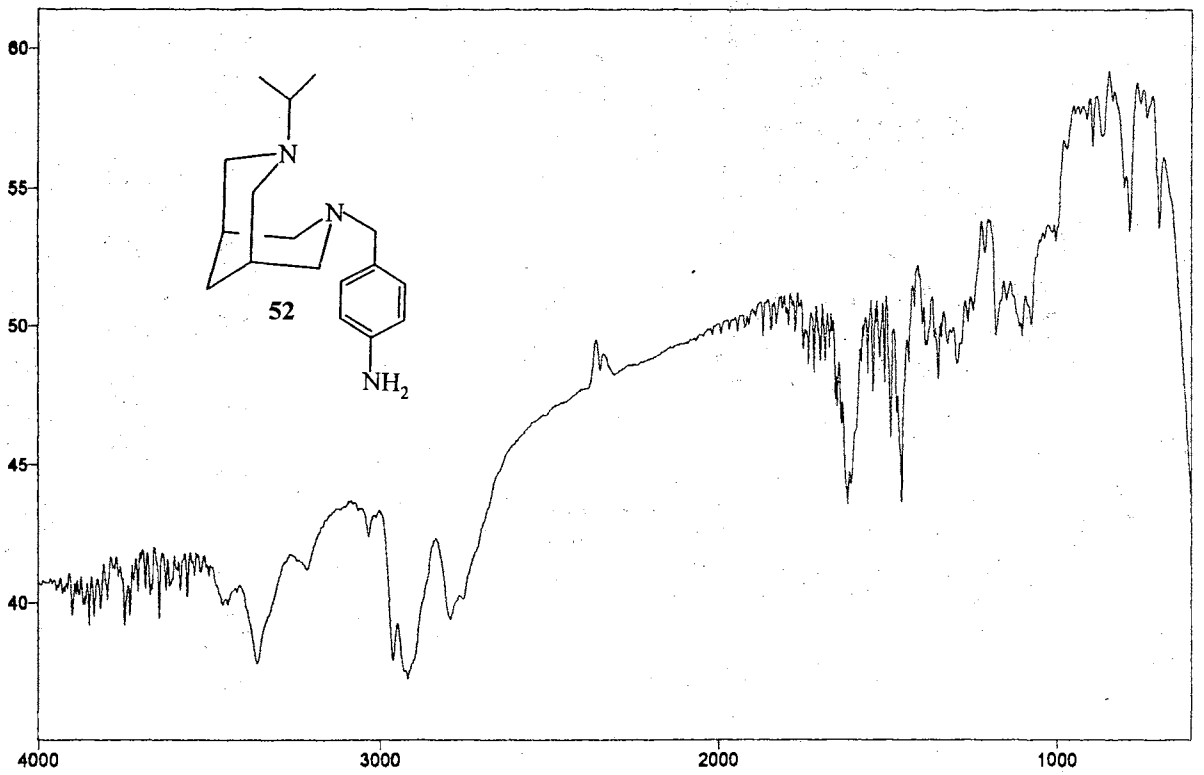
Plate XLIV



51

^{13}C NMR Spectrum of **51**

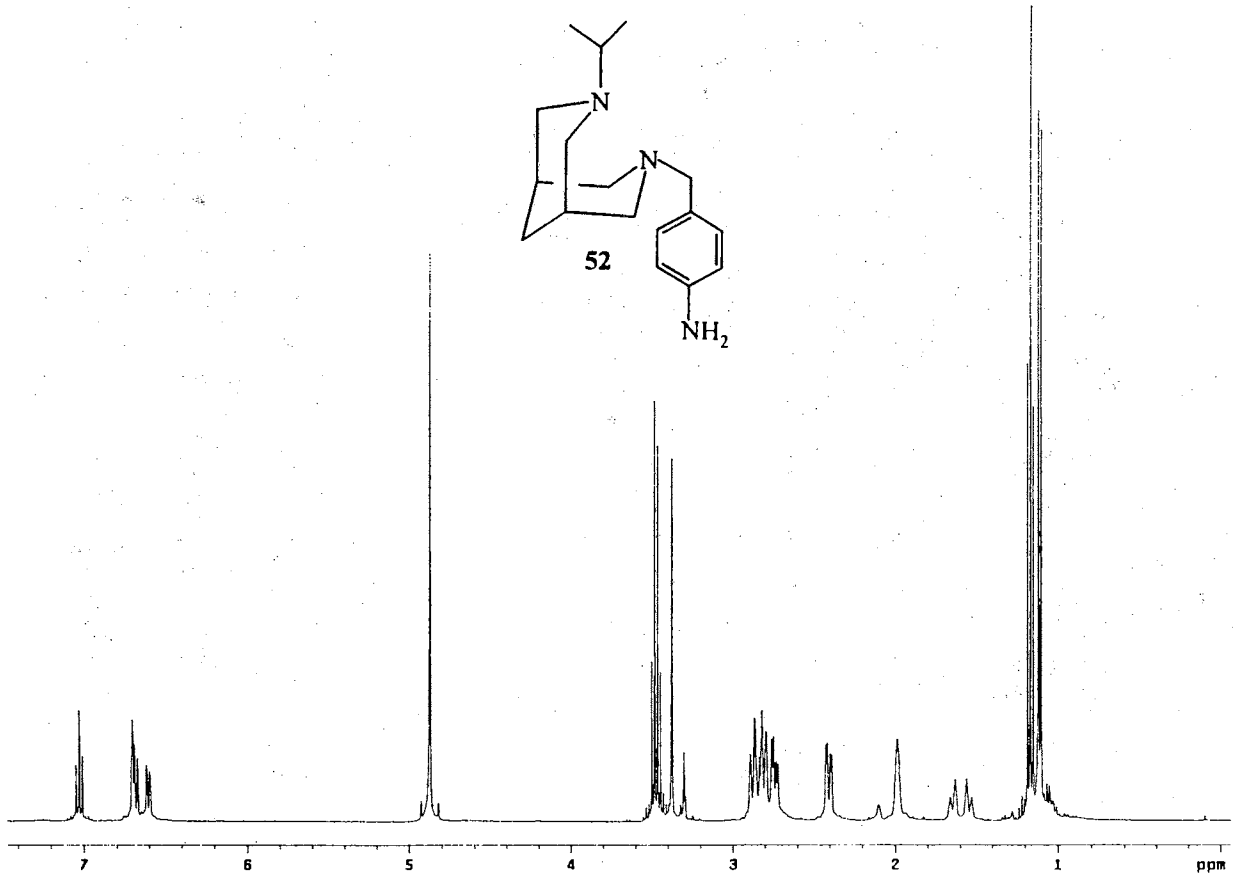
Plate XLV



52

IR Spectrum of **52**

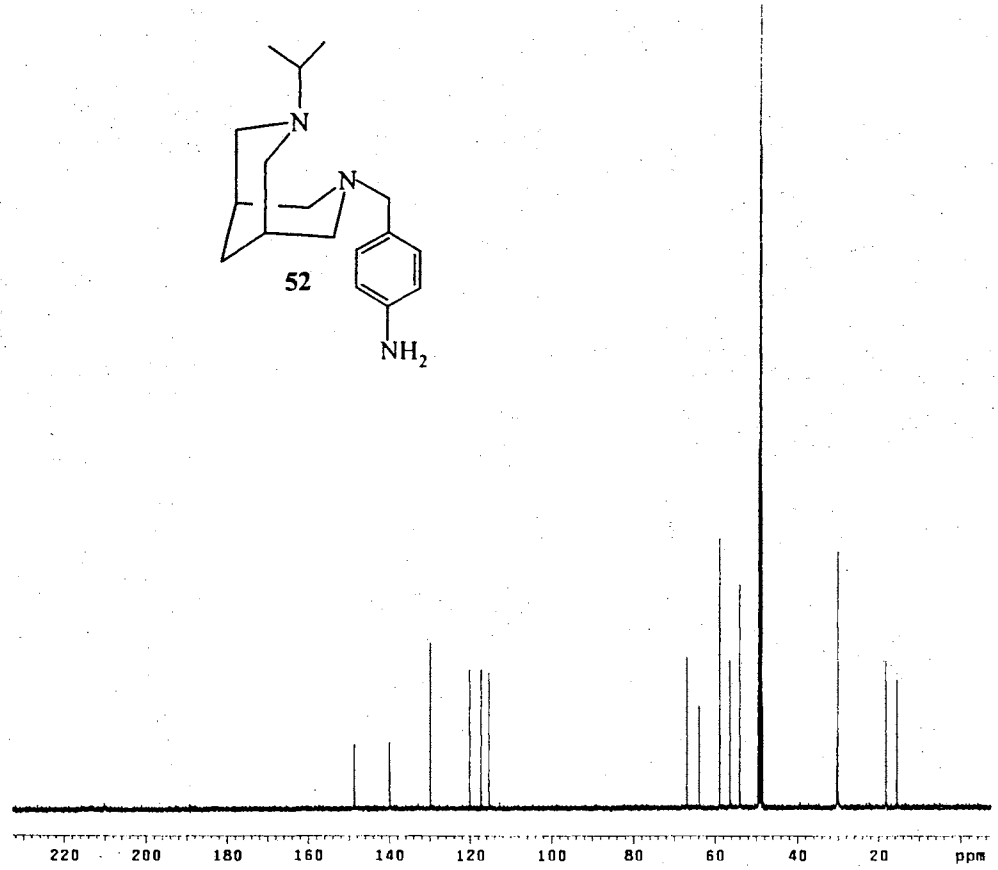
Plate XLVI



52

^{1}H NMR Spectrum of **52**

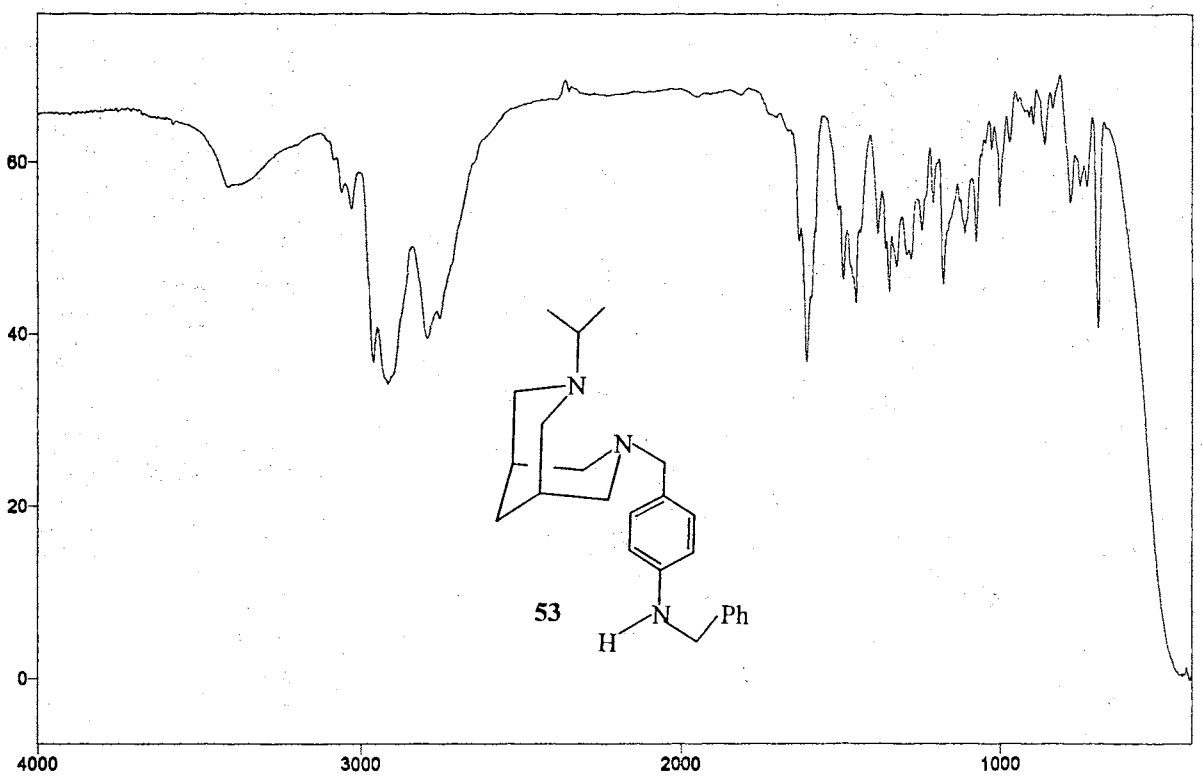
Plate XLVII



52

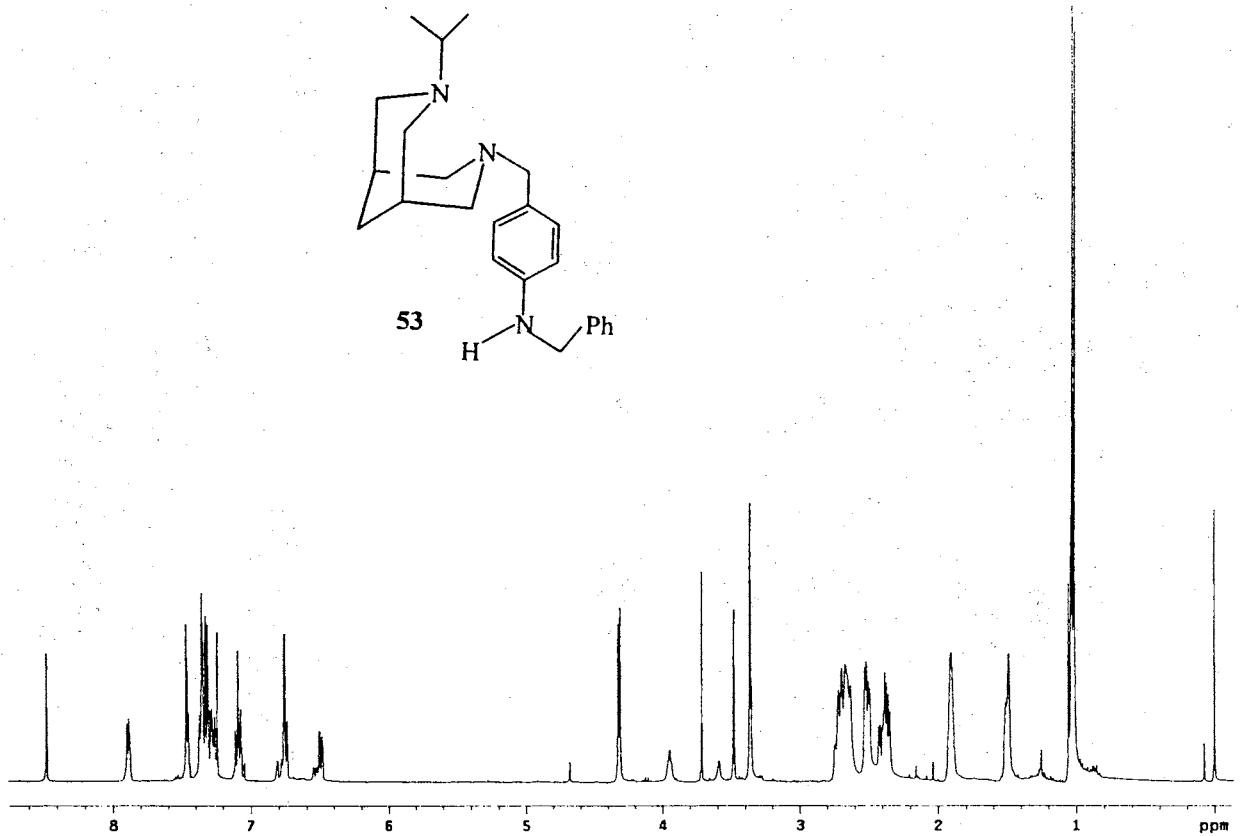
^{13}C NMR Spectrum of **52**

Plate XLVIII



IR Spectrum of **53**

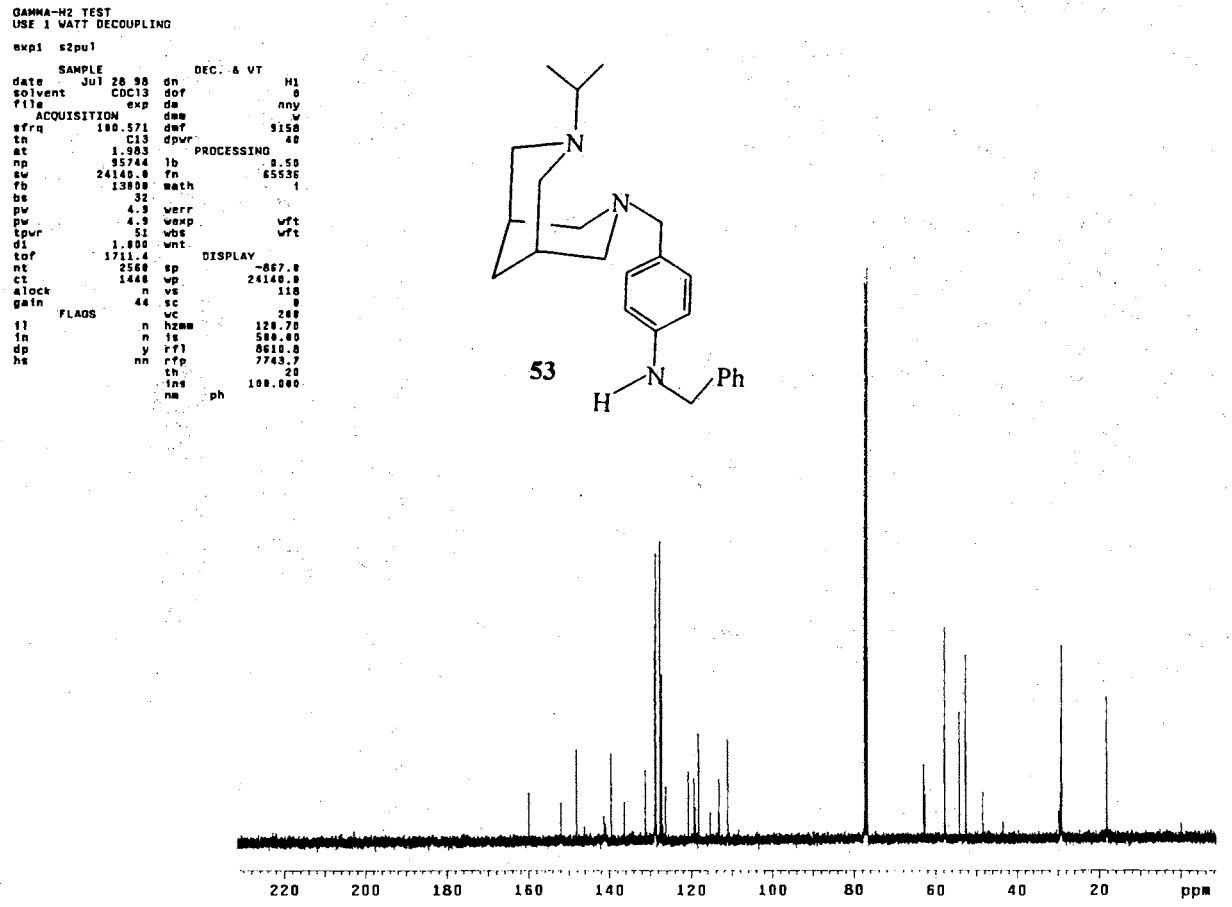
Plate XLIX



53

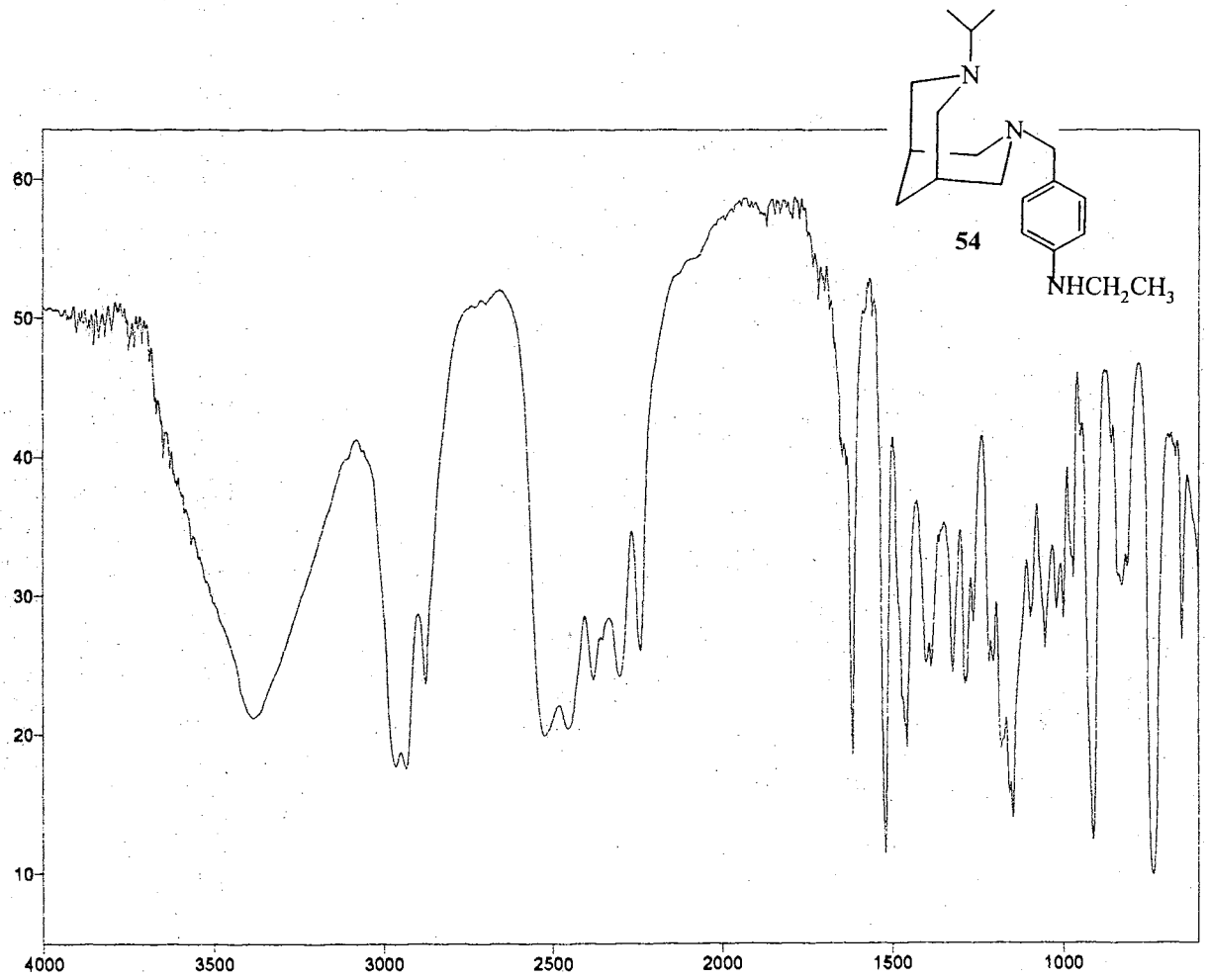
^{1}H NMR Spectrum of **53**

Plate L



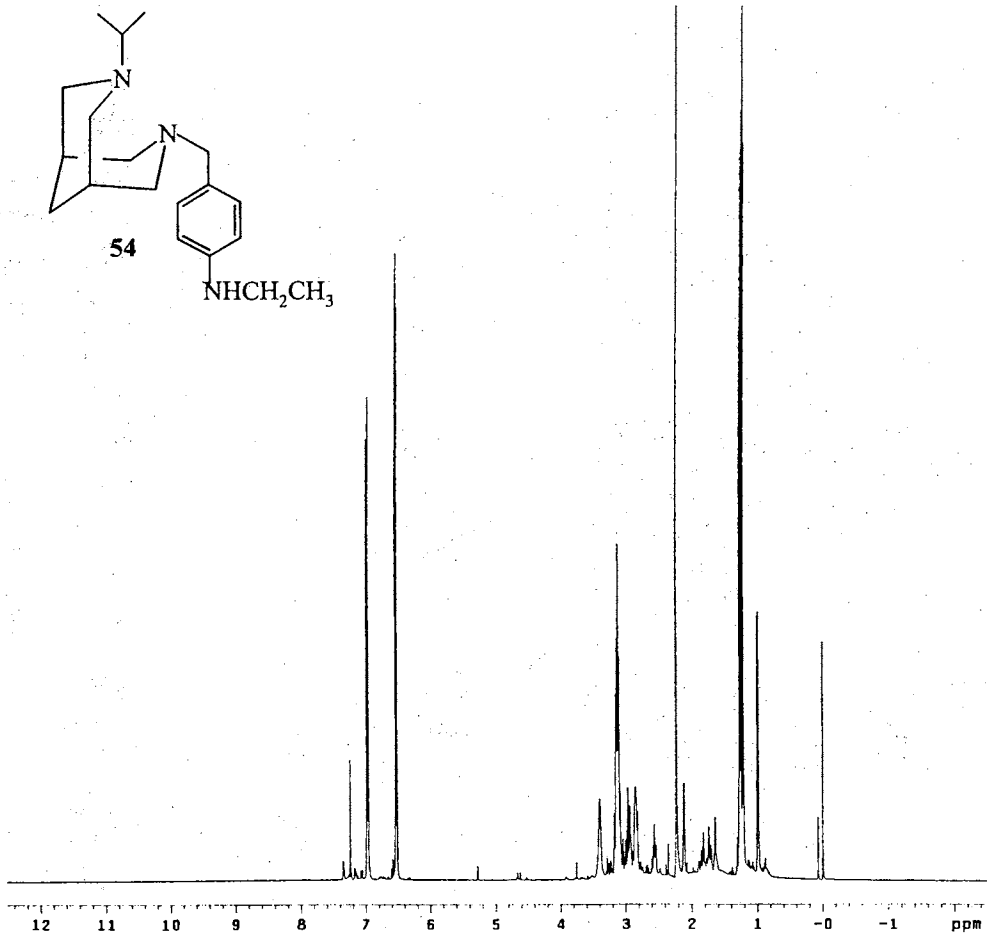
^{13}C NMR Spectrum of **53**

Plate LI



IR Spectrum of **54**

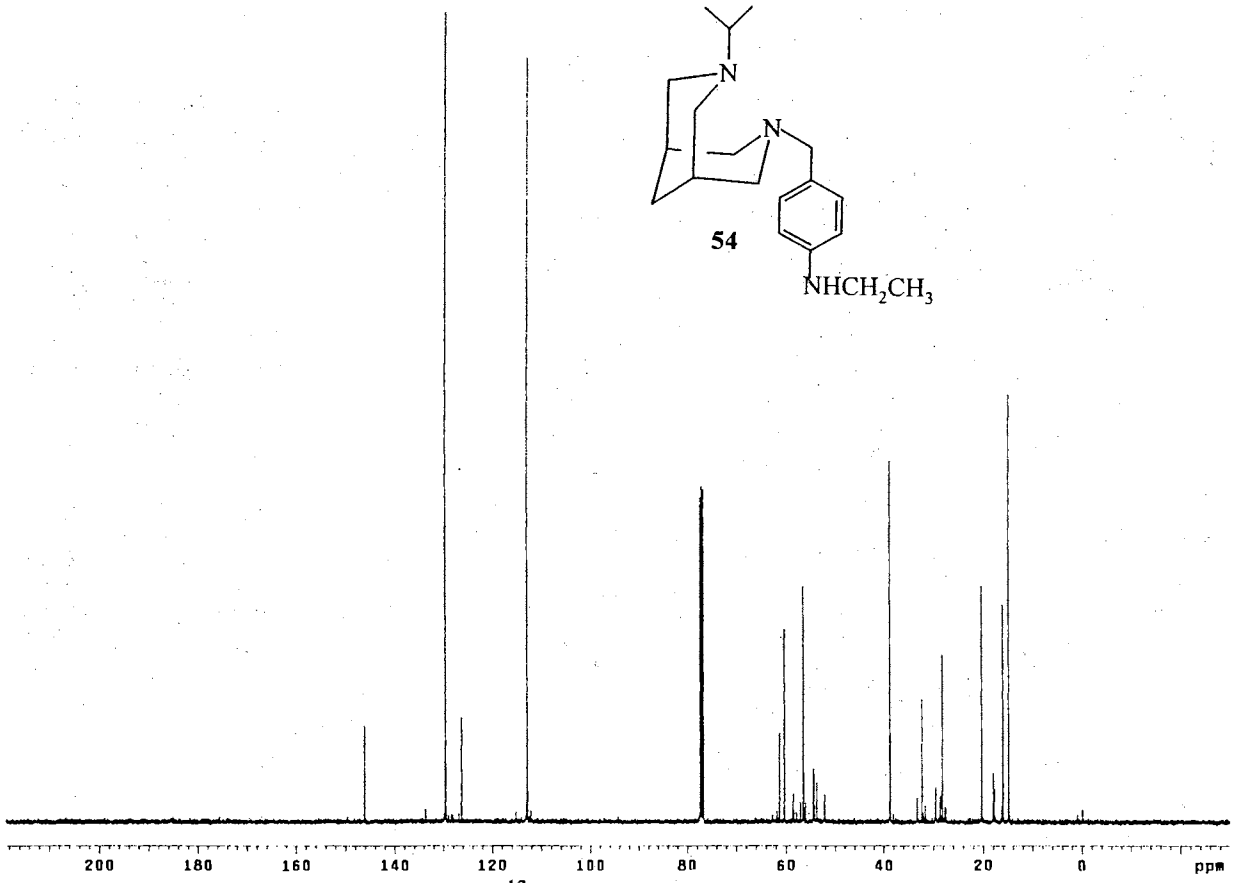
Plate LII



54

^{1}H NMR Spectrum of **54**

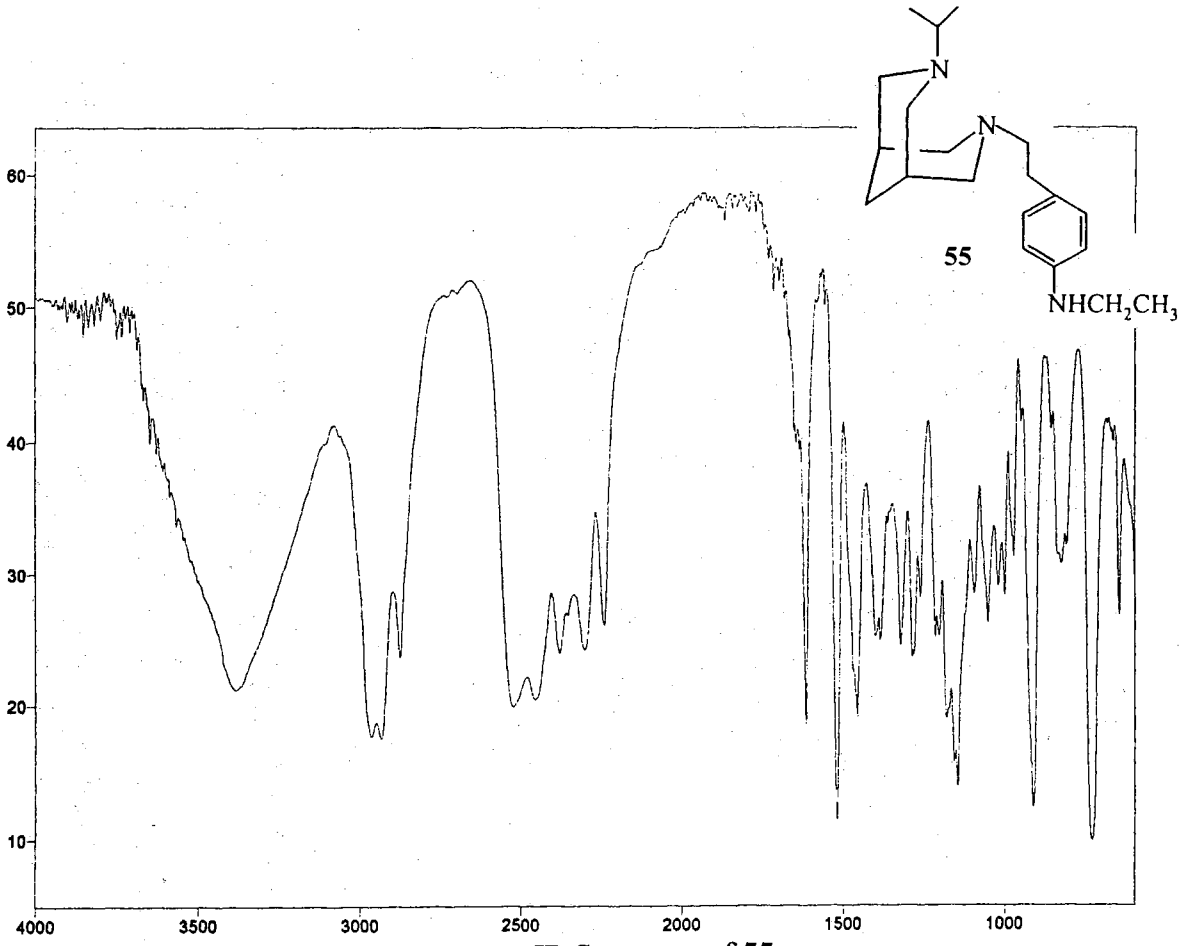
Plate LIII



54

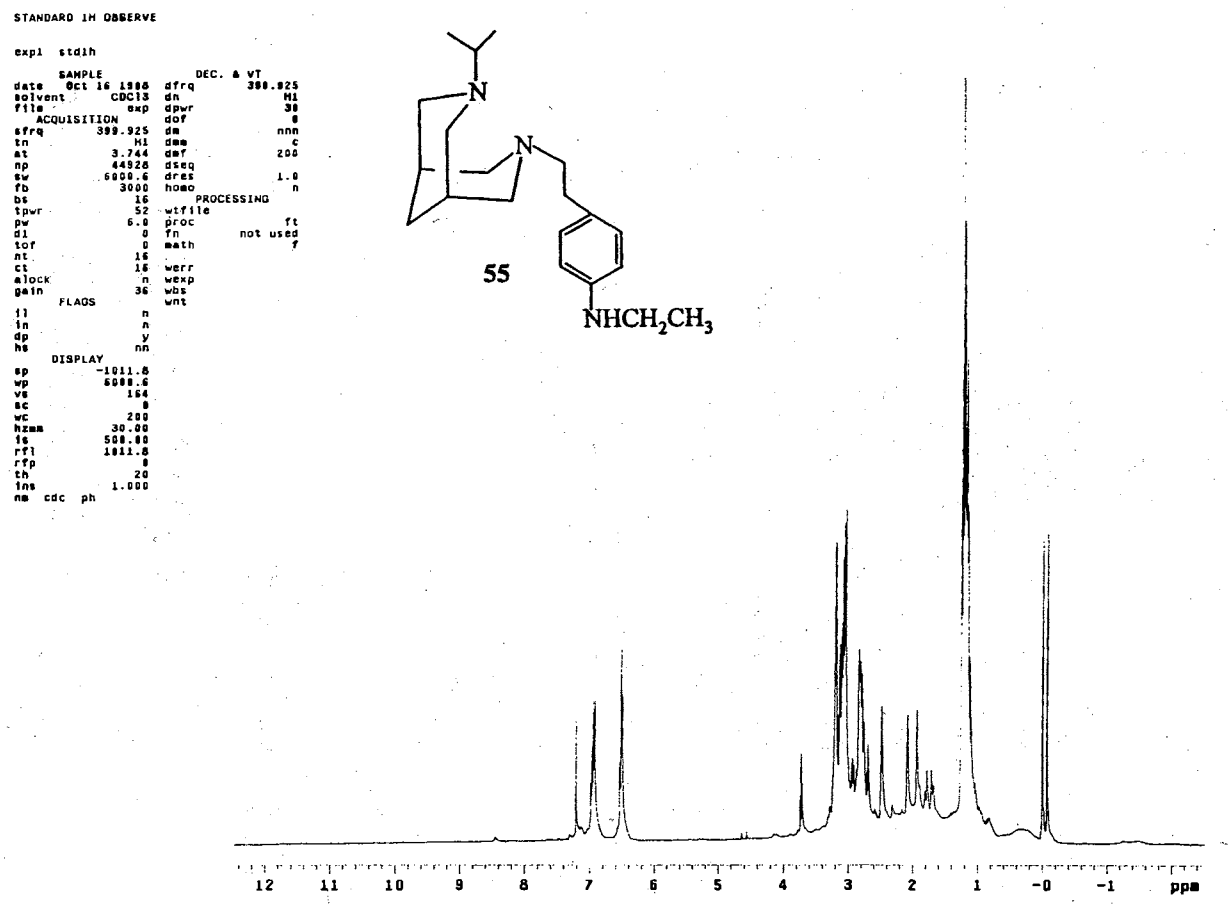
^{13}C NMR Spectrum of **54**

Plate LIV



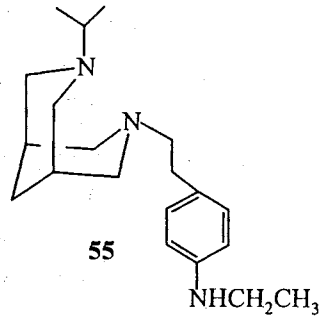
IR Spectrum of **55**

Plate LV



^{1}H NMR Spectrum of **55**

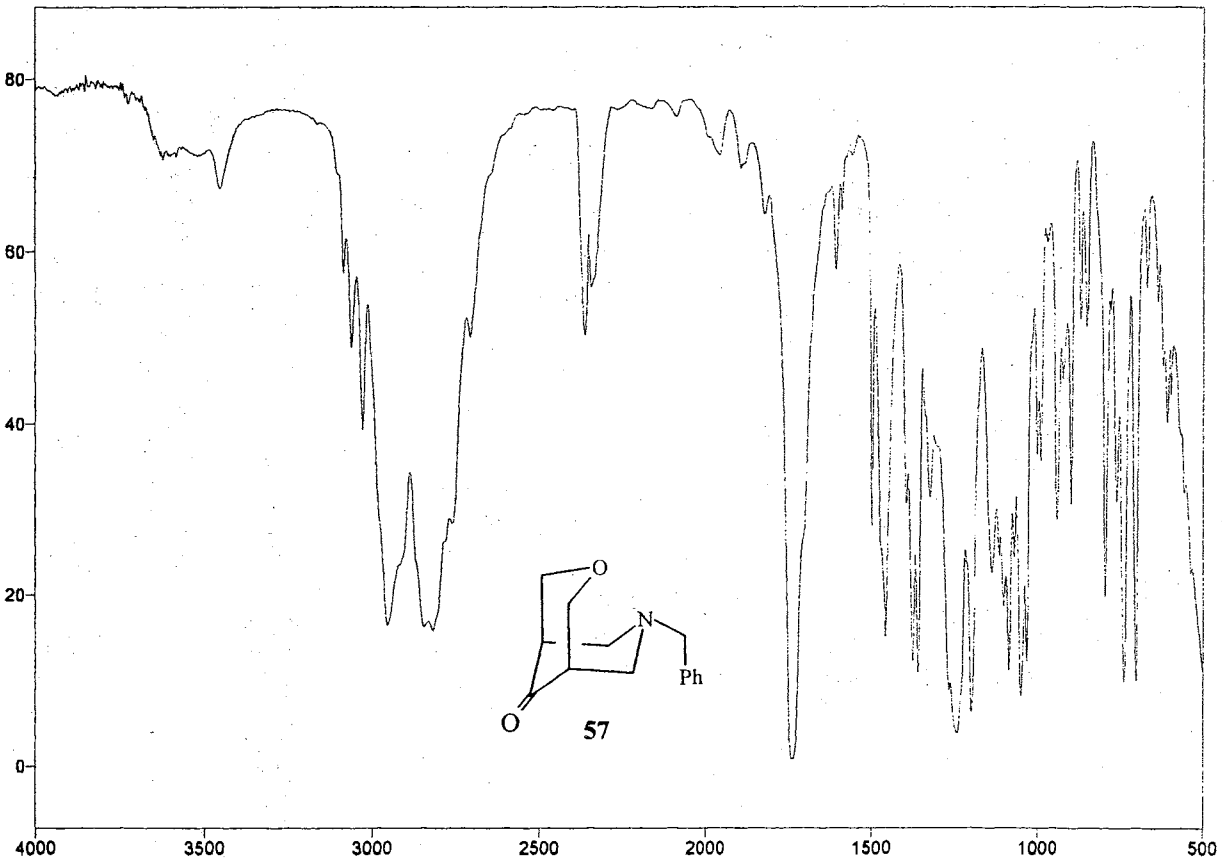
Plate LVI



55

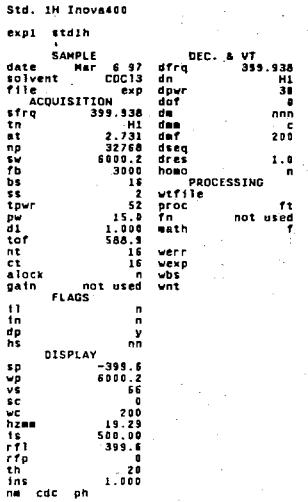
^{13}C NMR Spectrum of **55**

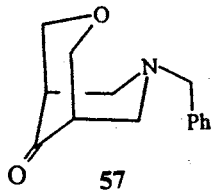
Plate LVII



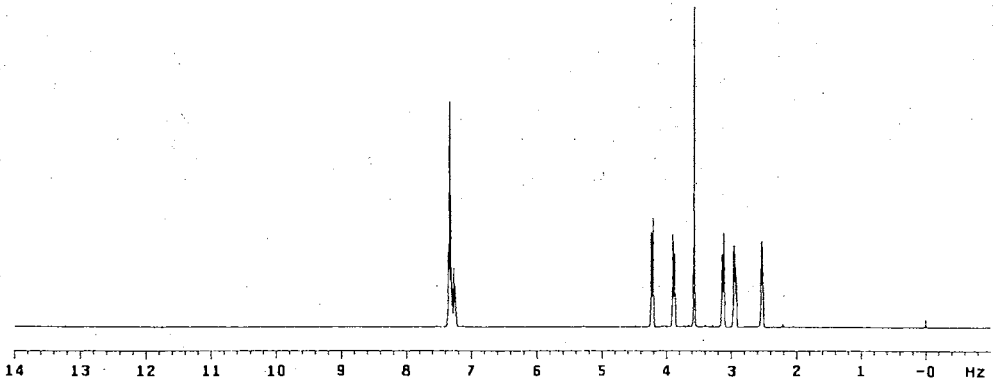
IR Spectrum of **57**

Plate LVIII



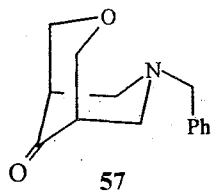


57

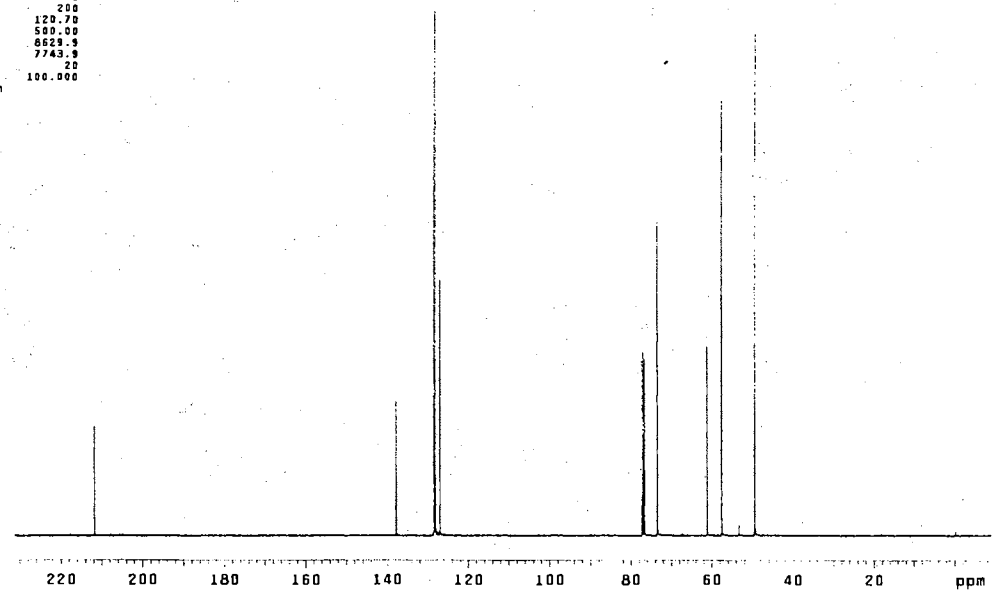


^{1}H NMR Spectrum of **57**

```
GAMMA-H2 TEST
USE 1 WATT DECOUPLING

exp1  s2pul

        SAMPLE                  DEC. & VT
date      Oct 24 97     dn                H1
solvent       CDCl3     dof                0
file           exp      dm               nny
   ACQUISITION          dmm                w
sfrq       100.573      dmf             9158
tn              C13     dpwr              40
at            1.983          PROCESSING
np           95744     lb              0.50
sw         24140.8     fn             65536
fb           13000     math              t
bs              32
pw             4.9     werr
pw             4.9     wexp             wft
tpwr            51     wbs              wft
d1          1.000      wnt
tof        1711.4           DISPLAY
nt           2560      sp             -886.0
ct           1536      wp            24140.0
alock           n      vs               109
gain           44      sc                 0
       FLAGS           wc               200
fl              n      hzmm          120.70
in              n      is            500.00
dp              y      rf1           8629.9
hs             nn      rfp           7743.9
                       th                20
                       ins           100.000
                       nm    ph
```

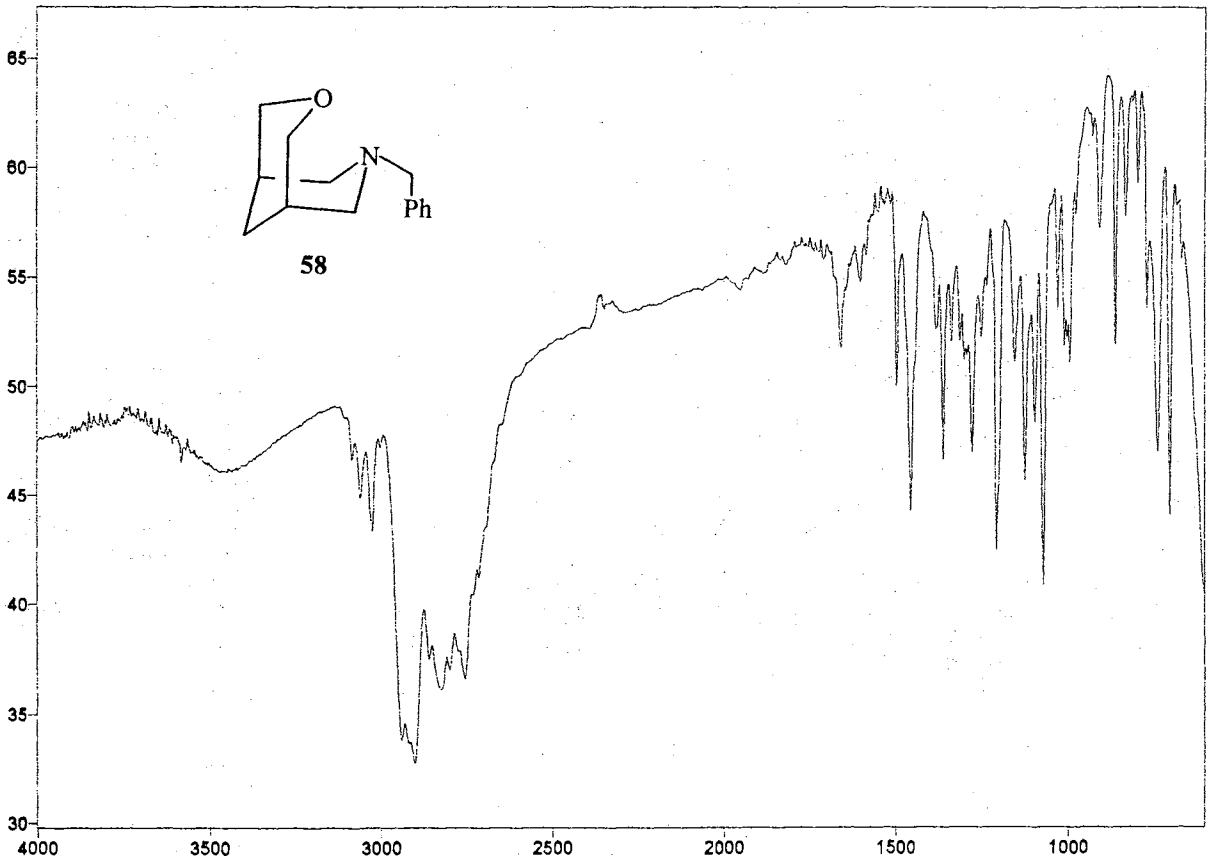


57



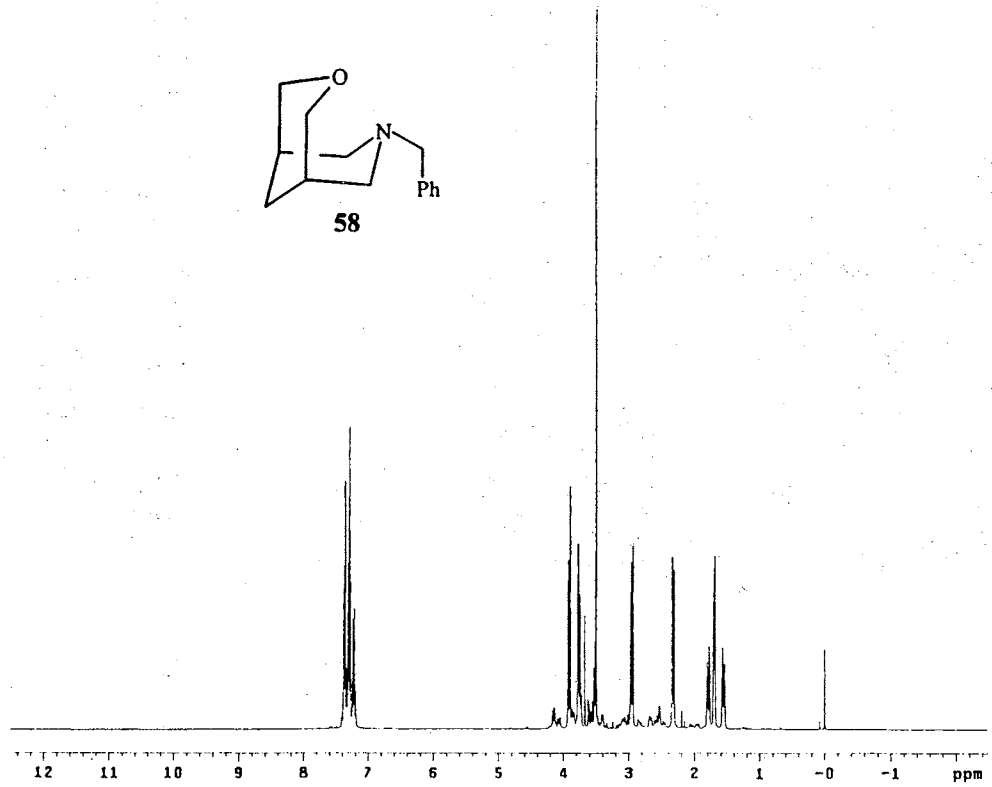
^{13}C NMR Spectrum of **57**

Plate LX



IR Spectrum of **58**

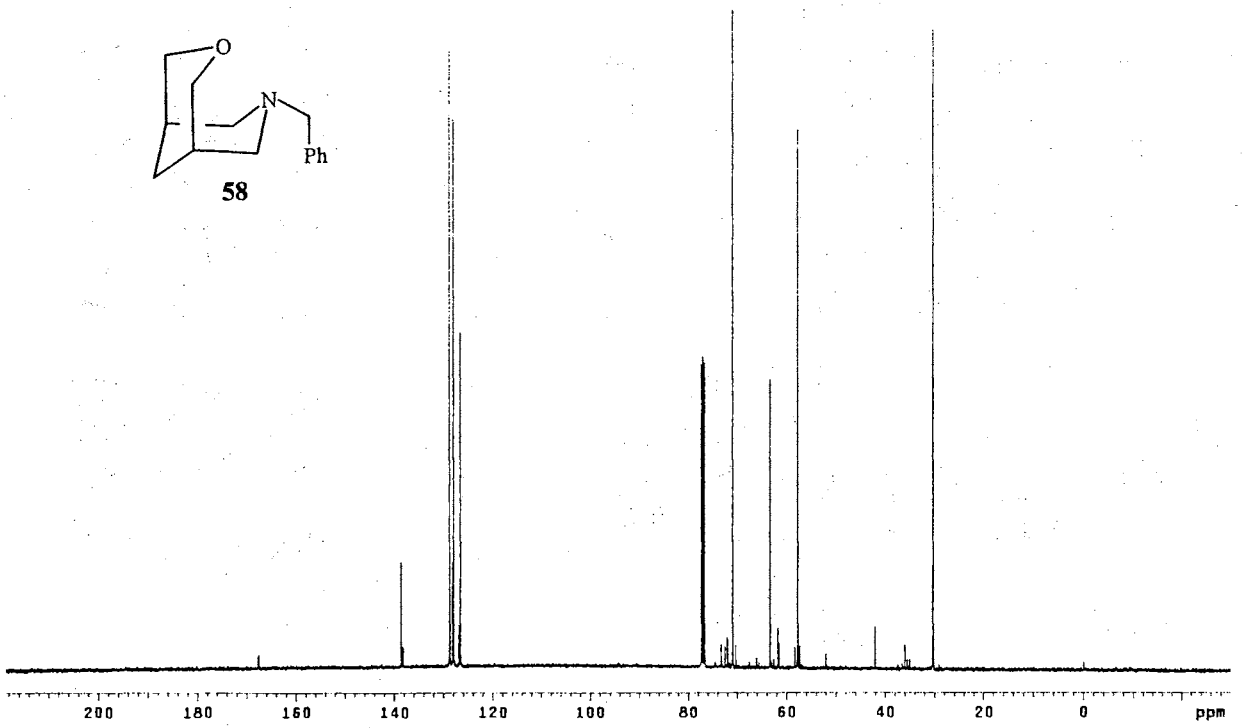
Plate LXI



58

^{1}H NMR Spectrum of **58**

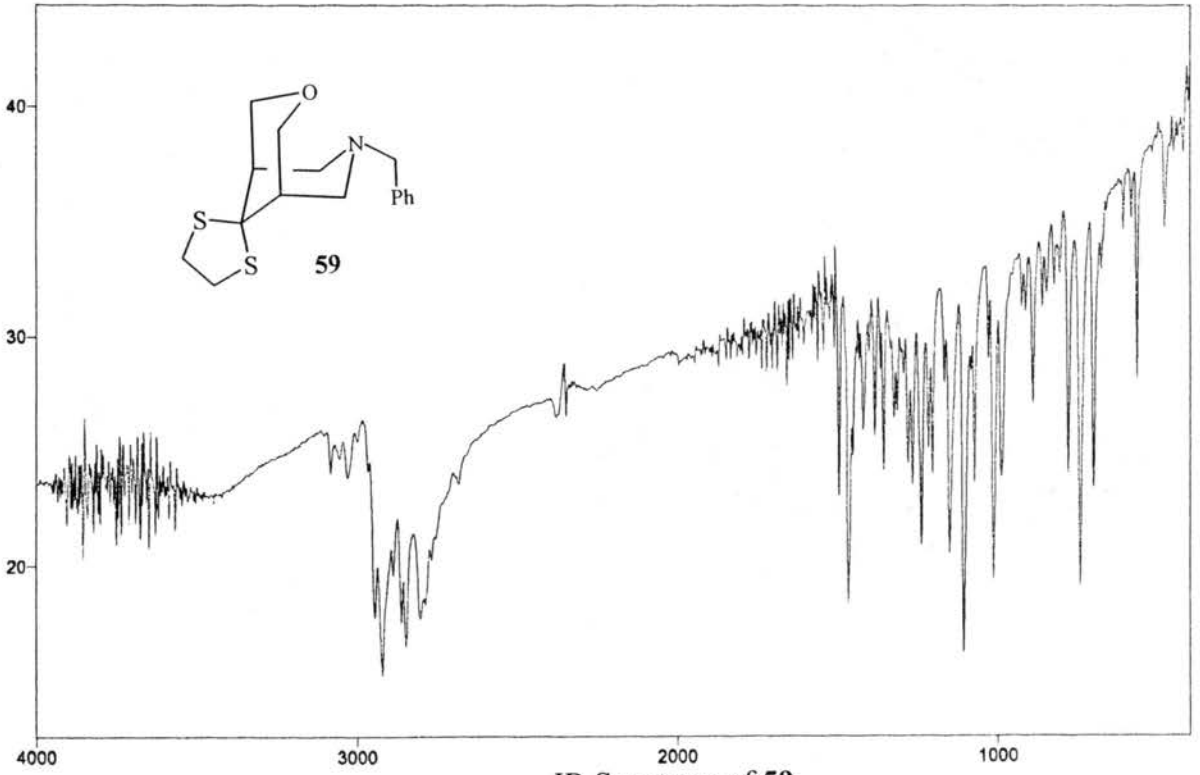
Plate LXII



58

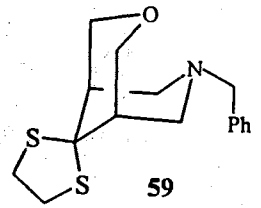
^{13}C NMR Spectrum of **58**

Plate LXIII



IR Spectrum of **59**

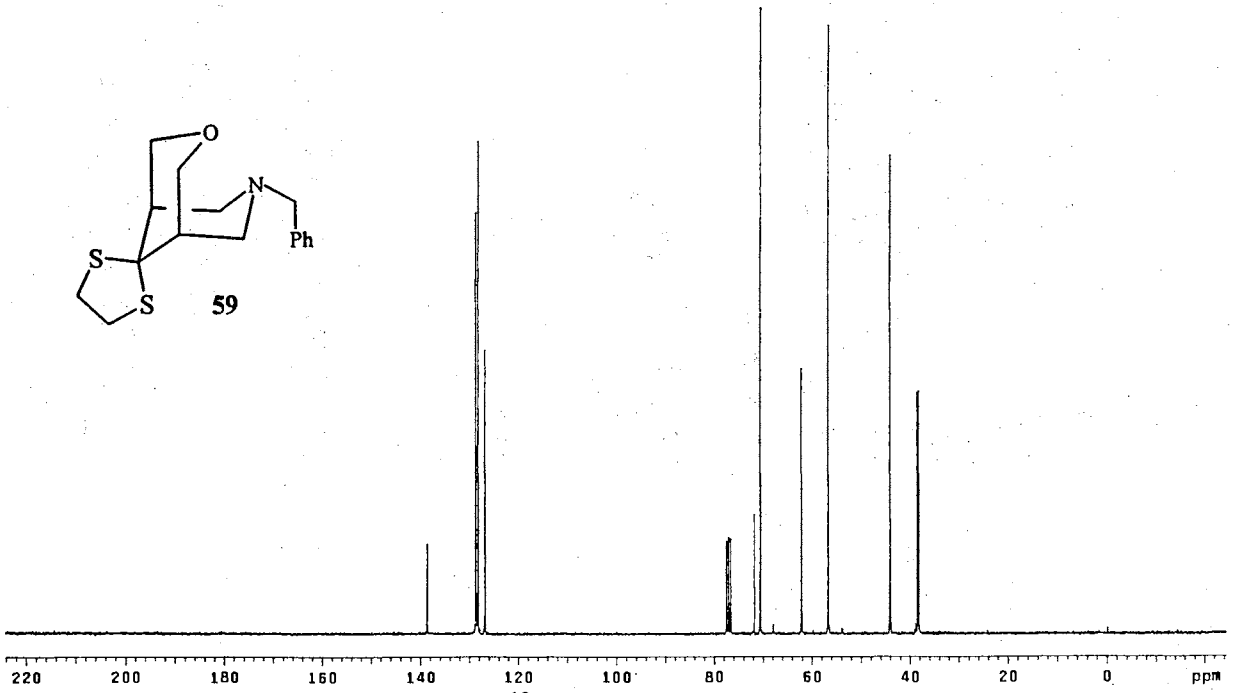
Plate LXIV



59

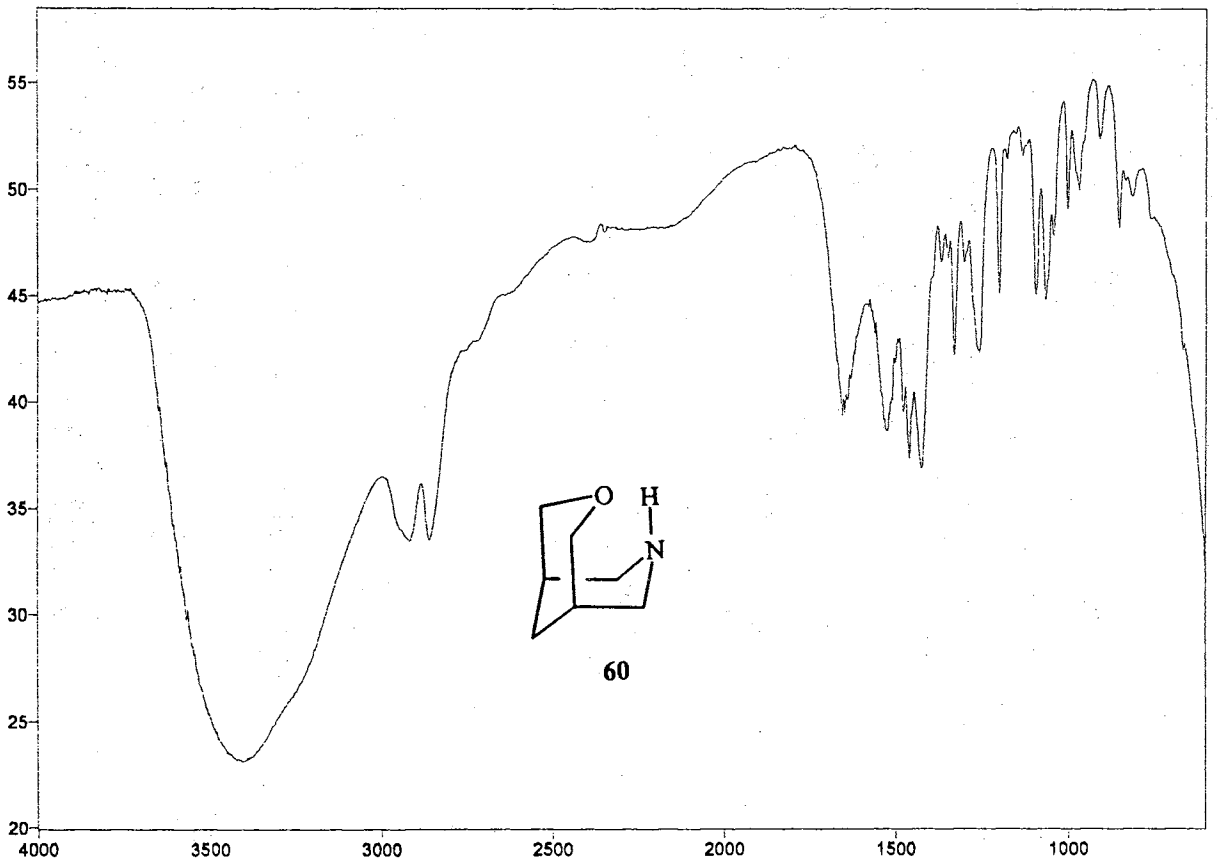
^{1}H NMR Spectrum of **59**

Plate LXV



^{13}C NMR Spectrum of **59**

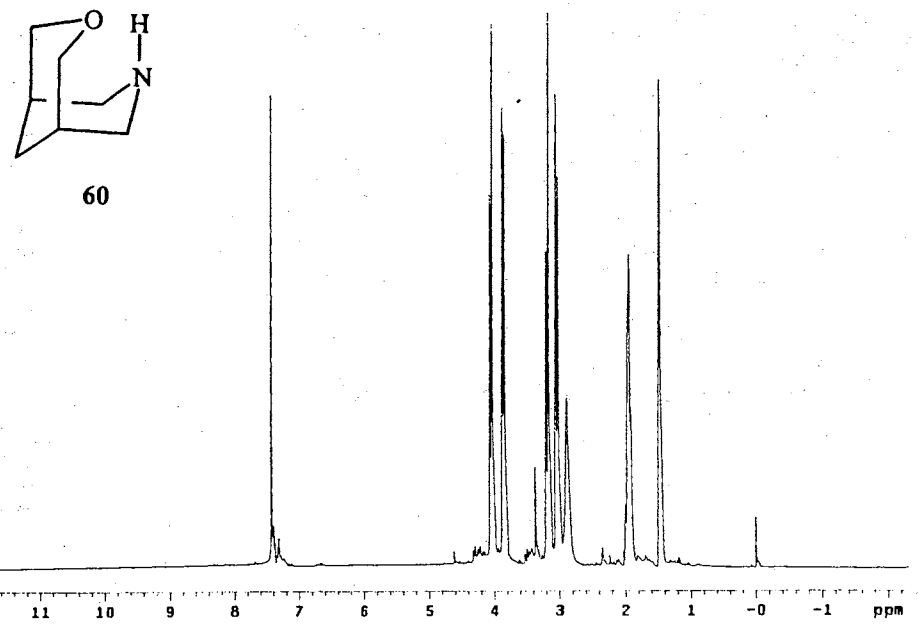
Plate LXVI



60

IR Spectrum of **60**

Plate LXVII



60

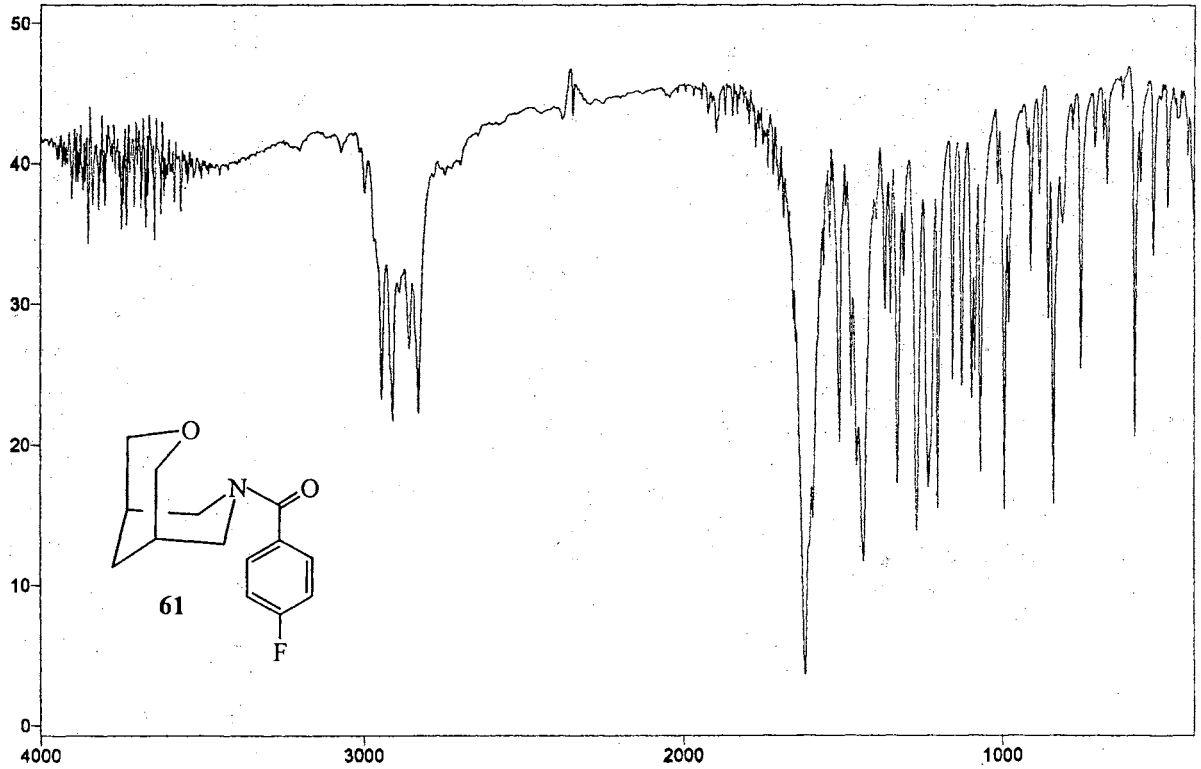
^{1}H NMR Spectrum of **60**

Plate LXVIII

60

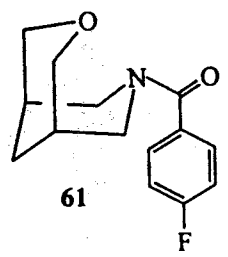
^{13}C NMR Spectrum of **60**

Plate LXIX



IR Spectrum of **61**

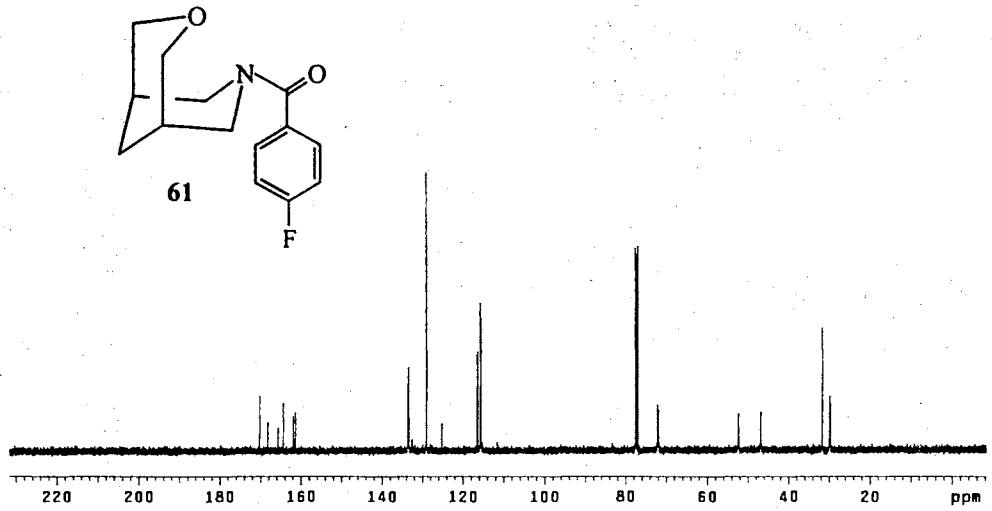
plate LXX



61

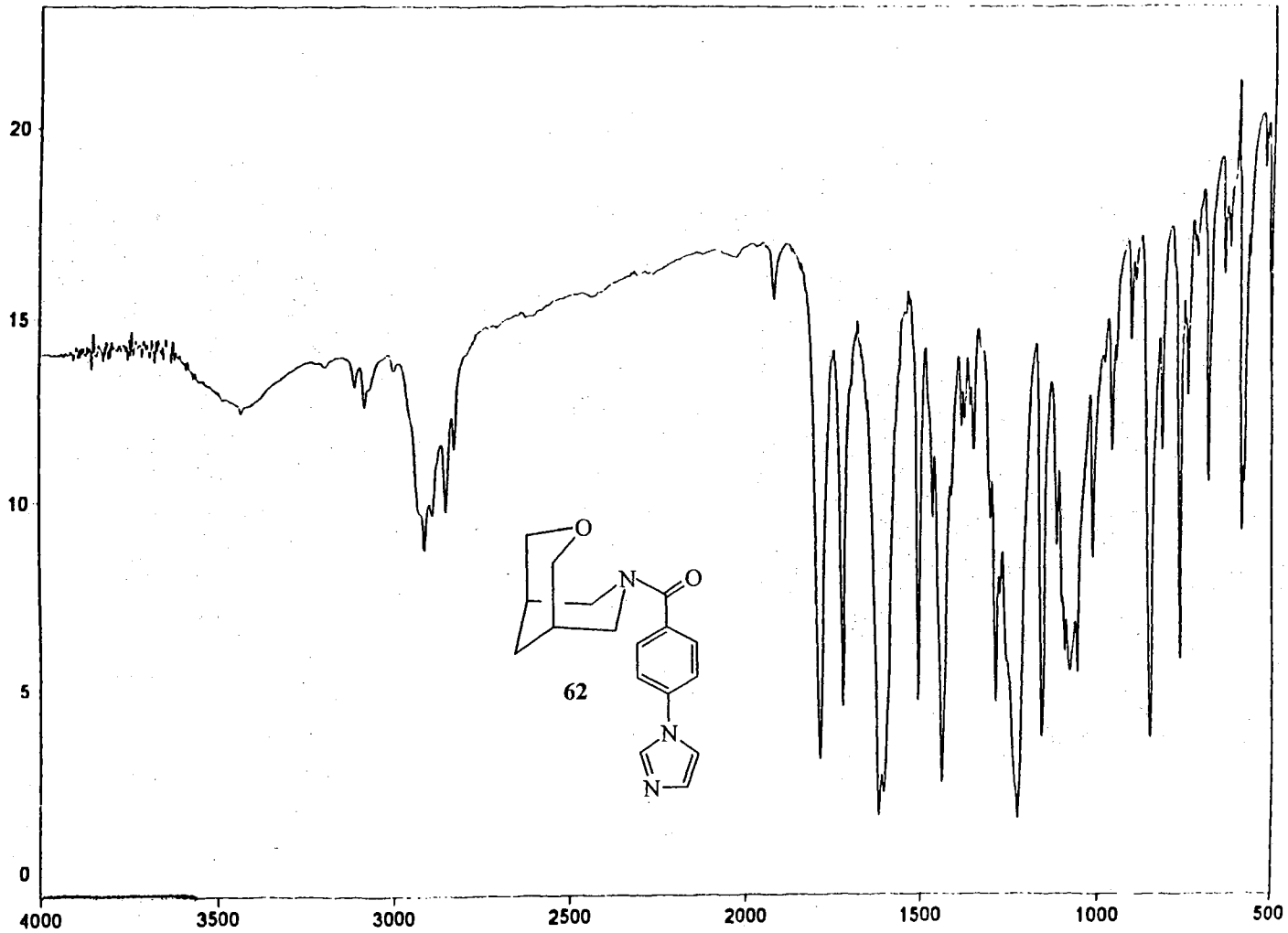
^{1}H NMR Spectrum of **61**

Plate LXXI



^{13}C NMR Spectrum of **61**

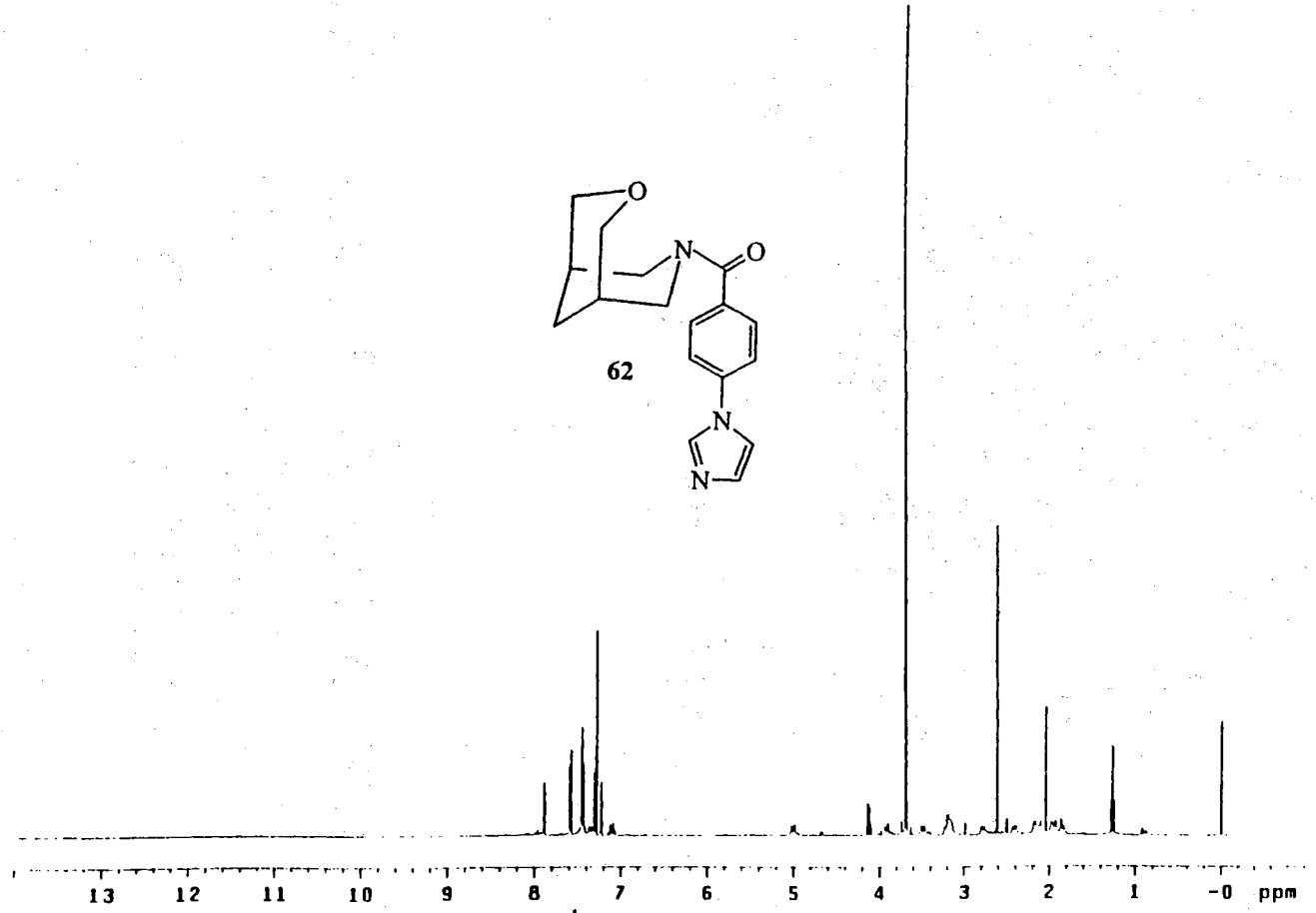
Plate LXXII



62

IR Spectrum of **62**

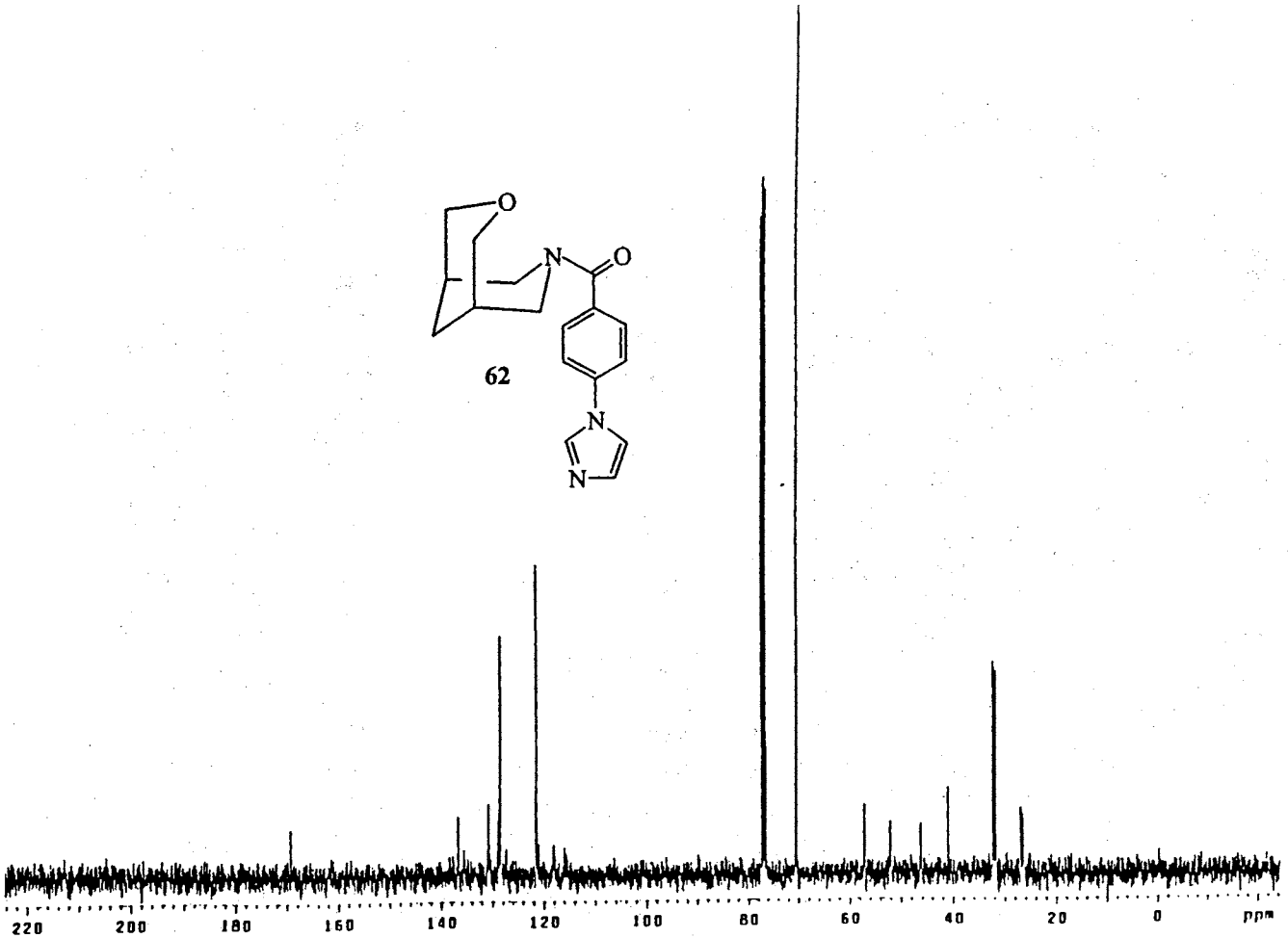
Plate LXXIII



62

^{1}H NMR Spectrum of **62**

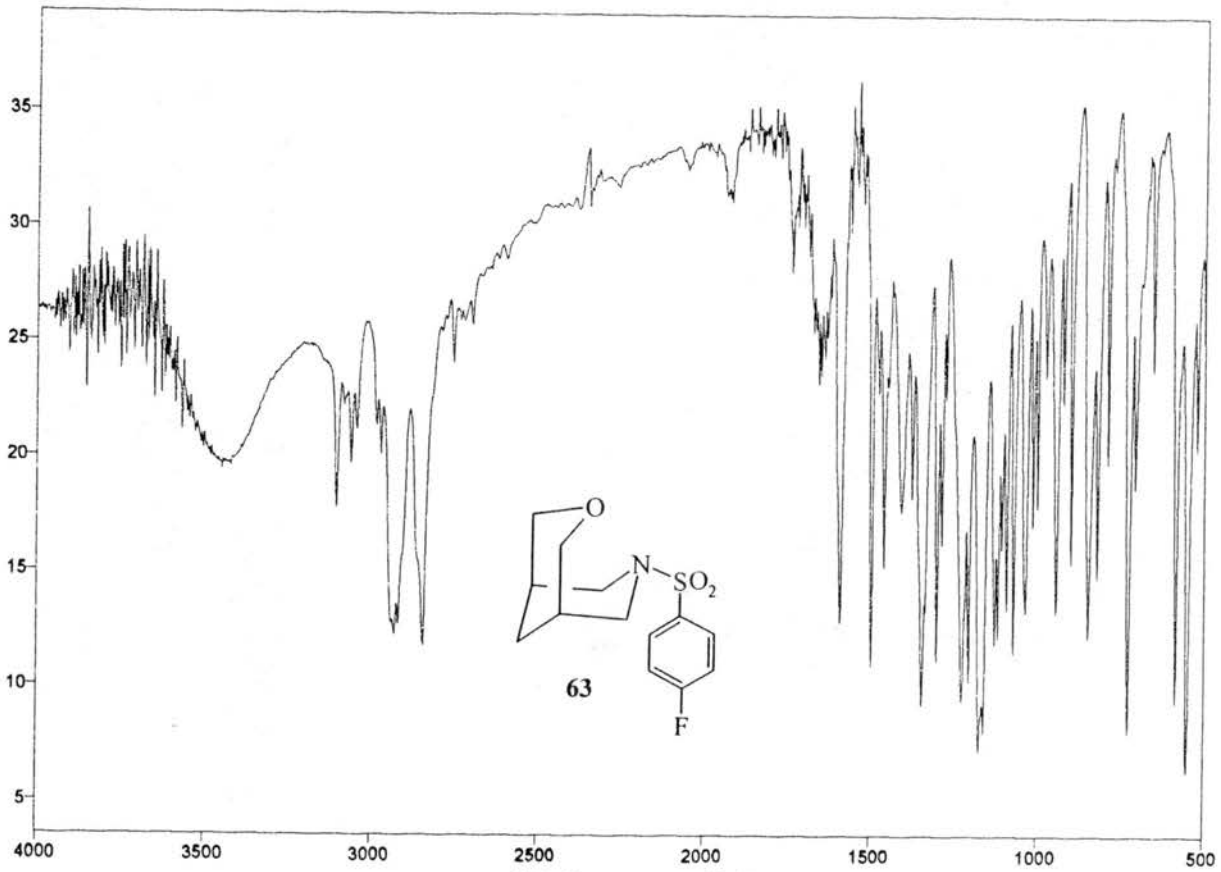
Plate LXXIV



62

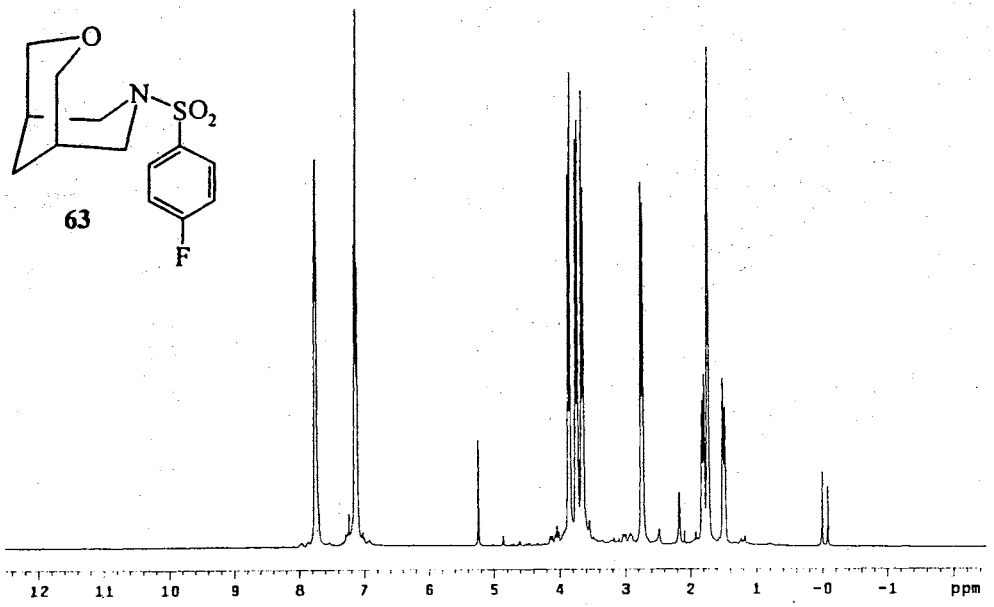
^{13}C NMR Spectrum of **62**

Plate LXXV



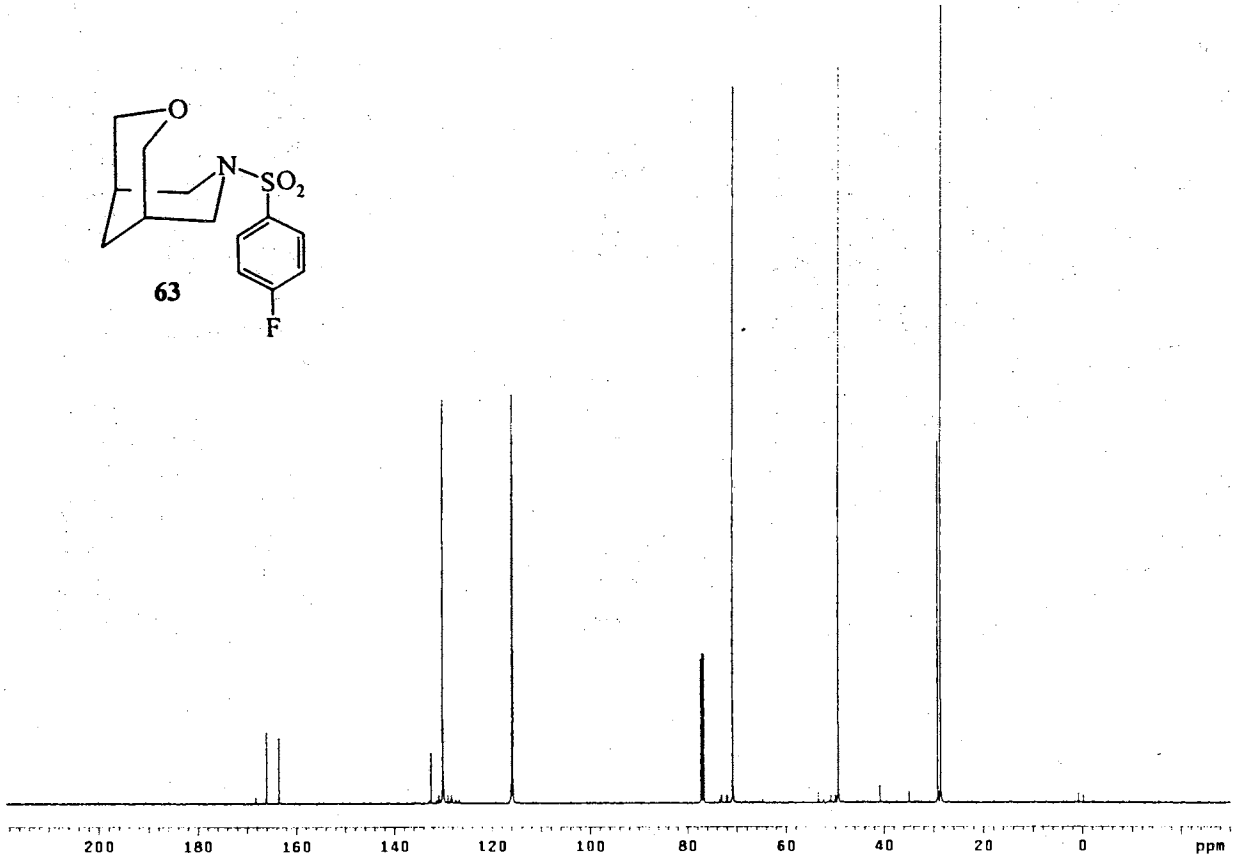
IR Spectrum of **63**

Plate LXXVI



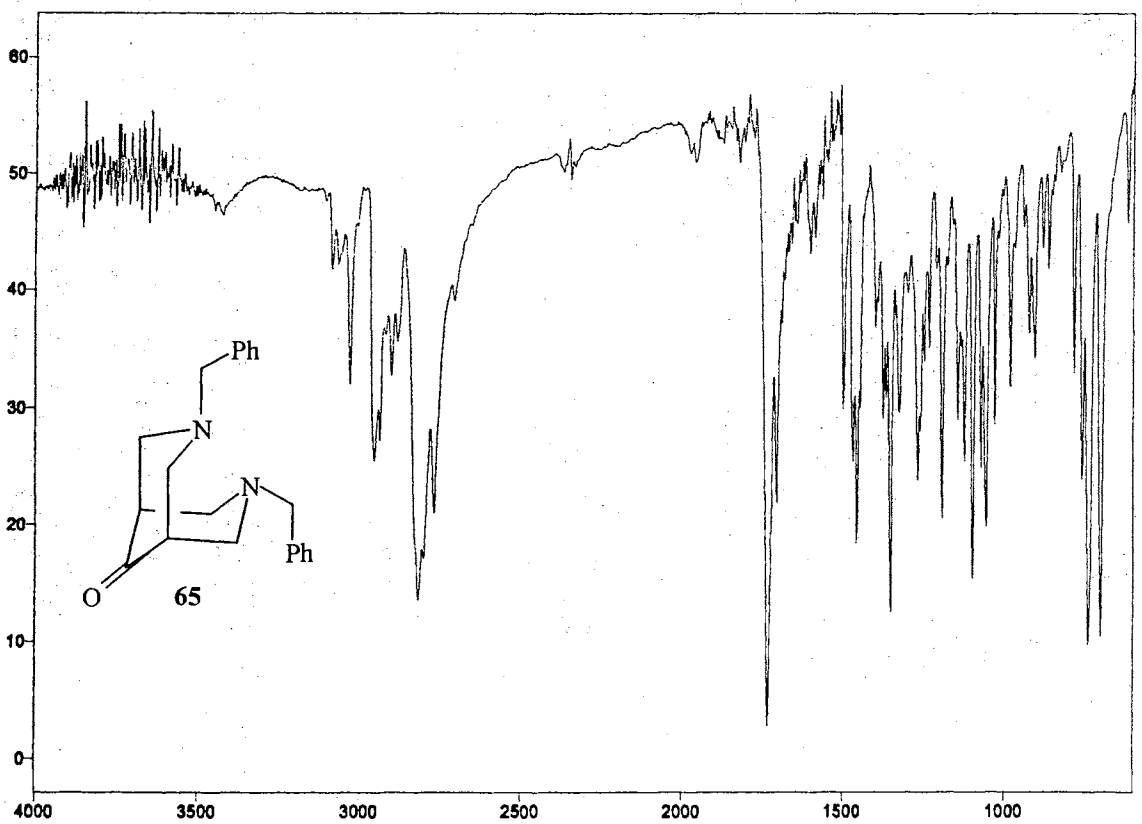
^{1}H NMR Spectrum of **63**

Plate LXXVII



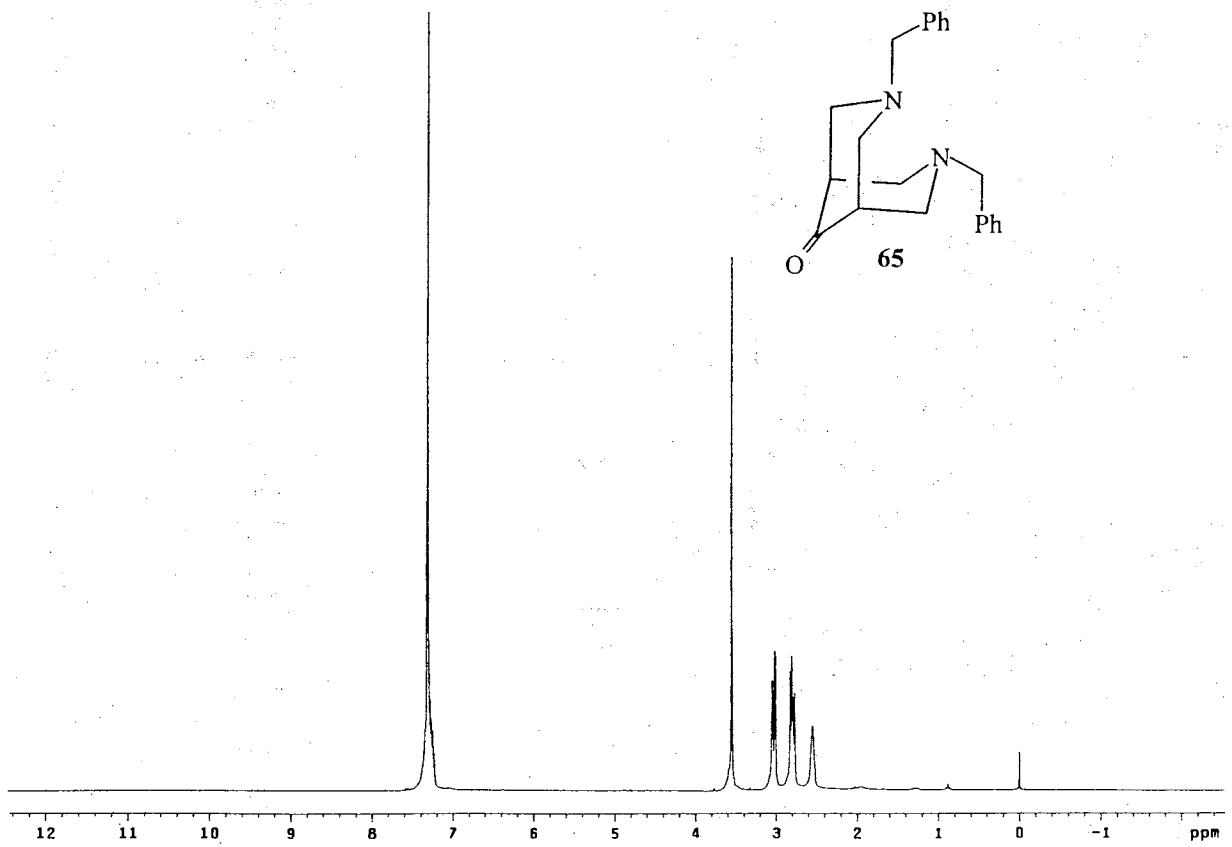
^{13}C NMR Spectrum of **63**

Plate LXXVIII



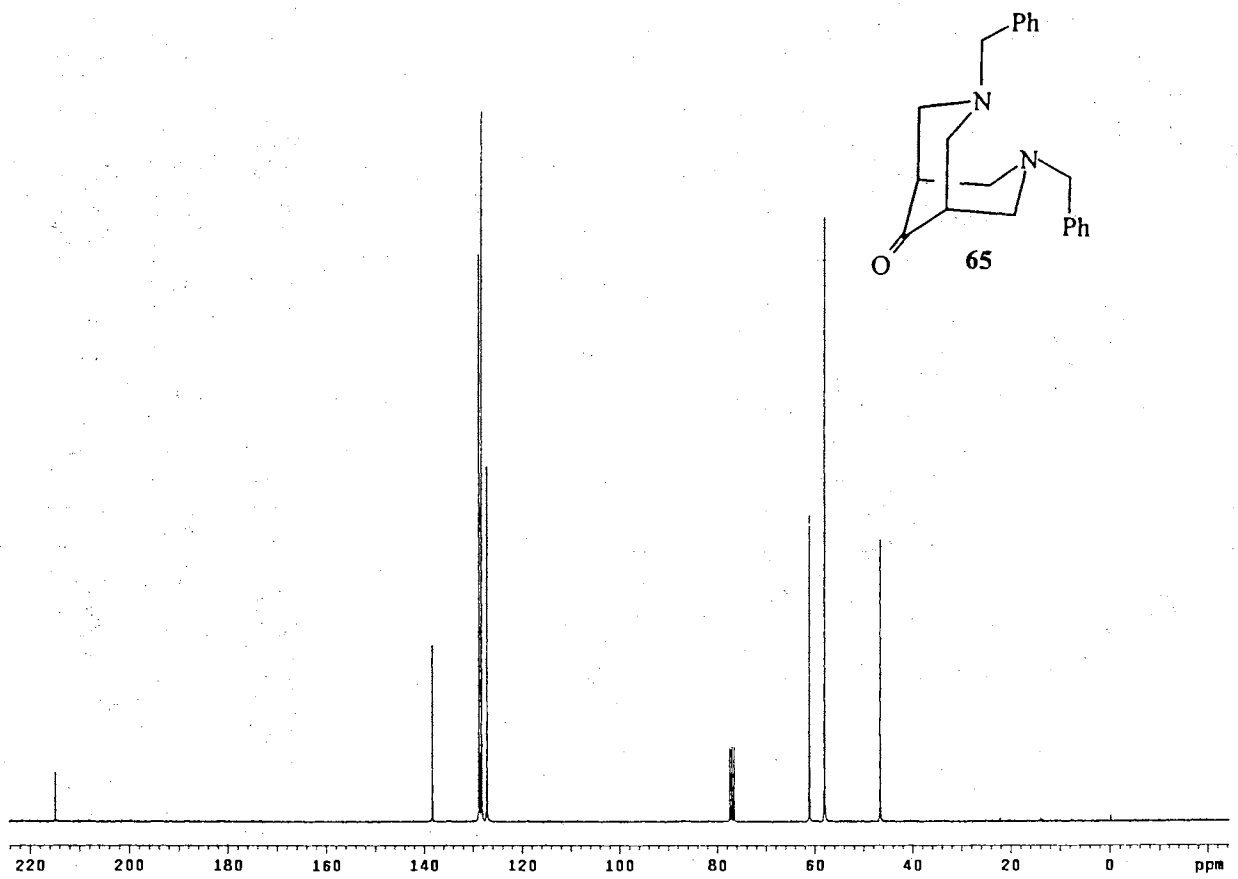
IR Spectrum of **65**

Plate LXXIX



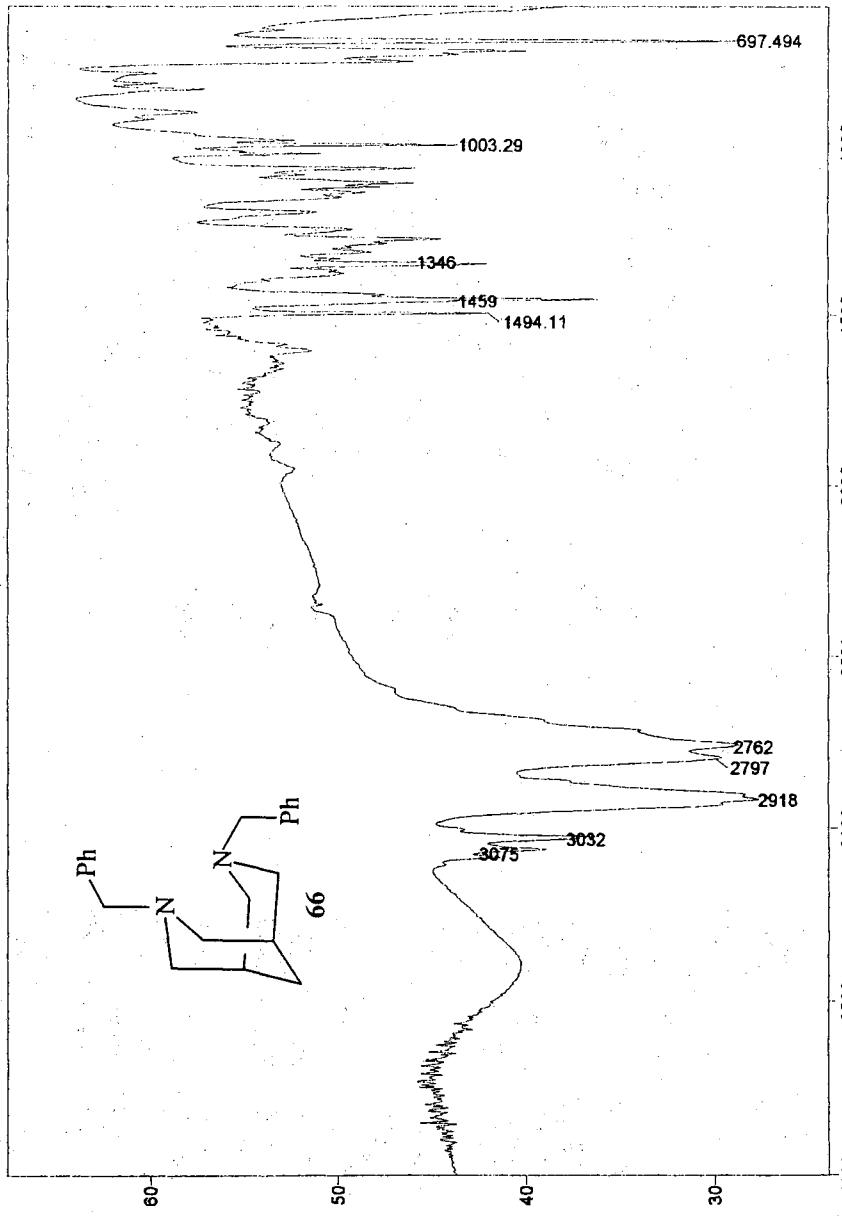
^{1}H NMR Spectrum of **65**

Plate LXXX



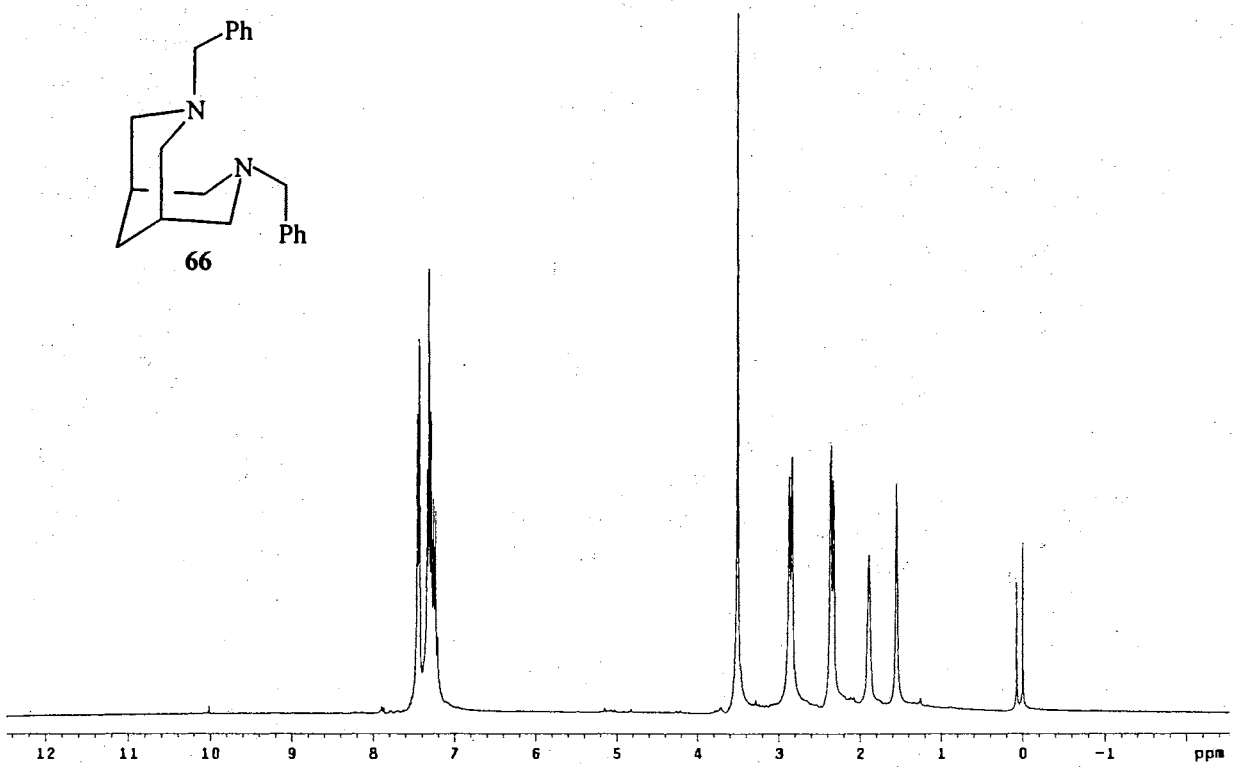
^{13}C NMR Spectrum of **65**

Plate LXXXI



IR Spectrum of **66**

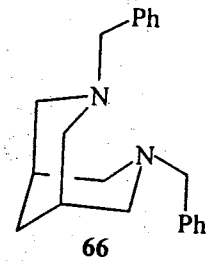
Plate LXXXII



66

^{1}H NMR Spectrum of **66**

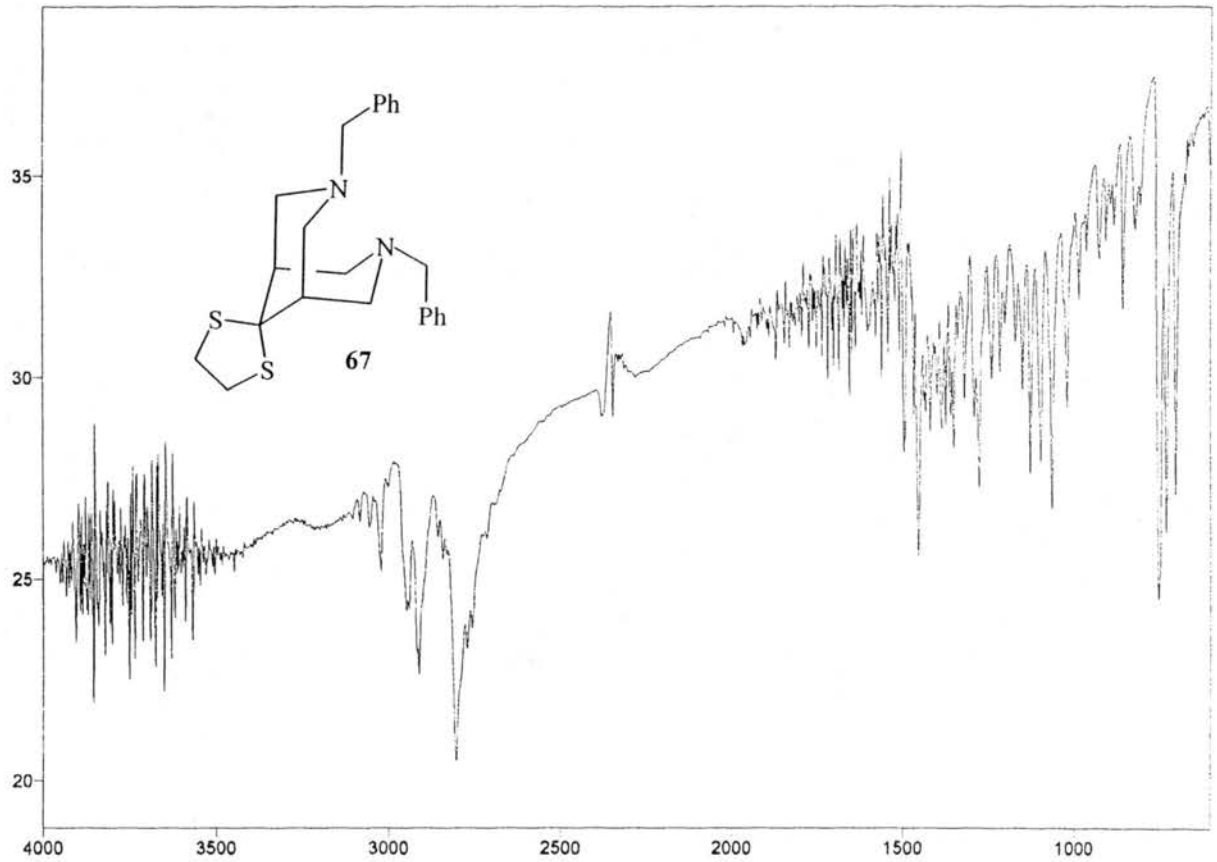
Plate LXXXIII



66

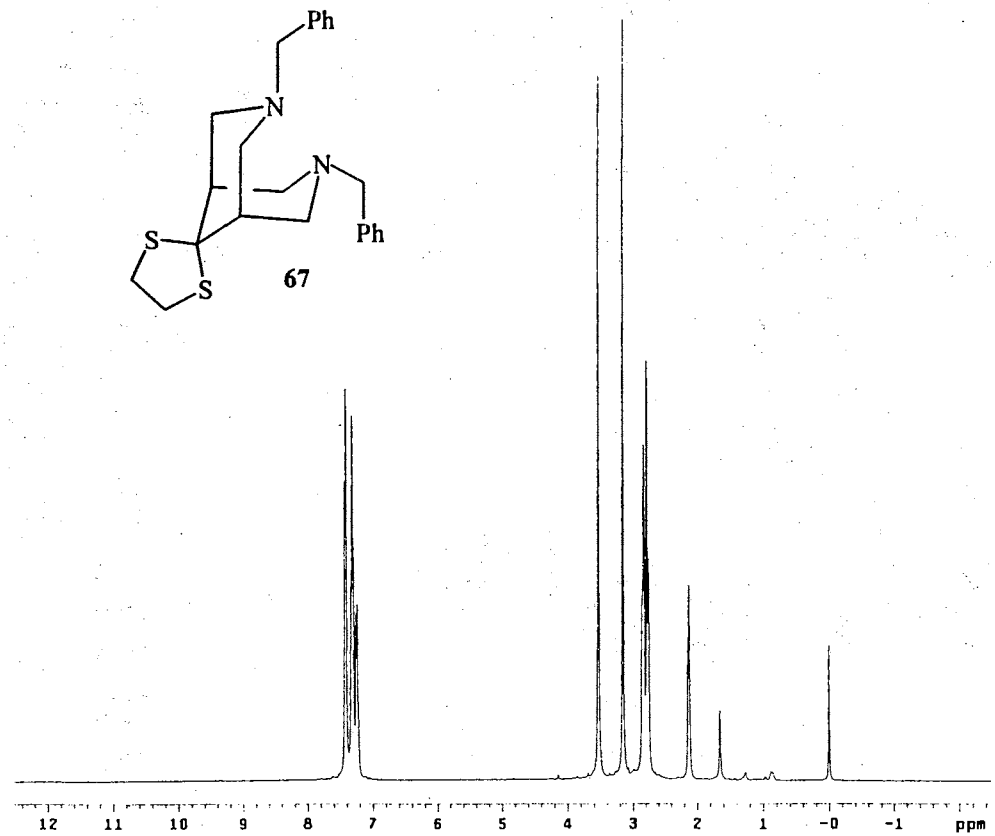
^{13}C NMR Spectrum of **66**

Plate LXXXIV



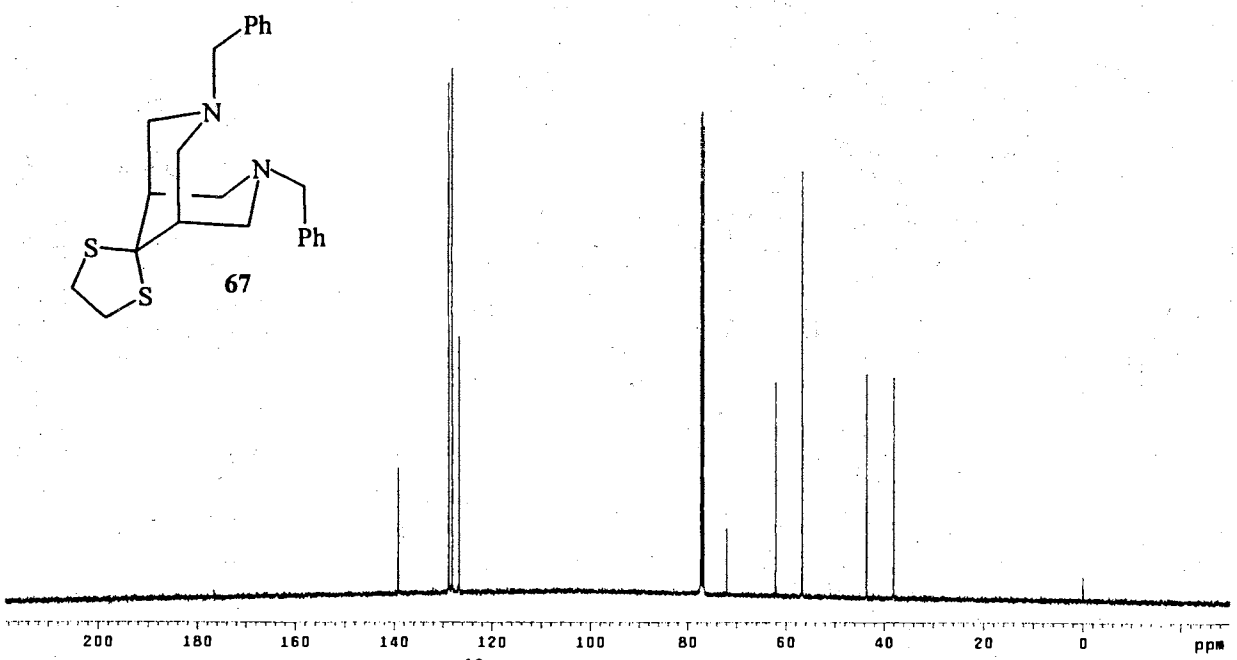
IR Spectrum of **67**

Plate LXXXV



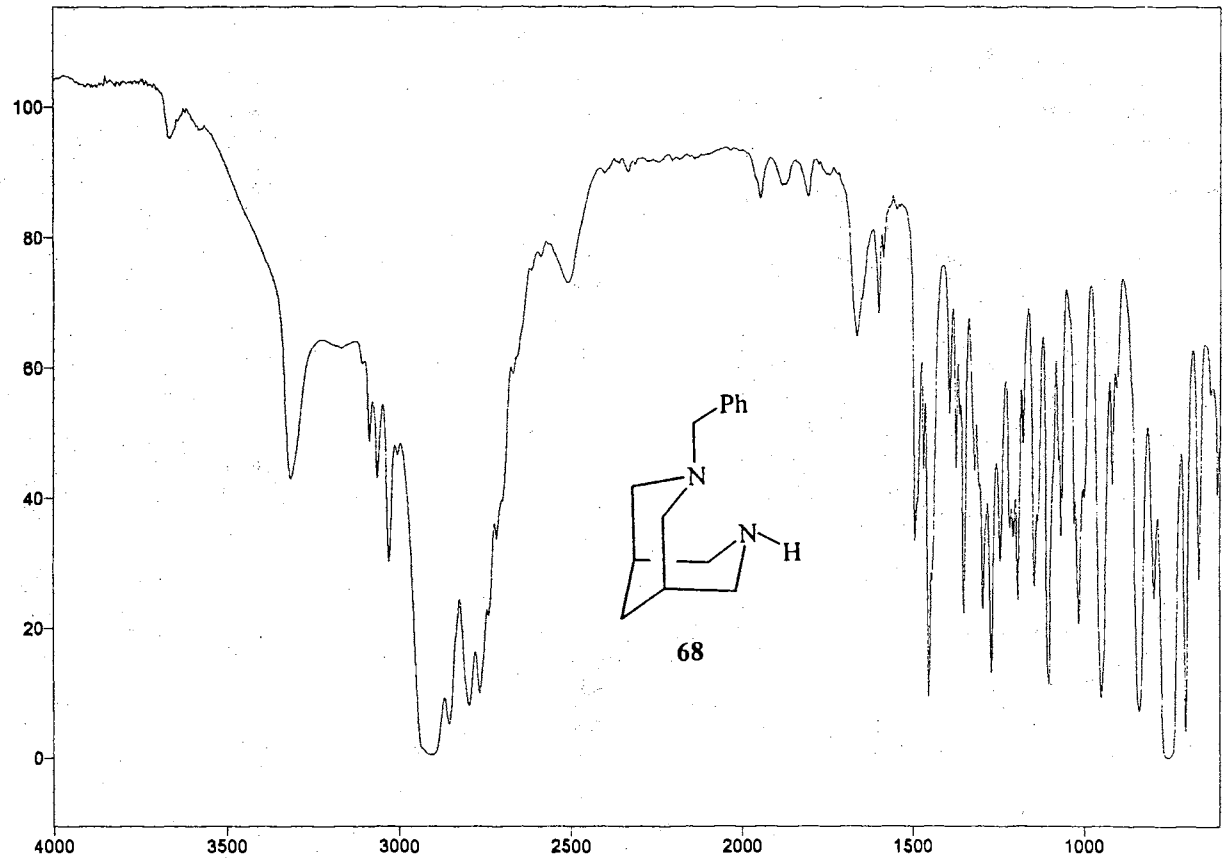
^{1}H NMR Spectrum of **67**

Plate LXXXVI



^{13}C NMR Spectrum of **67**

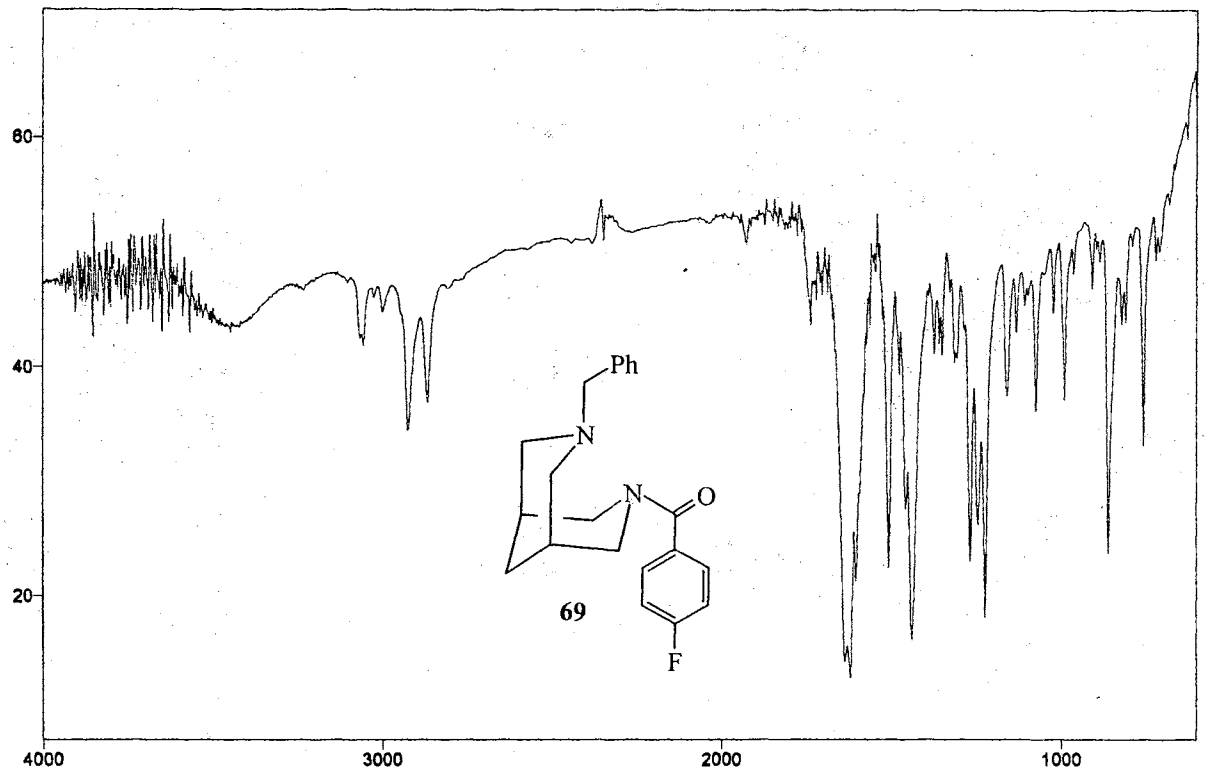
Plate LXXXVII



68

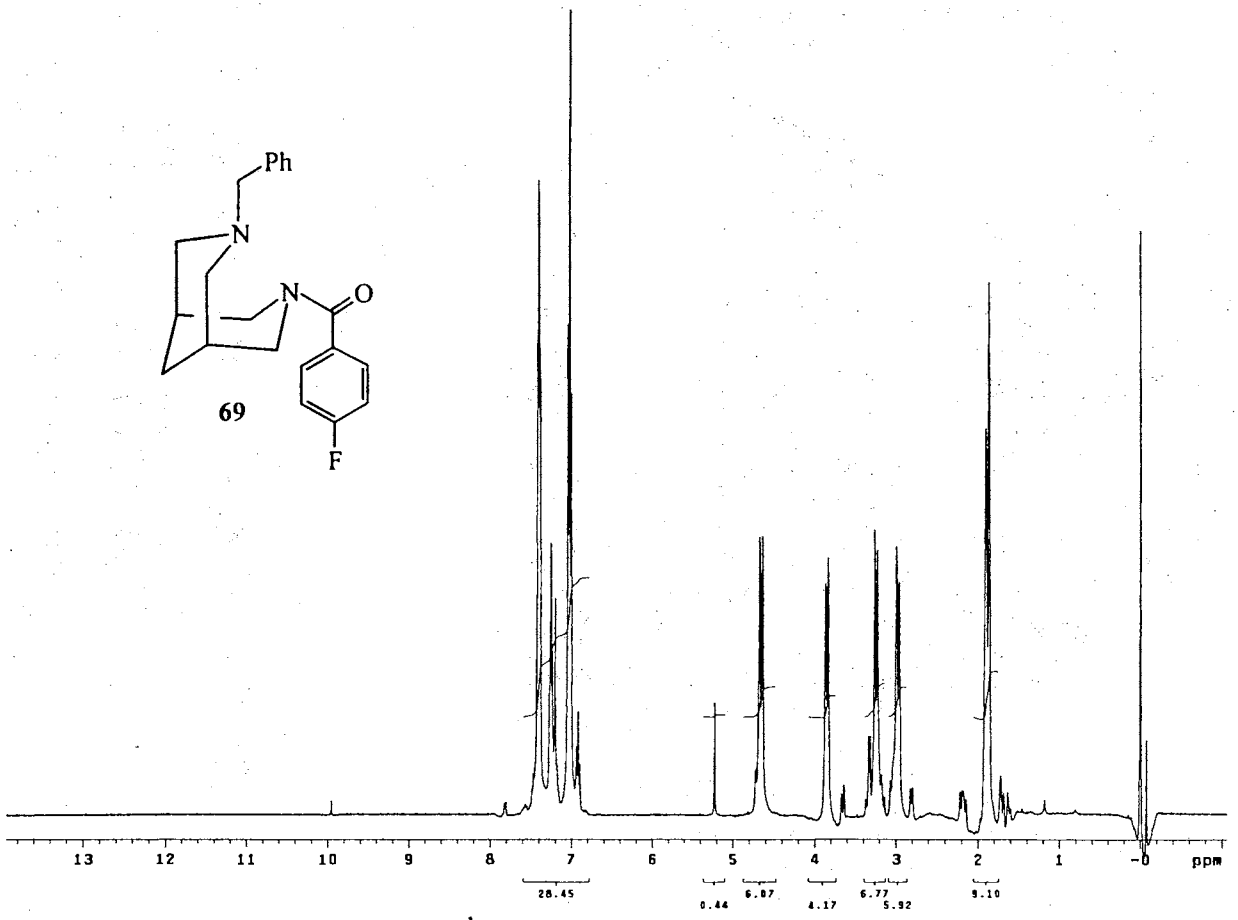
IR Spectrum of **68**

plate LXXXVIII



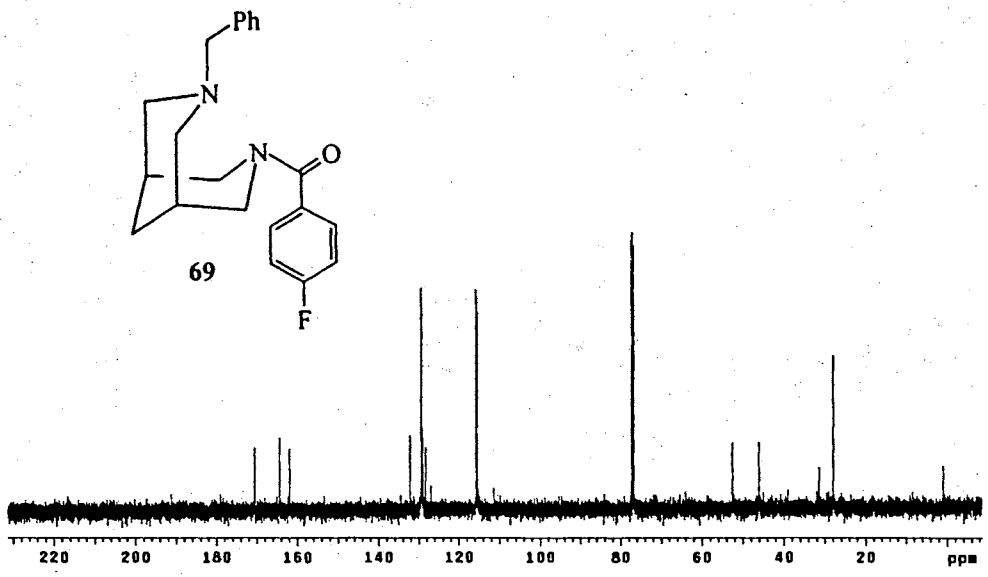
IR Spectrum of **69**

Plate LXXXIX



^{1}H NMR Spectrum of **69**

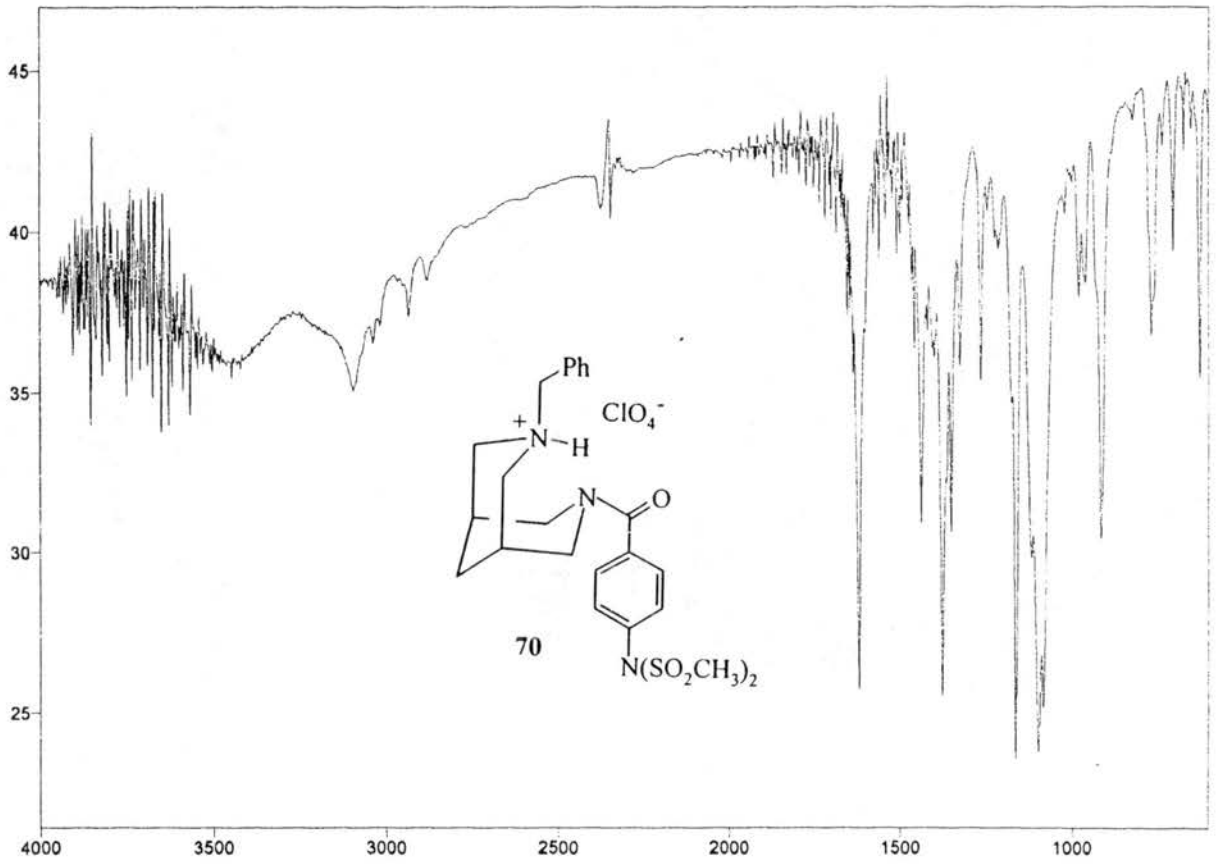
Plate XC



69

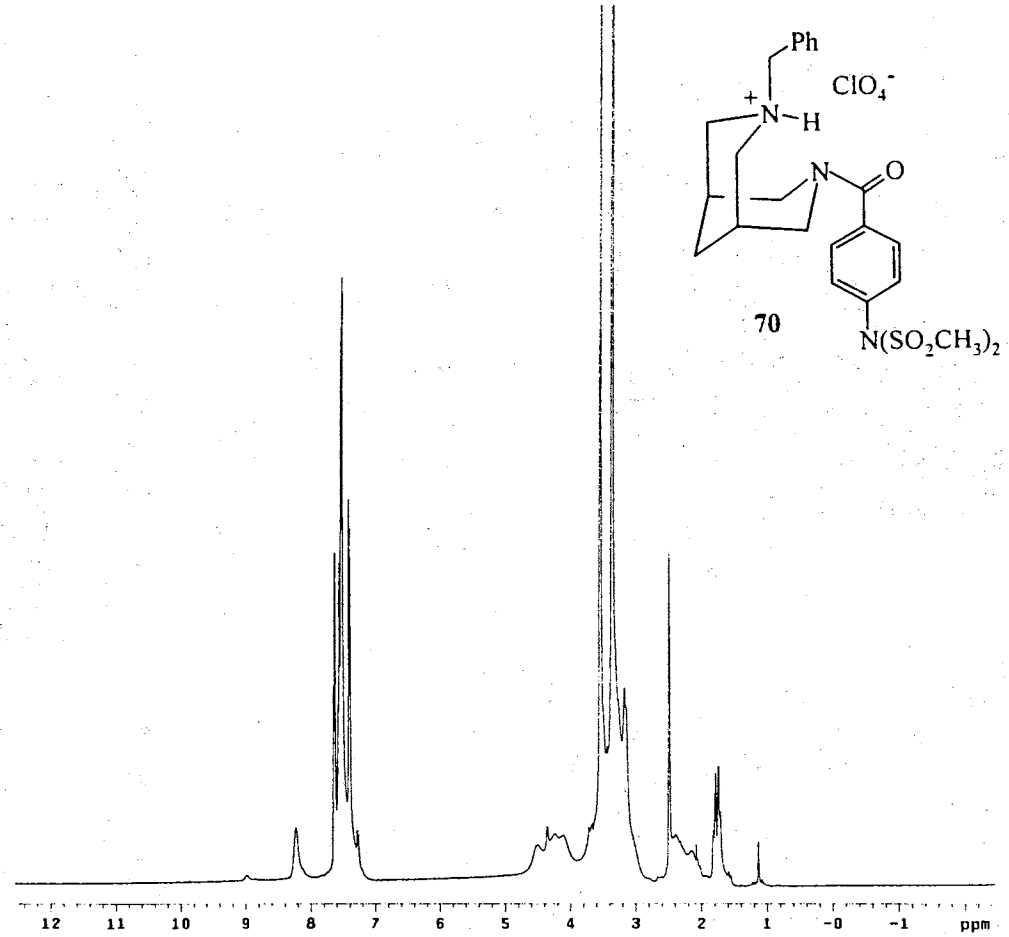
^{13}C NMR Spectrum of **69**

Plate XCI



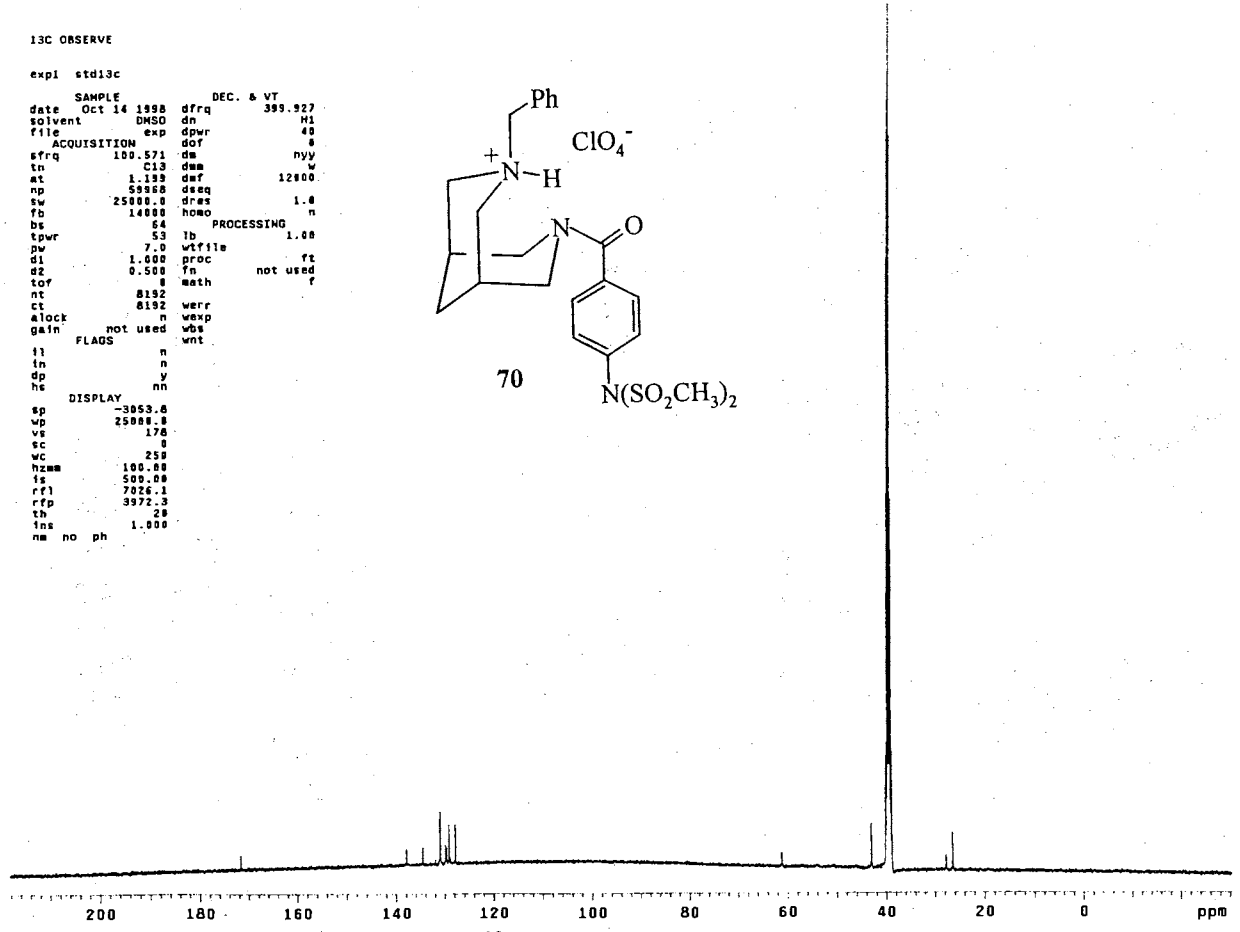
IR Spectrum of **70**

Plate XCII



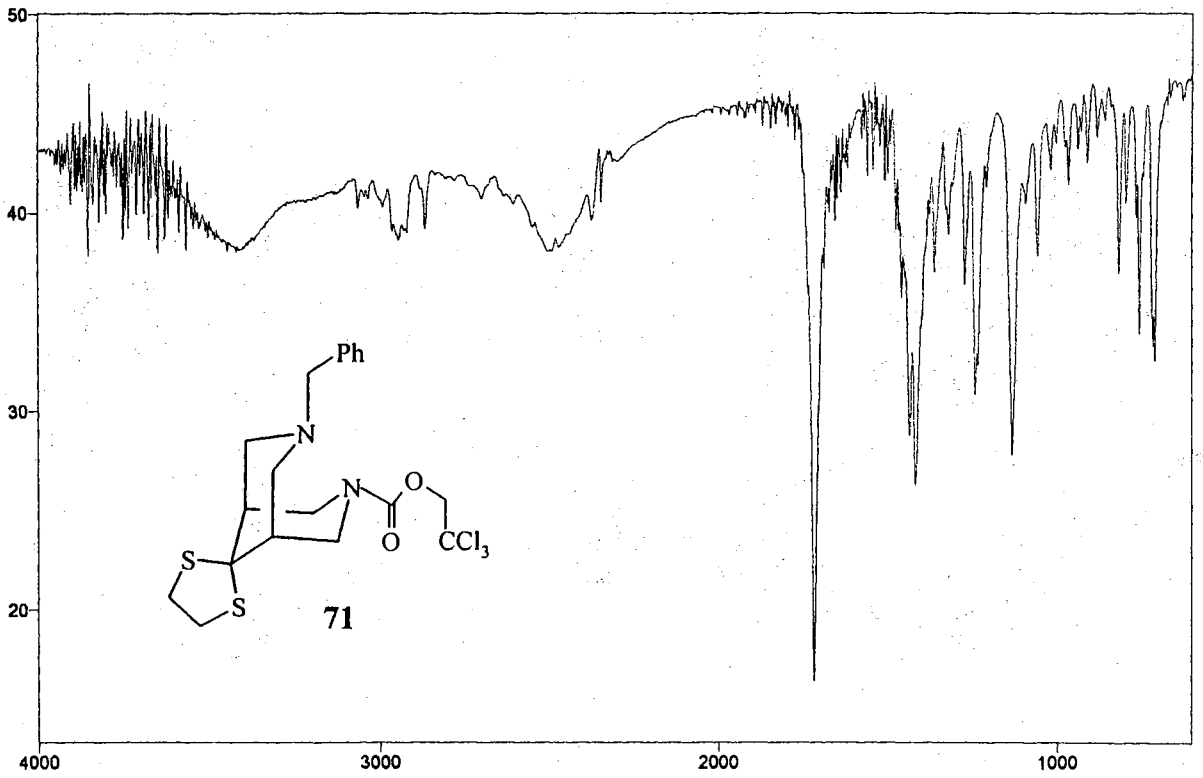
^{1}H NMR spectrum of **70**

Plate XCIII



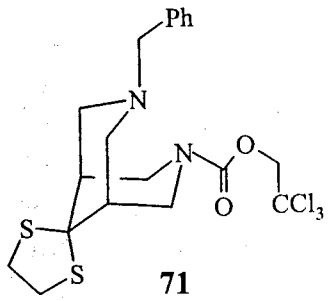
^{13}C NMR Spectrum of **70**

Plate XCIV

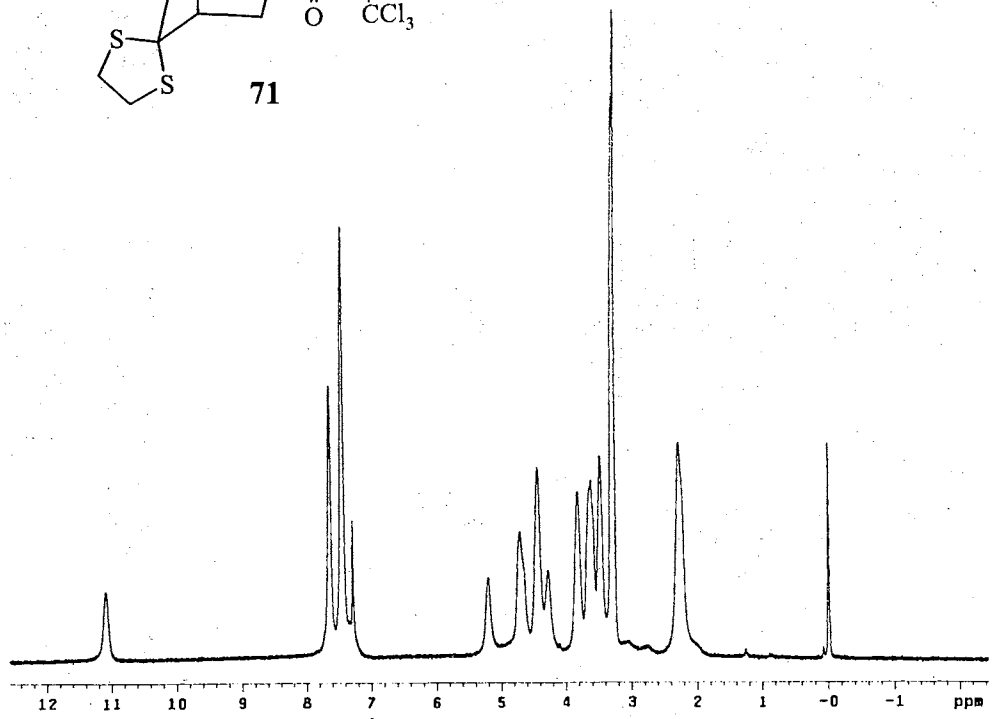


IR Spectrum of **71**

Plate XCV

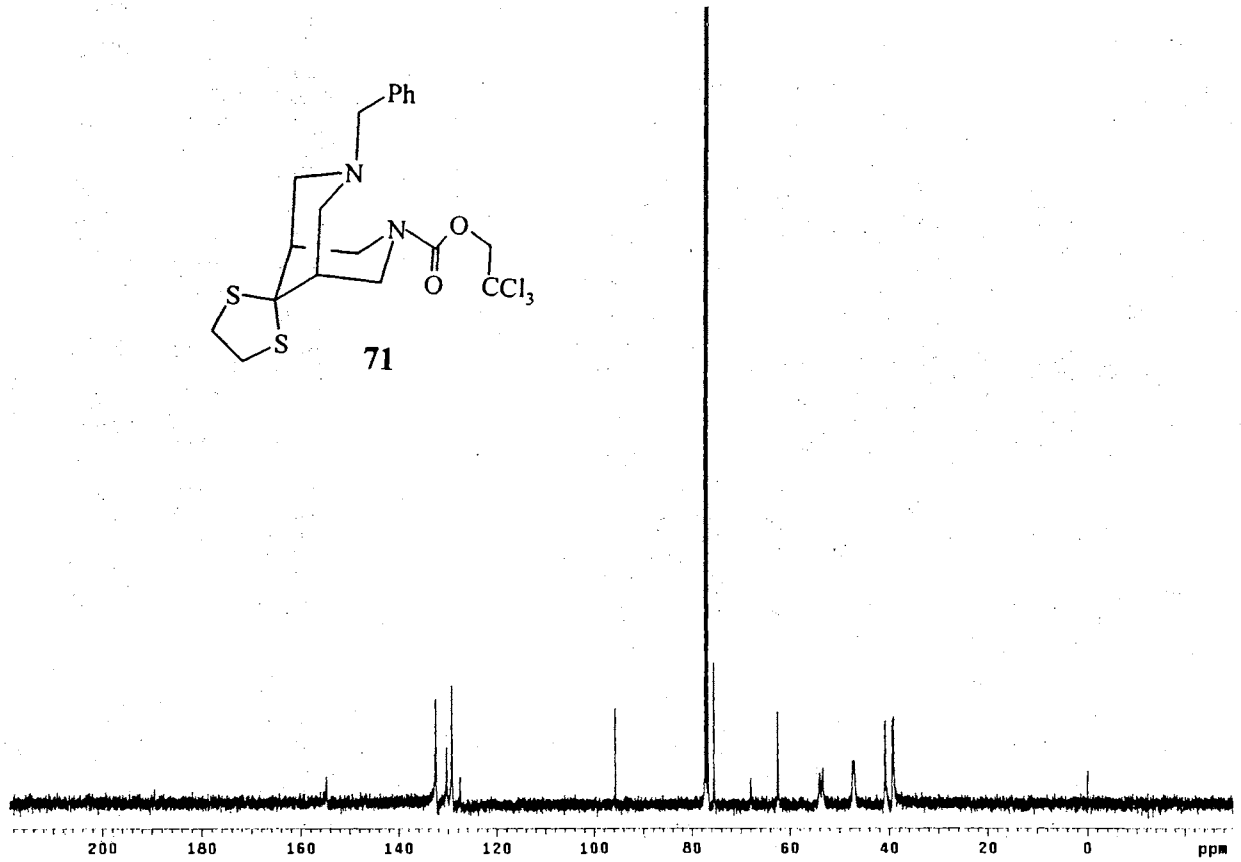


71



^{1}H NMR Spectrum of **71**

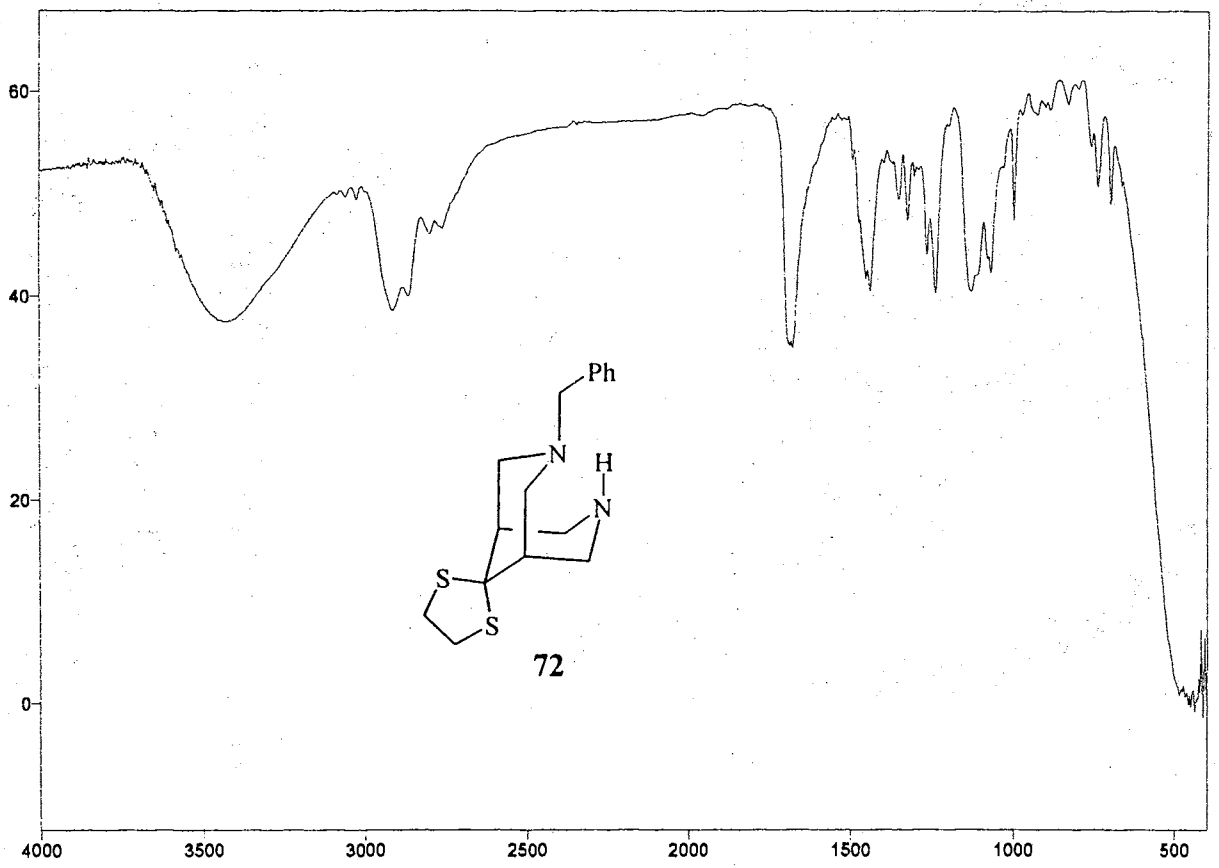
Plate XCVI



71

^{13}C NMR Spectrum of **71**

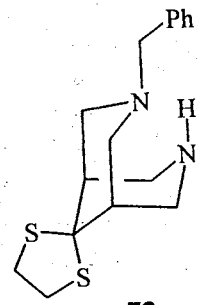
plate XCVII



72

IR Spectrum of **72**

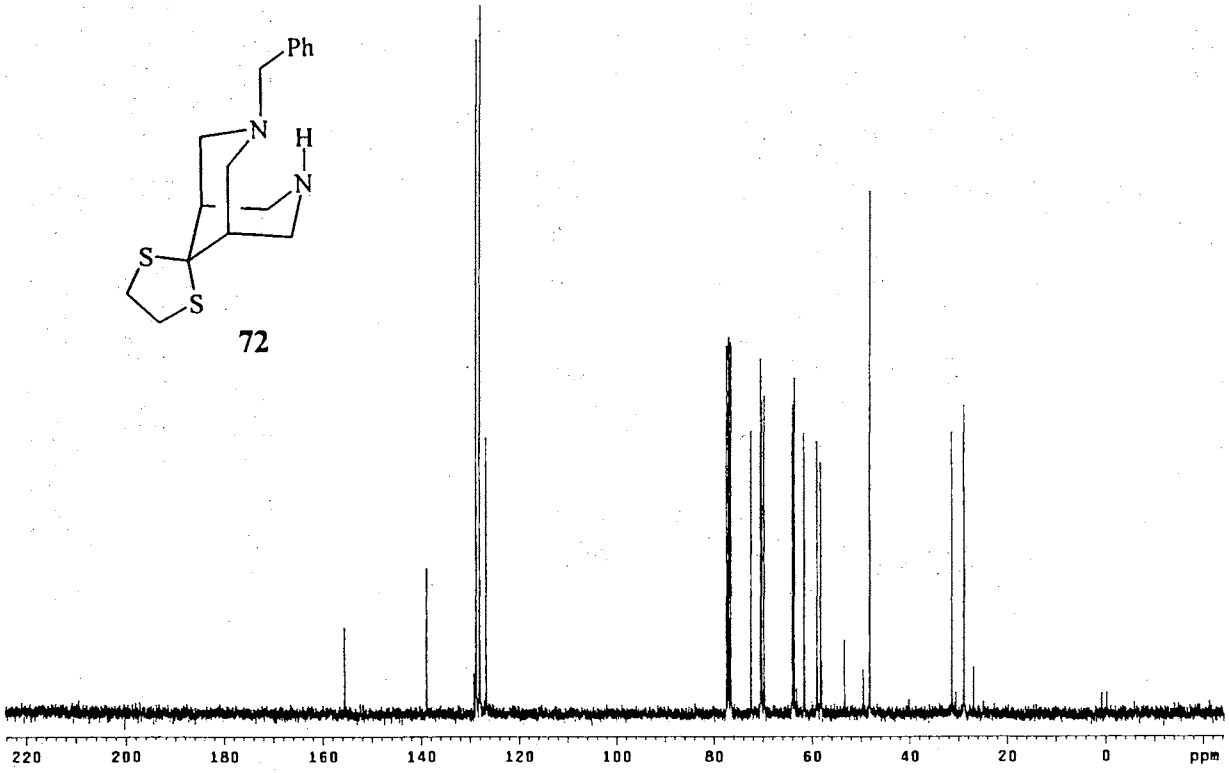
Plate XCVIII



72

^{1}H NMR Spectrum of **72**.

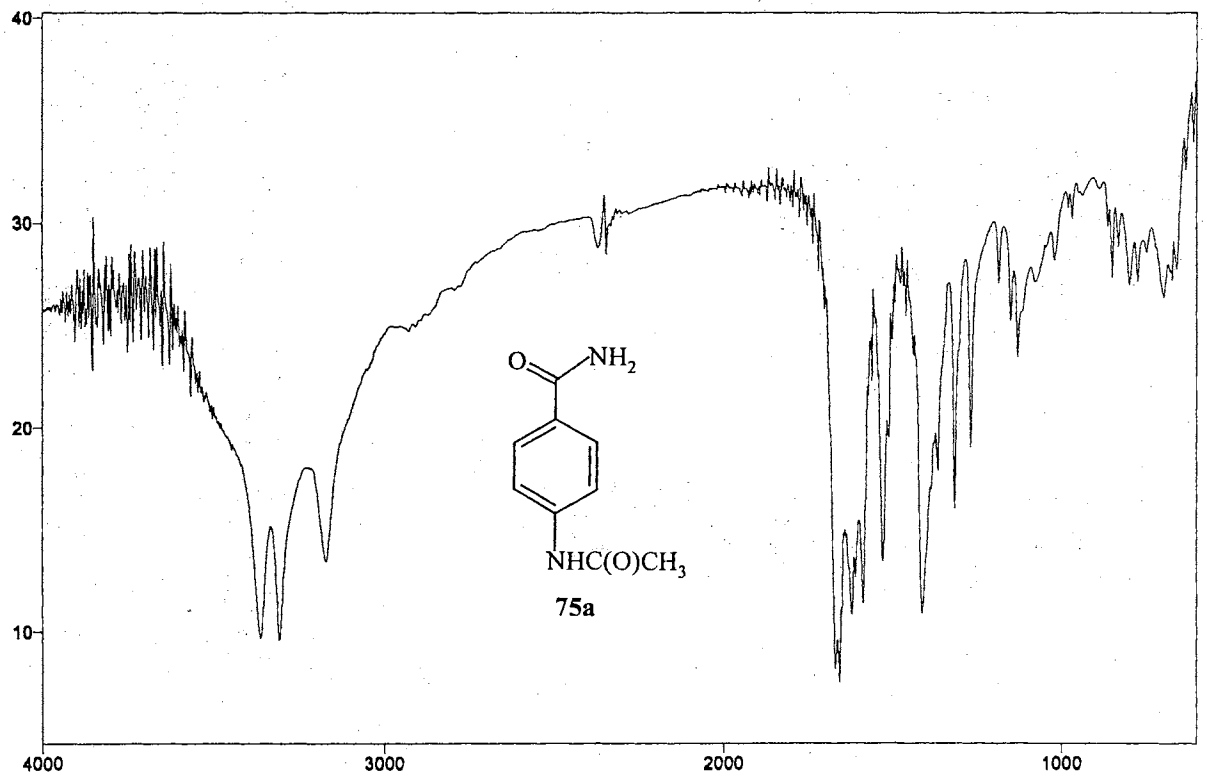
Plate XCIX



72

^{13}C NMR Spectrum of **72**

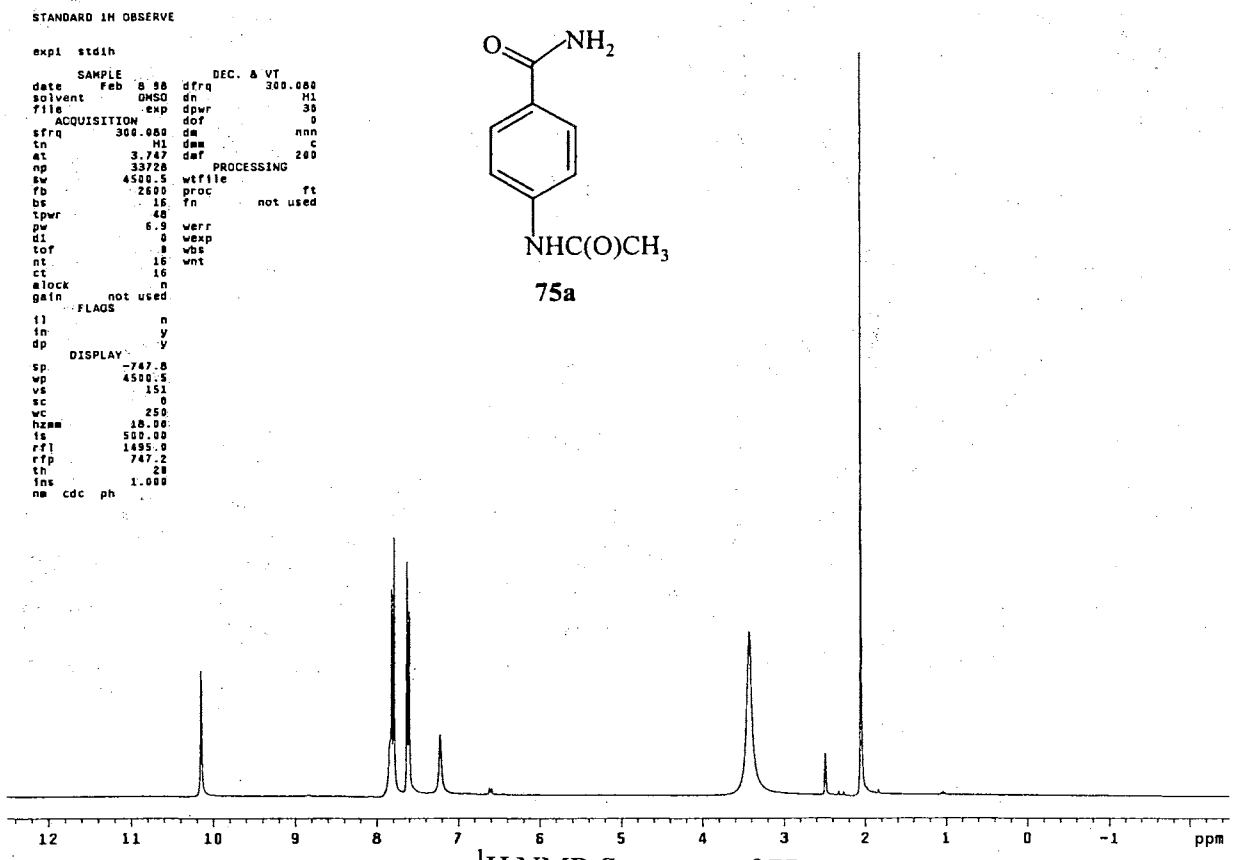
Plate C



75a

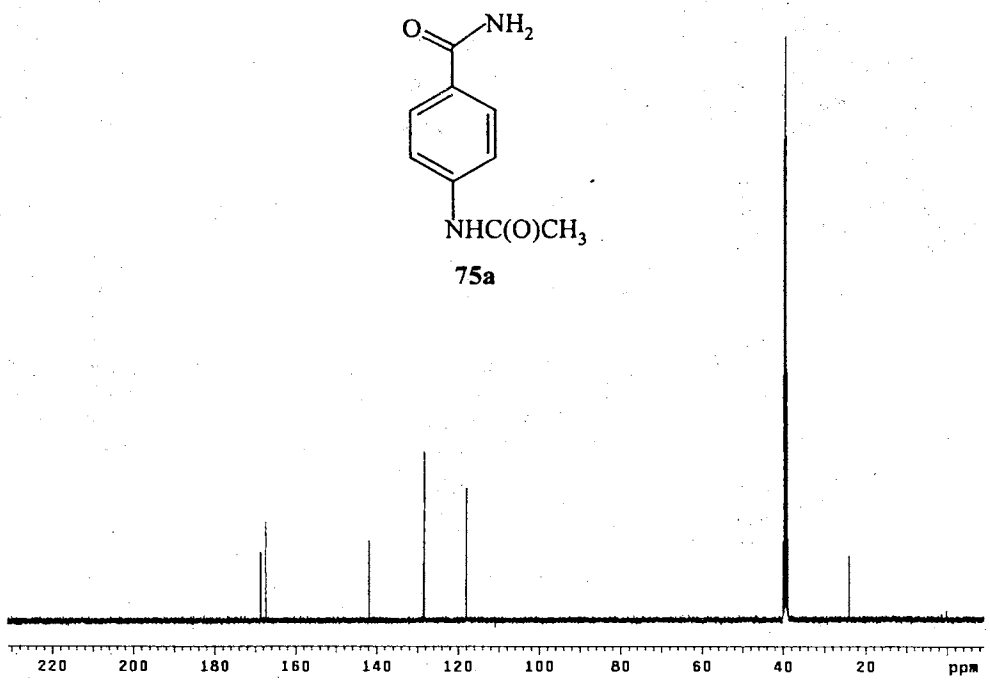
IR Spectrum of **75a**

Plate CI



^{1}H NMR Spectrum of **75a**

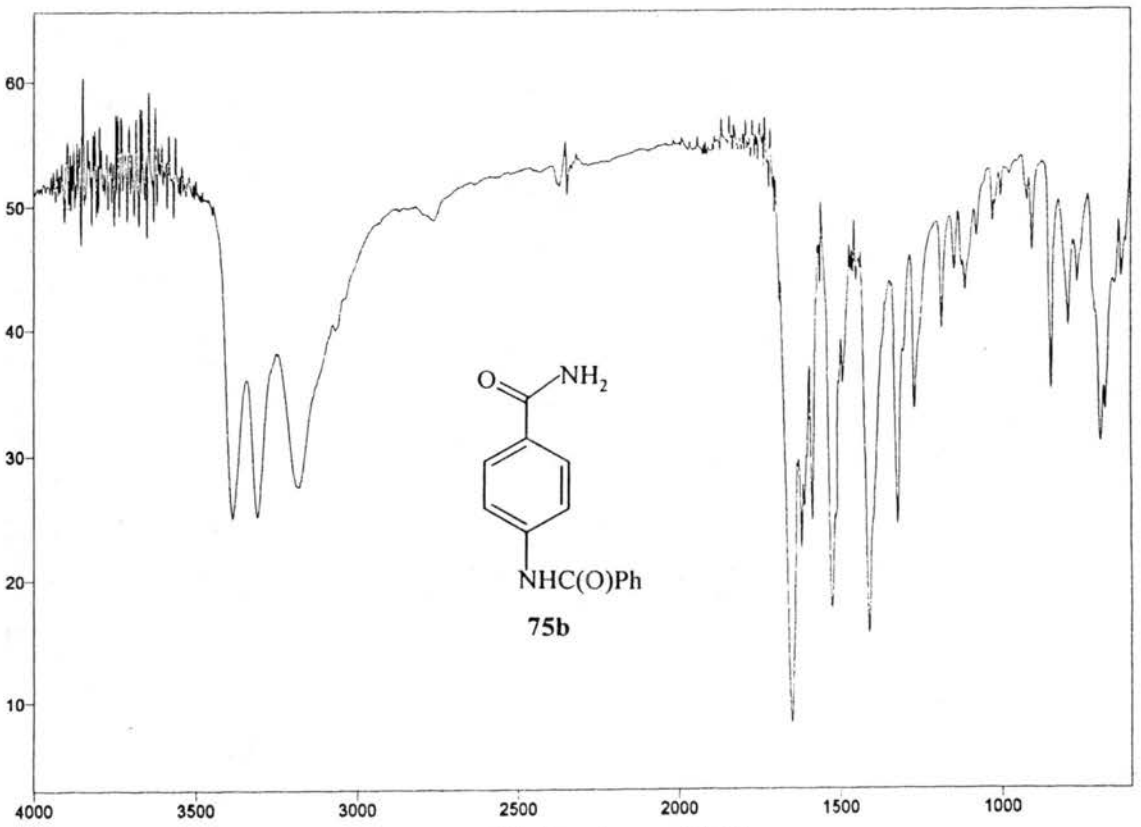
Plate CII



75a

^{13}C NMR Spectrum of **75a**

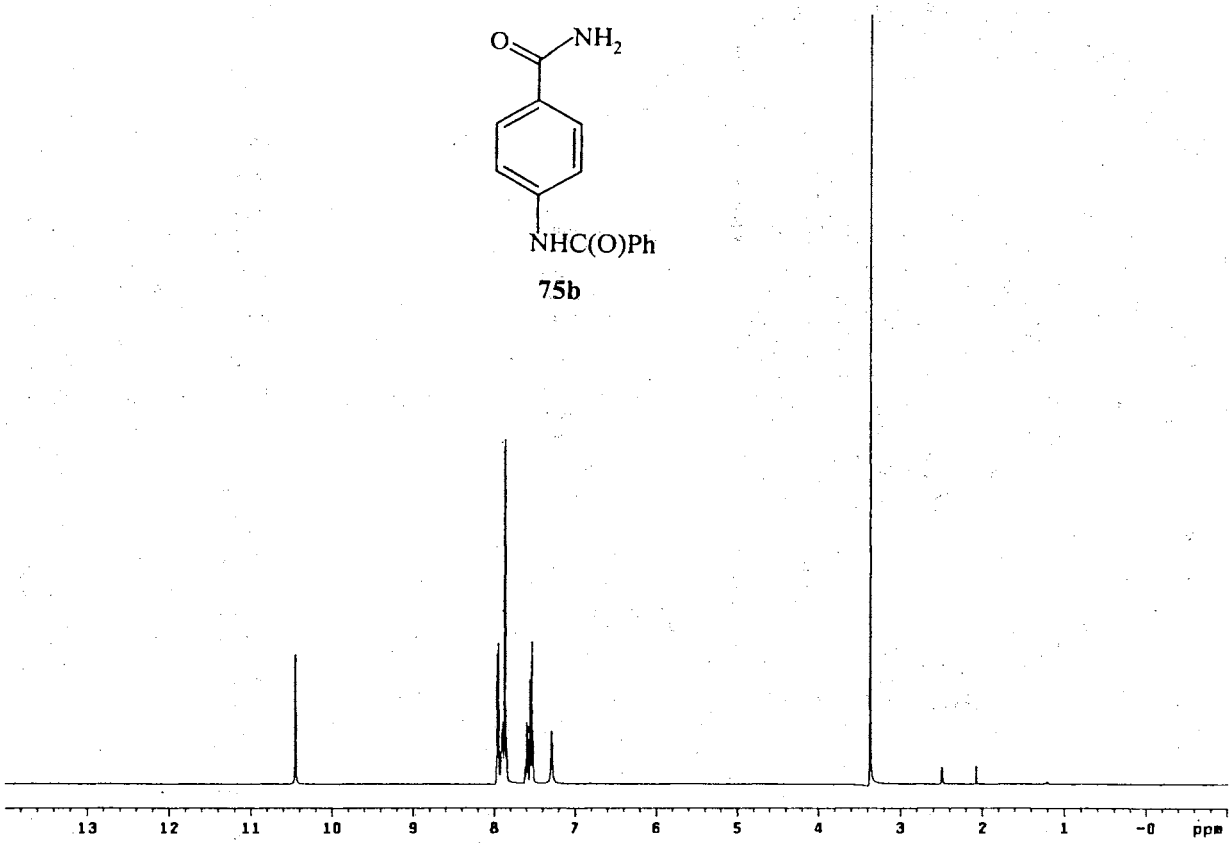
Plate CIII



75b

IR Spectrum of **75b**

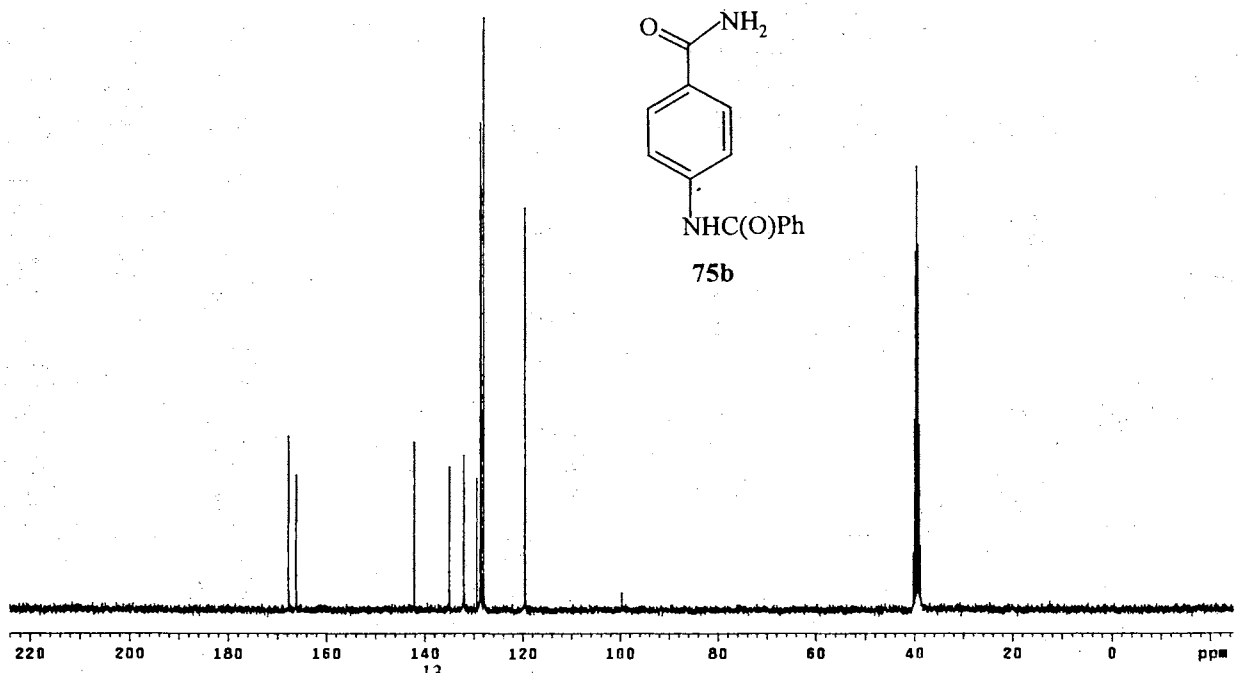
Plate CIV



75b

^{1}H NMR Spectrum of **75b**

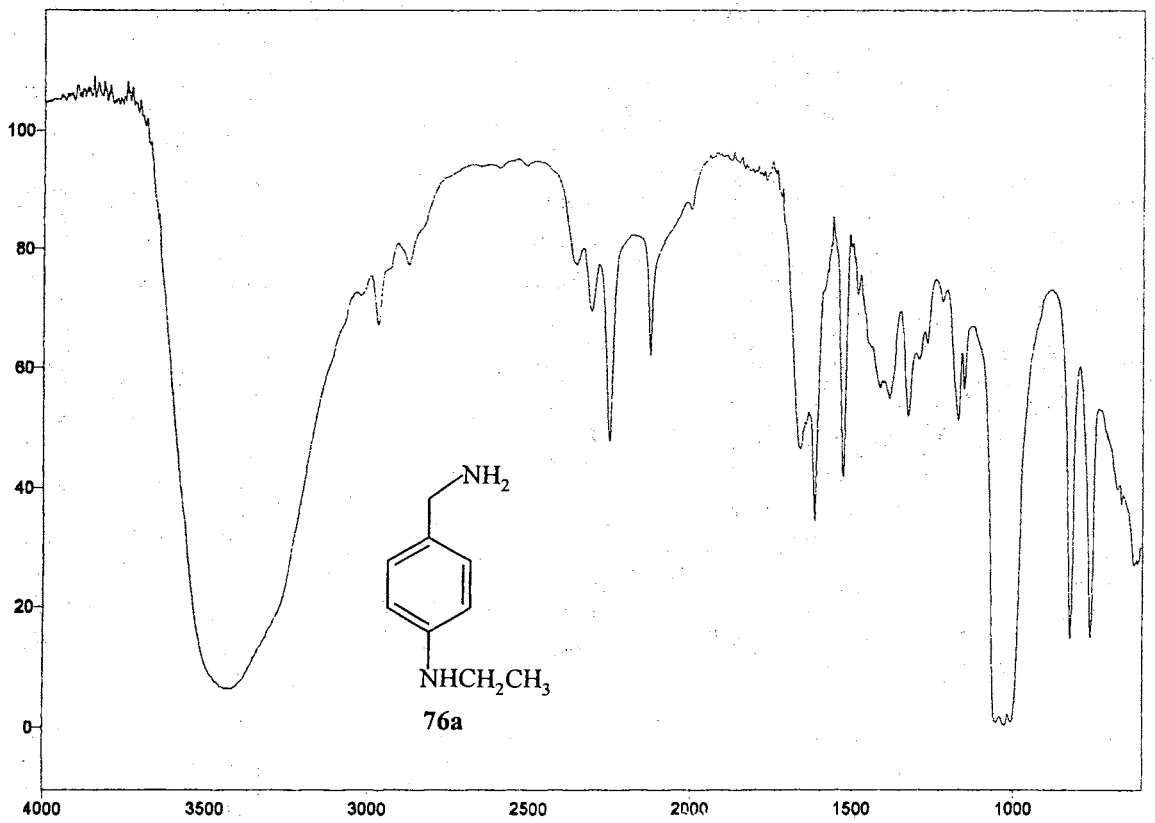
Plate CV



75b

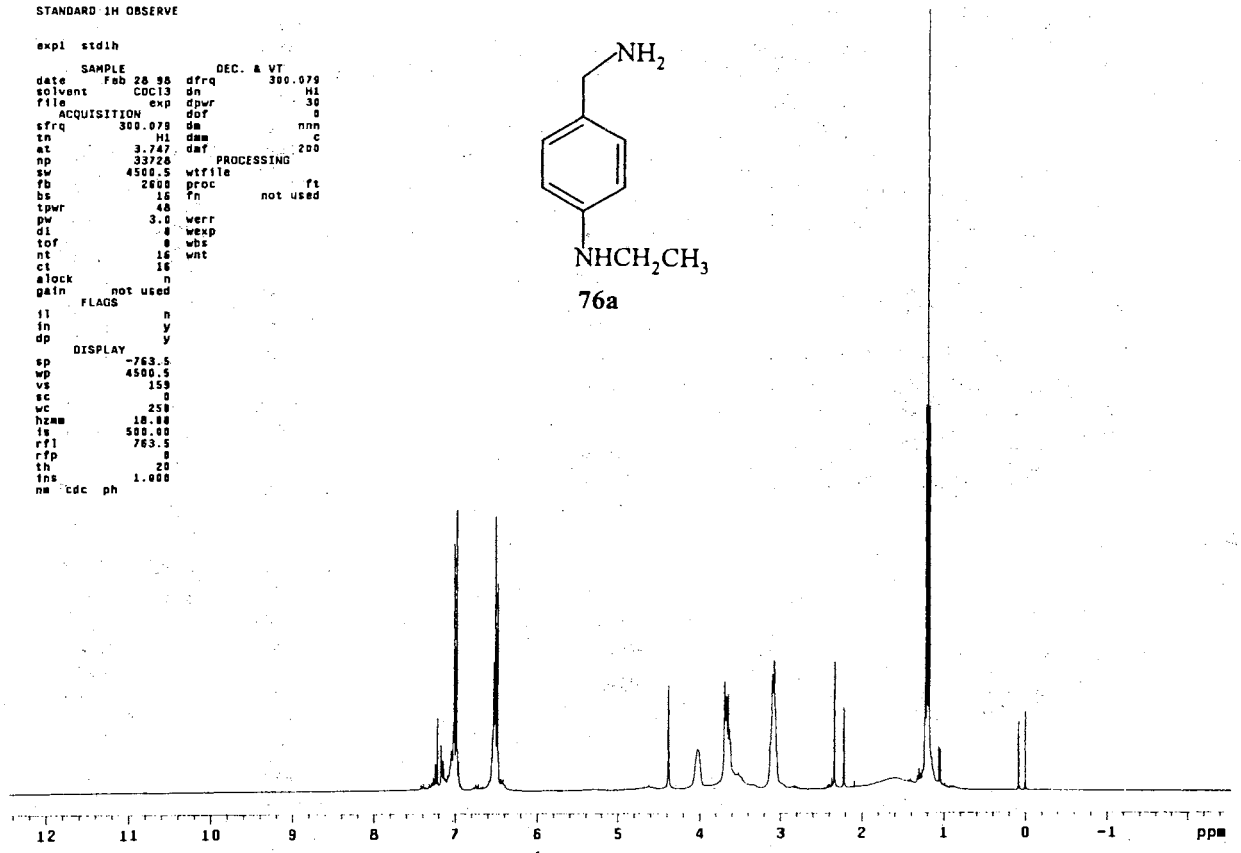
^{13}C NMR Spectrum of **75b**

Plate CVI



IR Spectrum of **76a**

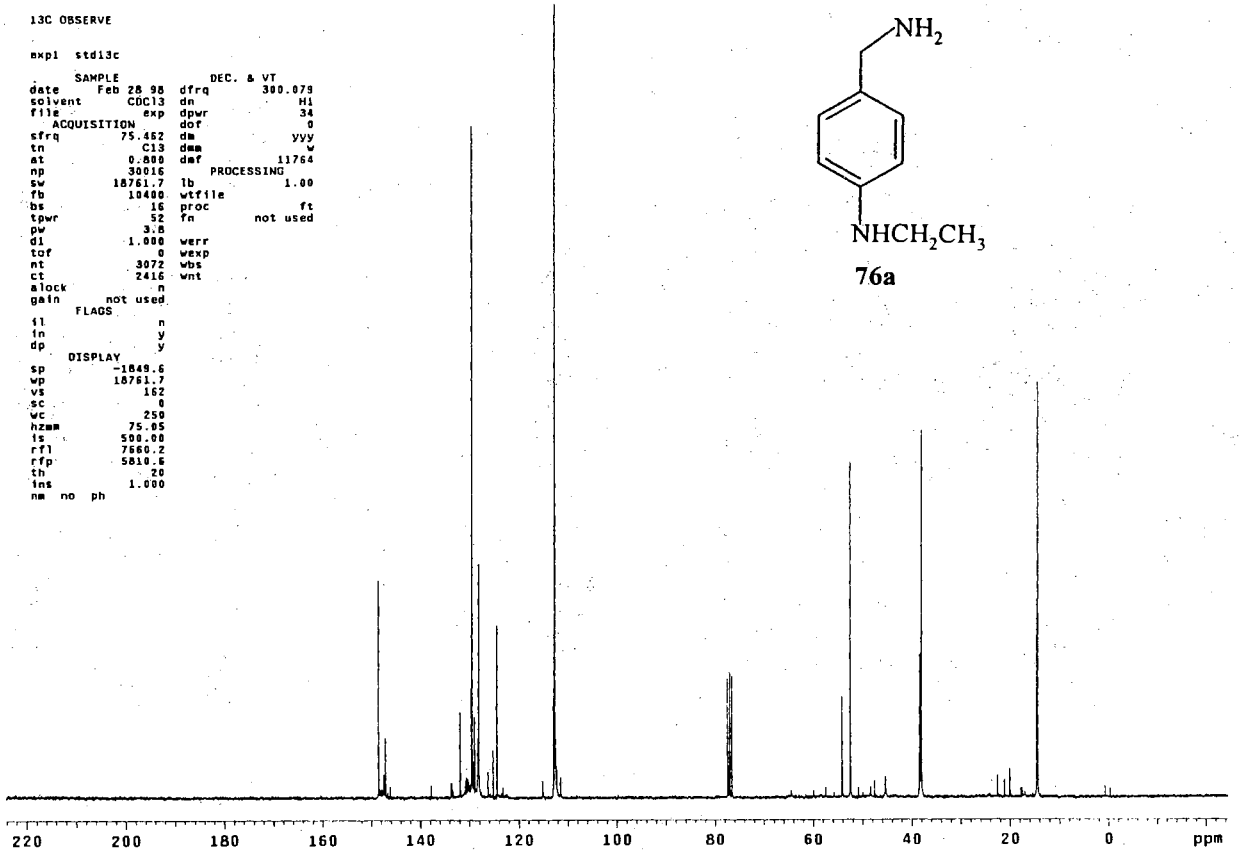
Plate CVII



76a

^{1}H Spectrum of **76a**

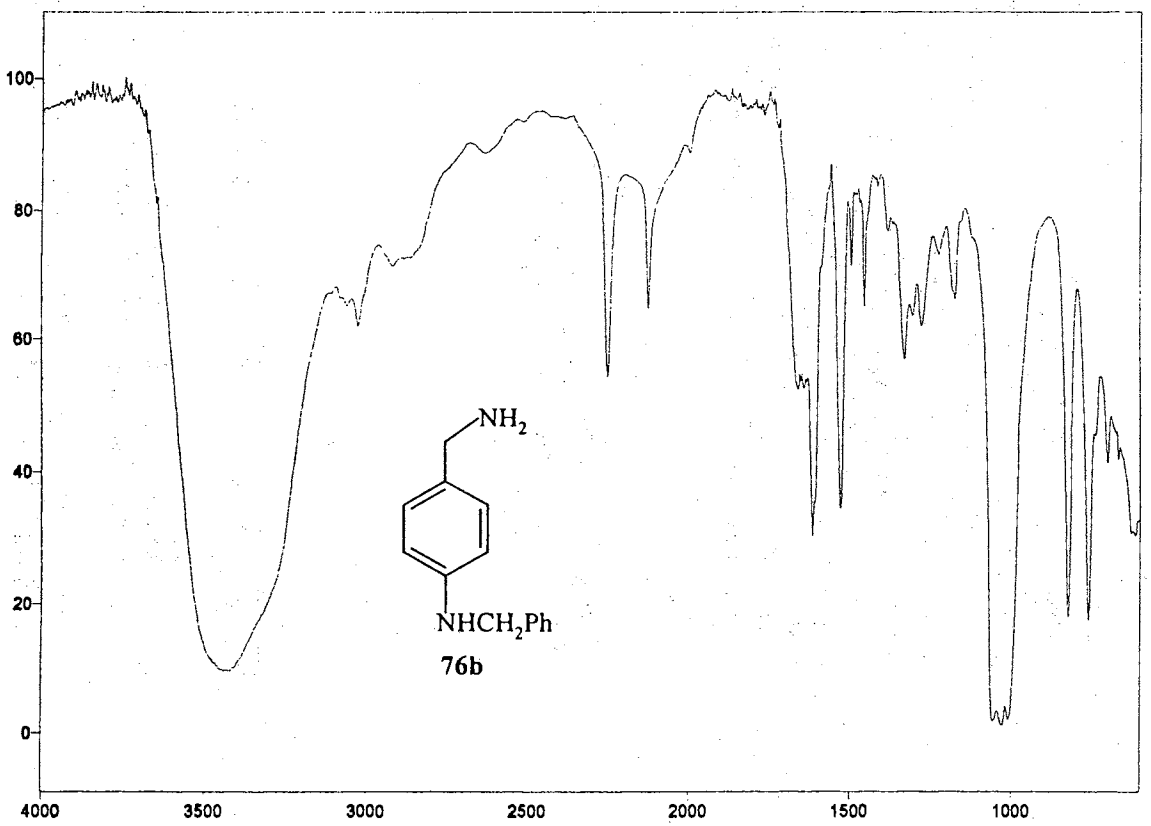
Plate CVIII



76a

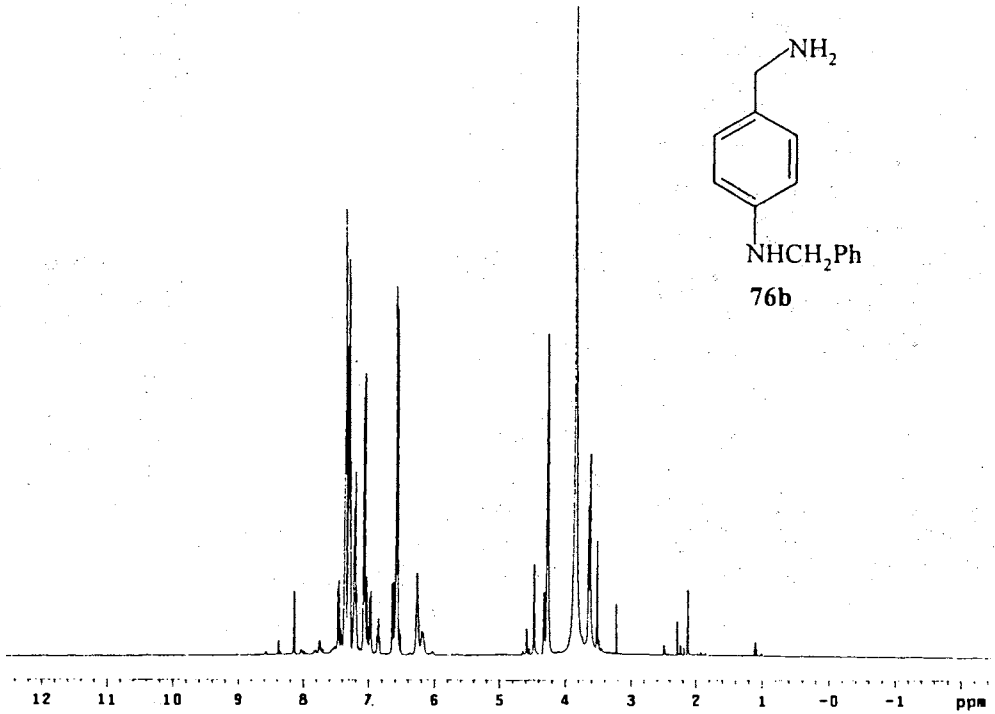
^{13}C Spectrum of **76a**

Plate CIX



IR Spectrum of **76b**

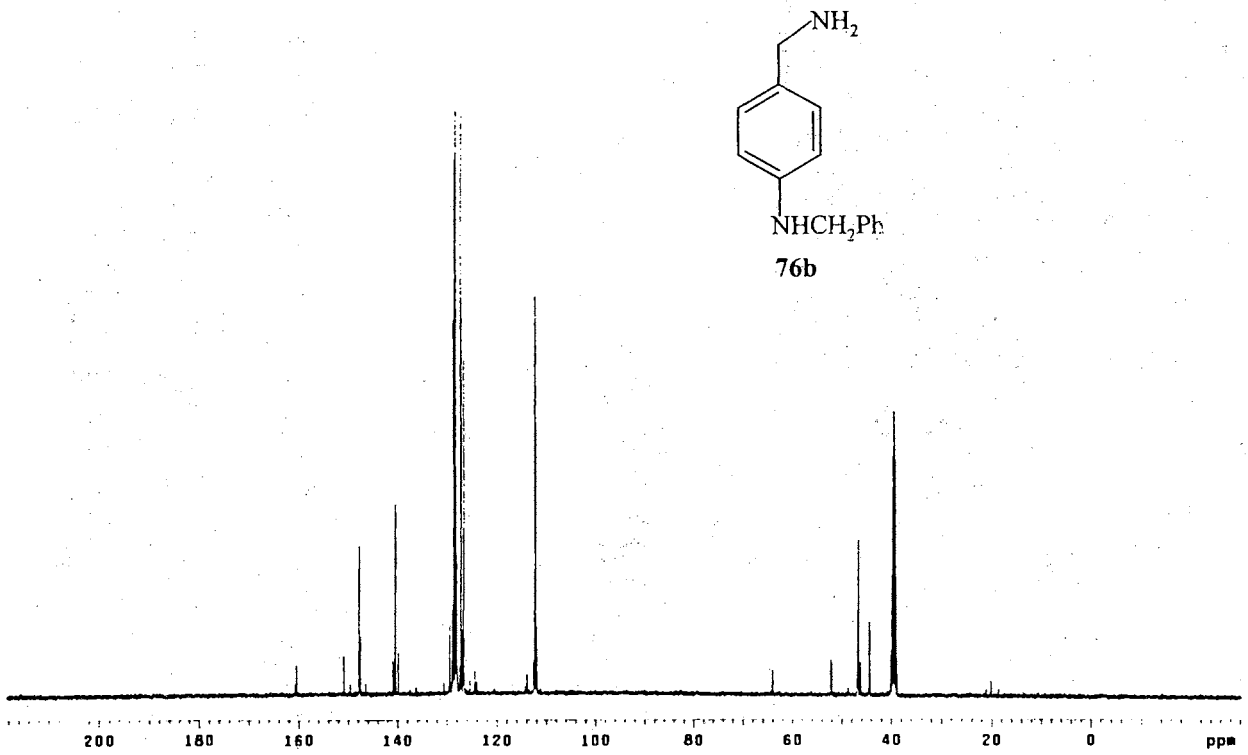
Plate CX



76b

^{1}H Spectrum of **76b**

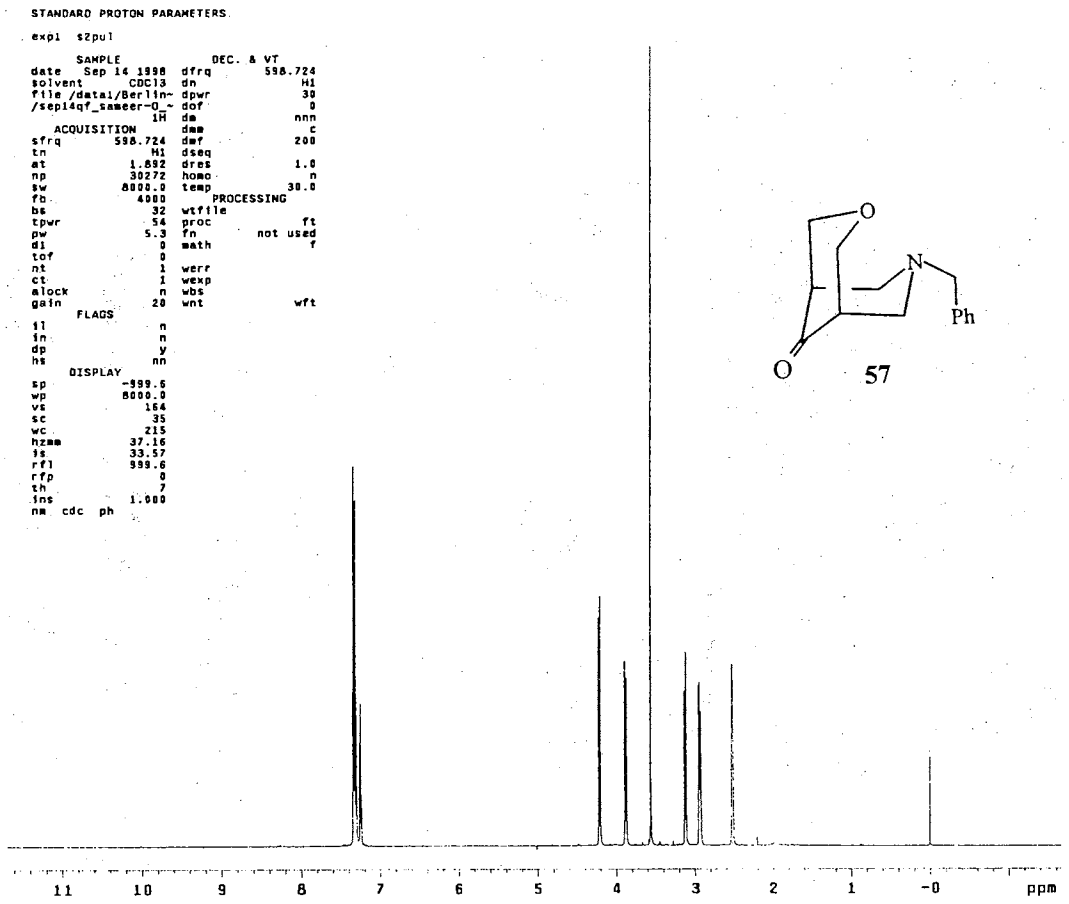
Plate CXI



76b

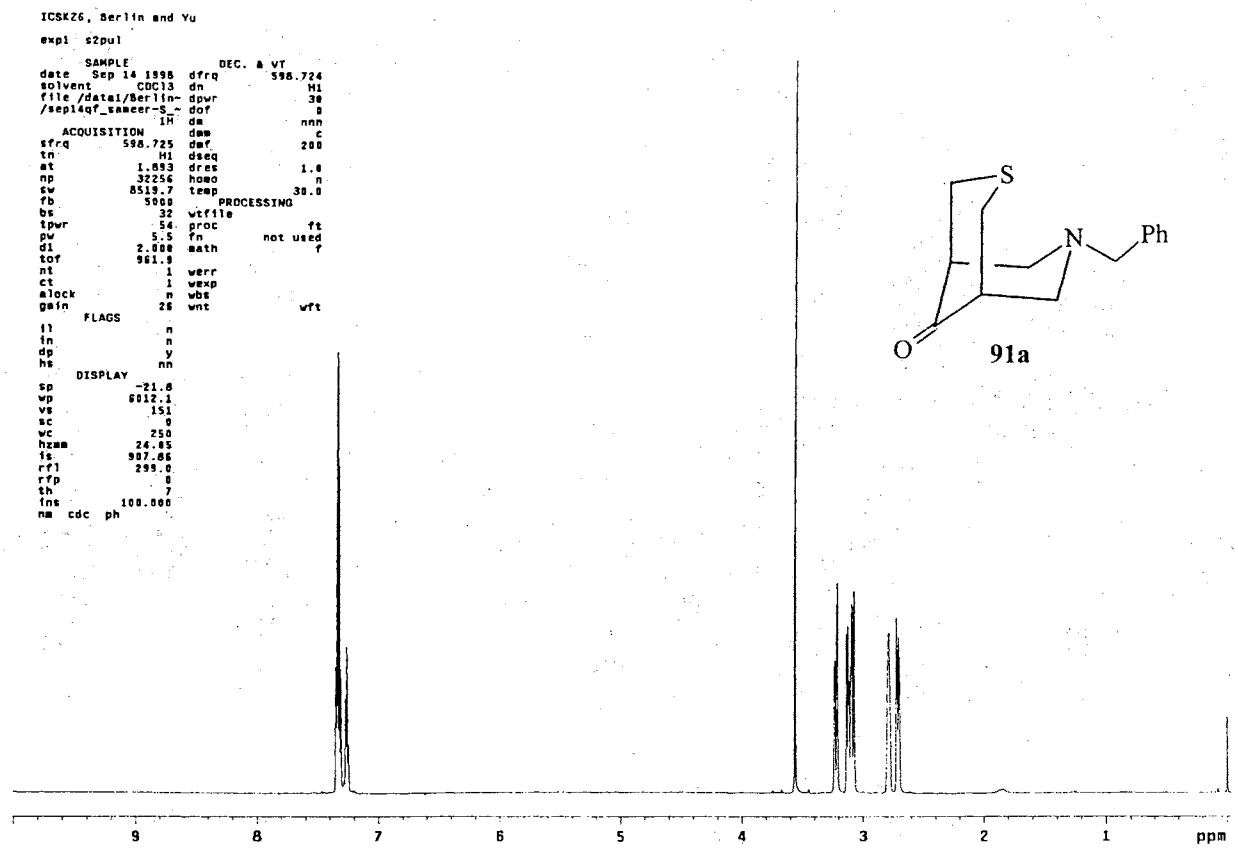
^{13}C Spectrum of **76b**

Plate CXII



^{1}H NMR Spectrum (600 MHz) of **57**

Plate CXIII



^{1}H NMR Spectrum (600 MHz) of **91a**

References

1. (a) Berlin, K. D.; Garrison, G. L.; Couch, K. M.; Tyagi, S.; Sangiah, S. 3,7-Diheterabicyclo[3.3.1]nonan-9-ones-Potential Synthons for Novel Heterocycles. *Main Group Chemistry News* **1995**, *3*, 6-12. (b) Jeyaraman, R.; Avila, S. Chemistry of 3-Azabicyclo[3.3.1]nonanes. *Chem. Rev.*, **1981**, 149.
2. Chiavarelli, S.; Del Carmine, R.; Michalek, H. Effect of Some Antiarrhythmic 1,5-Diphenyl-Bispidine Derivatives on *in vitro* Oxygen Uptake and Glucose Utilization of Rat Heart Muscle. *Ann. 1st Super. Sanita.* **1972**, *8*, 156-158.
3. Chiaverelli, S.; Toffler, F.; Mistiti, D. Synthesis of 1,5-Diphenylbispidines-9-ones.XII, Complex Salts of 1,5-Diphenyl-3,7-bis[1-carboxy-1-methylethyl]bispidin-9-one. *Ann. 1st. Super. Sanita* **1968**, *4*, 157; *Chem. Abstr.* **1968**, *70*, 6857r.
4. (a) Zefirov, N. S.; Palyulin, V. A. Conformational Analysis of Bicyclo[3.3.1]nonanes and Their Hetero analogs, in *Topics in Stereochemistry*, Volume 20, Eliel, E. L.; Wilen, S. H., Editors, J. Wiley & Sons: New York, 1991, pp 171-230. (b) Zefirov, N. S. Conformational Analysis of Bicyclo[3.3.1]nonanes. *Russ. Chem. Rev.* **1975**, *44*, 196-211. (c) Douglass, J. E.; Ratcliff, T. B. The Synthesis of Some 3,7-Dialkyl-3,7-diazabicyclo[3.3.1]nonanes and a Study of Their Conformations. *J. Org. Chem.* **1968**, *33*, 355-359.
5. (a) Hart, N. K.; Jones, S. R.; Lamberton, J. A. (+)-9-Aza-1-methyl-bicyclo[3.3.1]nonan-3-one, A New Alkaloid From *Euphorbia Atoto Forst. Aust. J. Chem.* **1967**, *20*, 561-563. (b) Henry, T. A. *Plant Alkaloids*, J. and A. Churchill Ltd.: London, 1956; p 75. (c) Pelletier, S. W. *Chemistry of the Alkaloids*; Van Nostrand: New York, 1970, p 503. (d) Shimizu, B.; Ogiso, A.; Iwai, I. Approach to

Synthesis of Diterpenoid Alkaloids. I. Mannich Reaction of 2,6-Disubstituted Cyclohexanones. *Chem. Pharm. Bull.* **1963**, *11*, 333-336. (e) Wiesner, K.; Valenta, Z. Chemistry of the Aconite-Garrya Alkaloid. *Prog. Chem. Org. Nat. Prod.* **1958**, *16*, 26-89.

6. Ruenitz, P. C.; Mokler, C. M. Analogues of Sparteine. 5. Antiarrhythmic Activity of Selected *N*, *N'*-Disubstituted Bispidines. *J. Med. Chem.* **1977**, *20*, 1668-1671.
7. (a) Kannel, W. B.; McGee, D. L.; Schatzkin, A. An Epidemiologic Perspective of Sudden Death: 26 Year Follow Up in the Framingham Study. *Drugs* **1984**, *28*, 1-16. (b) Morganroth, J.; Horowitz, L. N., Eds., *Sudden Cardiac Death*, Grune and Stratton: Orlando, Florida, 1973. (c) Eisenberg, M. S.; Bergner, L.; Hallstrom, A. P.; Cummins, R. O. Sudden Cardiac Death. *Sci. Am.* **1986**, *254*, 37-43.
8. (a) Schaffer, W. A.; Cobb, L. A. Recurrent Ventricular Fibrillation and Modes of Death in Survivors of Out-of-Hospital Ventricular Fibrillation. *N. Engl. J. Med.* **1975**, *293*, 259-262. (b) Lown, B.; Verrier, R. L. Neural Activity and Ventricular Fibrillation. *N. Engl. J. Med.* **1976**, *294*, 1165. (c) Raizes, G.; Wagner, G.; Hackel, D. Instantaneous Nonarrhythmic Cardiac Death in Acute Myocardial Infarction. *Am. J. Cardiol.* **1977**, *39*, 1. (d) Bigger, J. T. Jr.; Kleiss, J. L.; Kleiger, R.; Miller, J. P.; Rolnitzsky, L. M. The Relationships Among Ventricular Arrhythmias, Left Ventricular Dysfunction, and Mortality in the 2 Years After Myocardial Infarction. *Circulation* **1984**, *69*, 250-258. (e) Yusuf, S.; Teo, K. K. Approaches to Prevention of Sudden Death: Need For Fundamental Reevaluation. *J. Cardiovascular Electrophysiology* **1991**, *2*, S233-S239. (f) Link, M. S.; Homoud, M.; Foote, C. B.;

Wang, P. J.; Estes, N. A. M. Antiarrhythmic Drug Therapy for Ventricular Arrhythmias. *J. Cardiovascular Electrophysiology* **1996**, *7*, 653-669.

9. Herling, I. M.; Kotler, M. N.; Segal, B. L. Sudden Cardiac Death in Patients with Hypertrophic Cardiomyopathy. *Prac. Cardiol.* **1982**, *8*, 197.
10. Goodwin, J. F.; Oakley, C. M. The Cardiomyopathies. *Br. Heart J.* **1972**, *34*, 545.
11. (a) Jeresaty, R. M. Sudden Death in the Mitral Valve Prolapse-Click Syndrome. *Am. J. Cardiol.* **1976**, *37*, 317. (b) DeMaria, A. N.; Amsterdam, E. A.; Vismara, L. A. Arrhythmias in the Mitral Valve Prolapse Syndrome: Prevalence, Nature, and Frequency. *Ann. Intern. Med.* **1976**, *84*, 656.
12. (a) Schwartz, P. J.; Periti, M.; Malliani, A. The Long Q-T Syndrome. *Am Heart J.* **1975**, *89*, 378. (b) Moss, A. J.; Schwartz, P. G. Sudden Death and the Idiopathic Long Q-T Syndrome. *Am. J. Med.* **1979**, *66*, 6.
13. (a) Kaplan, M. A.; Fohen, K. L. Ventricular Fibrillation in the Wolff-Parkinson-White Syndrome. *Am. J. Cardiol.* **1969**, *24*, 259. (b) Dreifus, L. S.; Haiat, R.; Watanabe, Y. Ventricular Fibrillation: A Possible Mechanism of Sudden Death in Patients with Wolff-Parkinson-White Syndrome. *Circulation* **1971**, *43*, 520.
14. (a) Reiffel, J. A.; Estes, N. A. M.; Waldo, A. L.; Prystowsky, E. N.; DiBianco, R. A Consensus of Report on Antiarrhythmic Drug Use. *Clin. Cardiol.* **1994**, *17*, 103-116. (b) Roden, D. M. Risks and Benefits of Antiarrhythmic Therapy. *N. Engl. J. Med.* **1994**, *331*, 785-790.
15. (a) Billman, G. E.; Altschuld, R. A. *Burgers Medicinal Chemistry and Drug Discovery*, 5th Edition, Volume 4, Wiley: New York, 1997, p 73-99. (b) Martin, G.

V.; Kennedy, J. W. in Julian, D. and Braunwald, E., Eds., *Management of Acute Myocardial Infarction.* W. B. Saunders Co: London, 1994, p 71-105.

16. (a) Karmazyn, M.; Moffat, M. P. Role of Na^+/H^+ Exchange in Cardiac Physiology and Pathophysiology: Mediation of Myocardial Reperfusion Injury by the pH Paradox. *Cardiovasc. Res.* **1993**, *27*, 915-924. (b) Khandoudi, N.; Ho, J.; Karmazyn, M. Role of Na^+-H^+ Exchange in Mediating Effecrs of Endothelin-1 on Normal and Ischemic/Reperfused Hearts. *Circ. Res.* **1994**, *75*, 369-378.
17. (a) Lisa, F. D.; Tullio, R. De; Salamino, F.; Barbato, R.; Melloni, E.; Siliprandi, N.; Schiaffino, S.; Pantremoli, S. Specific Degradation of Troponin T and I by μ-Calpin and its Modulation by Substrate. *Biochem. J.* **1995**, *308*, 57-61. (b) Atsma, D. E.; Bastiaanse, E. M. L.; Jerewski, A.; van der Valk, L. J. M.; van der Laarse, A. Role of Calcium-Activated Neutral Protease (Calpain) in Cell Death in Cultered Neonatal Rat Cardiomyocytes During Metabolic Inhibition. *Circ. Res.* **1995**, *76*, 1071-1078.
18. (a) Hazen, S. L.; Ford, D. A.; Gross, R. W. Activation of a Membrane-Associated Phospholipase A_2 During Rabbit Myocardial Ischemia Which is Highly Selective for Plasmogen Substrate. *J. Biol. Chem.* **1991**, *266*, 5629-5633. (b) Armstrong, S. C.; Ganote, C. E. Effects of the Phospholipase Inhibitor Mepairine on Injury in Ischemic and Metabolically Inhibited Adult Isolated Myocytes. *Am. J. Pathol.* **1991**, *138*, 545-555. (c) Hostetler, K. Y.; Jellison, E. J. Role of Phospholipases in Myocardial Ischemia: Effects of Cardioprotective Agents on the Phospholipase A of Heart Cytosol and Sarcoplasmic Reticulum in vitro. *Mol. Cell. Biochem.* **1989**, *88*, 77-82.

19. (a) Opie, L. H.; Nathan, D.; Lubbe, W. F. Biochemical Aspects of Arrhythmogenesis and Ventricular Fibrillation. *Am. J. Cardiol.* **1979**, *43*, 131-148. (b) Curtis, M. J.; Pugsley, M. K.; Walker, M. J. Endogenous Chemical Mediators of Ventricular Arrhythmias in Ischemic Heart Disease. *Cardiovasc. Res.* **1993**, *27*, 703-719. (c) Billman, G. E. Role of ATP Sensitive Potassium Channel in Extracellular Potassium Accumulation and Cardiac Arrhythmias During Myocardial Ischemia. *Cardiovasc. Res.* **1994**, *28*, 762-769.

20. Adamovich, D. R. *The Heart*, Bireline Publishing Co.: New York, 1984, p 56.

21. (a) Touboul, P. *Selected Topics in Cardiac Arrhythmias*, Futura: Mount Kisco, New York, 1980, p 95. (b) Goldberger, A. L.; Curtis, G. P. *J. Electrocardiol.* **1982**, *15*, 397. (c) Nattel, S. Antiarrhythmic Drug Classifications: A Critical Appraisal of Their History, Present Status, and Clinical Relevance. *Drugs* **1991**, *41*, 672-701. (d) MacFadyen, R. J.; Prasad, N. Clinical Pharmacology and Classification of Antiarrhythmic Drugs. *Br. J. Hos. Med.* **1995**, *54*, 515-519.

22. Vaughan Williams, M.A. Classification of Antiarrhythmic Actions Reassessed After a Decade of New Drugs. *J. Clin. Pharmacol.* **1984**, *24*, 129-147.

23. (a) Kienzle, M. G.; Williams, P. D.; Zygmont, D.; Doherty, J. U.; Josephson, M. E. Antiarrhythmic Drug Therapy for Sustained Ventricular Tachycardia. *Heart and Lung* **1984**, *13*, 614-622. (b) Bristol, J. W.; Ed., *Cardiovascular Drugs*, John Wiley and Sons: New York, 1986.

24. El-Sherif, N. El.; Scherlag, B. J.; Lazzara, R.; Hope, R. R. Re-entrant Ventricular Arrhythmias in the Late Myocardial Infarction Period. Mechanism of Action of Lidocaine. *Circulation*, **1977**, *56*, 395.

25. Ariens, E. J., Ed., *Drug Design*, Academic Press: New York, 1977, Chapter 4.

26. Pratt, C.; Lichstein, E. Ventricular Antiarrhythmic Effects of Beta-Adrenergic Blocking Drugs: A Review of Mechanism and Clinical Studies. *J. Clin. Pharmacol.* **1982**, *22*, 335.

27. (a) Khan, M. M.; Logan, K. R.; NcComb, J. M.; Adgey, A. A. Management of Recurrent Ventricular Tachycardia Associated with Q-T Prolongation. *Am. J. Cardiol.* **1981**, *47*, 1301-1308. (b) Jackman, W. M.; Friday, K. J.; Anderson, J. L.; Aliot, E. M.; Clark, M.; Lazzara, R. The Long QT Syndromes: A Critical Review in New Clinical Observation and a Unifying Hypothesis. *Prog. Cardiovasc. Dis.* **1988**, *2*, 115-172.

28. Singh, B. N. Advantages of Beta Blockers Versus Antiarrhythmic Agents and Calcium Antagonists in Secondary Prevention After Myocardial Infarction. *Am. J. Cardiol.* **1990**, *66*, 9C-20C.

29. Singh, B. N.; Nademanee, K. Control of Arrhythmias by Selective Lengthening of Cardiac Repolarization: Theoretical Considerations and Clinical Observations. *Am. Heart J.* **1985**, *109*, 421-430 (b) Feld, G. K.; Venkatesh, N.; Singh, B. N. Pharmacological Conversion and Suppression of Experimental Canine Atrial Flutter. *Circulation* **1986**, *74*, 147-204.

30. Hohnloser, S. H.; Woosley, R. L. Sotalol. *N. Engl. J. Med.* **1994**, *331*, 31-38.

31. (a) Cairns, J.; Connolly, J. T. The Problem of Asymptomatic Ventricular Arrhythmias Among Survivors of Acute Myocardial Infarction: Role of Amiodarone. *ACC Am. J. Review* **1995**, *4*, 32-34. (b) Salerno, D. M.; Gillingham, K. J.; Berry, D. A.; Hodges, M. A Comparison of Antiarrhythmic Drugs for the

Suppression of Ventricular Ectopic Depolarizations: A Meta-Analysis. *Am. Heart J.* **1990**, *120*, 340-353. (c) Cairns, J. A.; Connolly, S. J.; Roberts, R. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIT): Rationale and Protocol. *Am. J. Cardiol.* **1993**, *72*, 87F-94F. (d) Camm, A. J.; Julian, D.; Janse, G. The European Myocardial Infarct Amiodarone Trial (EMIAT). *Am. J. Cardiol.* **1993**, *72*, 95F-98F. (e) Weinberg, B. A.; Miles, W. M.; Klein, L. S.; Bolander, J. E.; Dusman, R. E.; Stanton, M. S.; Langefeld, C.; Zipes, D. P. Five Year Follow-Up of 589 Patients Treated with Amiodarone. *Am. Heart J.* **1993**, *125*, 109-120. (f) Burkart, F.; Pfisterer, M.; Kiowski, W., Follath, F.; Burckhardt, D. Effects of Antiarrhythmic Therapy on Mortality in Survivors of Myocardial Infarction with Asymptomatic Complex Ventricular Arrhythmias. Basel Antiarrhythmic Study of Infarct Survival (BASIS). *J. Am. Coll. Cardiol.* **1990**, *16*, 1711-1718. (g) Ceremuzynski, L.; Kleczar, E.; Krzeminska-Pakula, M., Kuch, J.; Nartowicz, E.; Smielak-Korombei, J.; Dyduszynski, A.; Macieejewicz, J.; Zaleska, T.; Lazarczyk-Kedzia, E.; Motyka, J.; Paczkowska, B.; Sczaniecka, O.; Yusuf, S. Effect of Amiodarone on Mortality After Myocardial Infarction: A Double-Blind, Placebo-Controlled, Pilot Study. *J. Am. Coll. Cardiol.* **1992**, *20*, 1056-1062. (h) O'Nunain, S.; Ruskin, J. Cardiac Arrest. *Lancet* **1993**, *341*, 1641-1647. (i) Doval, H. C.; Nul, D. R.; Grancelli, H. O.; Perrone, S. V.; Bortman, G. R. Randomized Trial of Low-Dose Amiodarone in Severe Congestive Heart Failure. *Lancet.* **1994**, *344*, 493-498. (j) Singh, B. N.; Vaughan Williams, E. M. The Effect of Amiodarone, a New Antianginal Drug on Cardiac Muscle. *Br. J. Pharmacol.* **1970**, *39*, 657-662.

32. Koch-Weser, J. Medical Intelligence: Drug Therapy. *N. Eng. J. Med.* **1979**, *300*, 473-477.

33. (a) Anderson, J. L.; Askins, J. C.; Gilbert, E. M.; Menlove, R. L.; Lutz, J. R. Multicenter Trial of Sotalol for Suppression of Frequent, Complex Ventricular Arrhythmias: A Double-Blind, Randomized, Placebo-Controlled Evaluation of Two Doses. *J. Am. Coll. Cardiol.* **1986**, *8*, 752-762. (b) Deedwina, P. C. Supressant Effects of Conventional Beta Blockers and Sotalol on Complex and Repetitive Ventricular Premature Complexes. *Am. J. Cardiol.* **1990**, *65*, 43A-50A. (c) Julian D. G.; Prescott, R. J.; Jackson, F. S.; Szekely, P. Controlled Trial of Sotalol for One Year After Myocardial Infarction. *Lancet.* **1982**, *1*, 1142-1147. (d) Borggrefe, M.; Hief, C.; Chen, X.; Breithardt, G. Acute and Long Term Efficacy of Oral Sotalol in Patients With Sustained Ventricular Tachycardia or Out-of -Hospital Cardiac Arrest. *Circulation* **1992**, *86*, I-533.

34. Lumma, W. C.; Wohl, R. A.; Davey, D. D.; Argentieri, T. M.; DeVita, R. J.; Gomez, R. P.; Jain, V. K.; Marisca, A. J.; Morgan, T. K.; Reiser, H. J.; Sullivan, M. E.; Wiggins, J.; Wong, S. S. Rational Design of 4-[(Methylsulfonyl)amino]benzamides as Class III Antiarrhythmic Agents. *J. Med. Chem.* **1987**, *30*, 755-758.

35. Morgan, T. M.; Randall, L.; Lumma, W. C.; Nickisch, K.; Wohl, R. A.; Phillips, G. B.; Gomez, R. P.; Lind, J. M.; Lampe, J. W.; DiMeo, S. V. Synthesis and Cardiac Electrophysiologic Activity of *N*-Substituted-4-(1*H*-imidazole-1-yl)benzamides: New Selective Class III Agents. *J. Med. Chem.* **1990**, *33*, 1091-1097.

36. Butera, J. A.; Spinelli, W.; Anantharaman, V.; Marcopulos, N.; Parsons, R. W.; Moubarak, I. F.; Cullinan, C.; Bagli, J. F. Synthesis and Selective Class III

Antiarrhythmic Activity of Novel *N*-Heteroaralkyl-Substituted 1-(Aryloxy)-2-propanolamine and Related Propylamine Derivatives. *J. Med. Chem.* **1991**, *34*, 3212-3228.

37. Singh, B. N.; Nadamanee, K.; Baky, S. H. Calcium Antagonists. Clinical Use in the Treatment of Arrhythmias. *Drugs*, **1983**, *25*, 125.
38. Schamroth, L.; Krikler, D. M.; Garatt, C. Immediate Effects of Intravenous Verapamil in Cardiac Arrhythmias. *Br. Med. J.* **1972**, *1*, 660.
39. Betriu, A., Chaitman, B. A.; Bourassa, M. G.; Brevers, G.; Scholle, J. M.; Bruneau, P.; Gagne, P.; Chabot, M. Beneficial Effects of Intravenous Diltiazem in the Acute Management of Paroxysmal Supraventricular Tachyarrhythmias. *Circulation* **1983**, *67*, 88.
40. (a) Kass, R. S.; Scheuer, T. Calcium and Cardiac Physiology, in Flaim, S. F.; Zelis, R., Eds., *Calcium Blockers*, Urban and Schwarzenberg: Baltimore-Munich, 1982, p 3. (b) Singh, B. N.; Vaughan Williams, E. M. *Cardiovasc. Res.* **1972**, *6*, 109.
41. Dahl, G.; Isenberg, G. Decoupling of Heart Muscle Cells: Correlation with Increased Cytoplasmic Calcium Activity and with Changes of Nexus Ultrastructure. *J. Membr. Biol.* **1980**, *53*, 63.
42. DeMello, W. C. Modulation of Junctional Permeability. *Fed. Proc.* **1984**, *43*, 2692.
43. Millar, J. S.; Vaughan Williams, E. M. Anion Antagonism-A Fifth Class of Antiarrhythmic Action? *Lancet.* **1981**, *1*, 1291.
44. Harron, D. W. G.; Allen, J. D.; Wilson, R.; Shanks, R. G. Effects of Alinidine on Experimental Cardiac Arrhythmias. *J. Cardiovasc. Pharmacol.* **1982**, *4*, 221.

45. Millar, J. S.; Vaughan Williams, E. M. Pacemaker Selectivity: Influence on Rabbit Atria of Ionic Environment and of Alinidine, a Possible Anion Antagonist. *Cardiovasc. Res.* **1981**, *15*, 335.

46. Woosley, R. L. Antiarrhythmic Drugs. *Ann. Rev. Pharmacol. Toxicol.* **1991**, *31*, 427-455.

47. Scholz, H. Classification and Mechanisms of Action of Antiarrhythmic Drugs. *Fund. Clin. Pharmacol.* **1994**, *8*, 385-390.

48. Pratt, C. M.; Moye, L. A. The Cardiac Arrhythmia Suppression Trial-Casting Suppression in a Different Light. *Circulation* **1995**, *91*, 245-247.

49. Rosen, M. R. For the European Group on Arrhythmias The Sicilian Gambit: A New Approach to Classification of New Arrhythmic Drugs Based on Their Actions on Arrhythmogenic Mechanisms. *Eur. Heart J.* **1991**, *12*, 1112-31.

50. Ruenitz, P. C.; Mokler, C. M. Antiarrhythmic Activity of Some *N*-Alkylbispidinesbenzamides. *J. Med. Chem.* **1979**, *22*, 1142-1146.

51. (a) Binnig, F.; Raschack, M.; Treiber, H. J. Cardioactive Bispidones and Bispidines. U.S. Patent 3,963,449, 1976; *Chem. Abstr.* **1976**, *84*, 15067x. (b) Binnig, F.; Friedrich, L.; Hoffmann, H. P.; Kreiskott, H.; Mueller, C.; Raschack, M. Bispidines Derivatives, Their Preparation and Drugs Containing Same. U.S. Patent 4,183935, 1980; *Chem. Abstr.* **1979**, *90*, 121568h. (c) Binnig, F.; Mueller, C. D.; Raschack, M.; von Philipsborn, G. Bispidines Derivatives and Antiarrhythmic Compositions. U.S. Patent 4,556,662, 1985; *Chem. Abstr.* **1983**, *98*, 16738f.

52. Nador, K.; Kraiss, G.; Siako, K.; Paroczai, M.; Karpati, E.; Szporny, L. 3,7-Diazabicyclo[3.3.1]nonanes Having Antiarrhythmic Activity. U.S. Patent 4,451,473, 1984; *Chem. Abstr.* **1983**, *99*, 5654v.

53. (a) Garrison, G. L.; Berlin, K. D.; Scherlag, B. J.; Lazzara, R.; Patterson, E.; Fazekas, T.; Sangiah, S.; Chen, C. L.; Schubot, F. D.; van der Helm, D. Novel 3,7-Diheterabicyclo[3.3.1]nonanes That Possess Predominant Class III Antiarrhythmic Activity in 1-4 Day Post Infarction Dog Models: X-ray Diffraction Analysis of 3-[4-(1H-Imidazol-1-yl)benzoyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane Dihydroperchlorate. *J. Med. Chem.* **1996**, *39*, 2559-2570. (b) Chen, C. L.; Sangiah, S.; Berlin, K. D.; Scherlag, B. J.; Patterson, E.; Lazzara, R. BRB-I-28: A Novel Class Ib Antiarrhythmic Agent. *Cardiovascular Drug Reviews* **1994**, *12*, 237-253. (c) Chen, C. L.; Sangiah, S.; Patterson, E.; Berlin, K. D.; Garrison, G. L.; Dunn, W.; Nan, Y.; Scherlag, B. J.; Lazzara, R. Effects of BRB-I-28, A Novel Antiarrhythmic Agent, and its Derivatives on Cardiac Na^+, K^+ ATPase and Mg^{2+}-Activated ATPase Activities and Contractile Forces. *Res. Comm. Chem. Pathol. Pharmacol.* **1992**, *78*, 3-16. (d) Alavi, F. K.; Clarke, C. R.; Sangiah, S.; Berlin, K. D.; Zisman, S. A.; Garrison, G. L.; Scherlag, B. J.; Lazzara, R. Disposition of BRB-I-28 (7-Benzyl-7-aza-3-thiabicyclo[3.3.1]nonanes Hydroperchlorate), A Novel Antiarrhythmic Agent. *Drug Invest.* **1991**, *3(5)*, 317-323. (e) Bailey III, B. R.; Berlin, K. D.; Holt, E. M.; Scherlag, B. J.; Lazzara, R.; Brachmann, J.; van der Helm, D.; Powell, D. R.; Pantaleo, N. S.; Ruenitz, P. C. Synthesis, Conformational Analysis, and Antiarrhythmic Properties of 7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one, 7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonane Hydroperchlorate, and 7-Benzyl-9-phenyl-

3-thia-7-azabicyclo[3.3.1]nonan-9-ol Hydroperchlorate and Derivatives: Single-Crystal X-ray Diffraction Analysis and Evidence for Chair-Chair and Chair-Boat Conformers in the Solid State. *J. Med. Chem.* **1984**, *27*, 758-767. (f) Berlin, K. D.; Scherlag, B. J.; Clarke, C. R. Otiv, S. R.; Zisman, S. A.; Sangiah, S.; Mulekar, S. V. Salts of 3-Azabicyclo[3.3.1]nonanes as Potential Antiarrhythmic Agents, and Precursors Thereof. U.S. Patent 5,084,572, 1992; *Chem. Abstr.* **1991**, *115*, 114550c. (g) Thompson, M. D.; Smith, G. S.; Berlin, K. D.; Holt, E. M.; Scherlag, B. J.; van der Helm, D.; Muchmore, S. W.; Fidelis, K. A. Synthesis and Antiarrhythmic Properties of Novel 3-Selena-7-azabicyclo[3.3.1]nonanes and Derivatives. Single-Crystal X-ray Diffraction Analysis of 7-Benzyl-3-selena-7-azabicyclo[3.3.1]nonan-9-one and 7-Benzyl-3-selena-7-azabicyclo[3.3.1]nonane Hydroperchlorate. *J. Med. Chem.* **1987**, *30*, 780-788.

54. Smith, G. S.; Thompson, M. D.; Berlin, K. D.; Holt, E. M.; Scherlag, B. J.; Patterson, E.; Lazzara, R. A Study of the Synthesis and Antiarrhythmic Properties of Selected 3,7-Diheterabicyclo[3.3.1]nonanes with Substituted at the 2,4-Positions and at the 9-Position. *Eur. J. Med. Chem.* **1990**, *25*, 1-8.

55. Beatch, G. N.; Abraham, S.; MacLeod, B. A.; Yoshida, N. R.; Walker, M. J. A. Antiarrhythmic Properties of Tedisamil (KC8857), a Putative Transient Outward K^+ Current Blocker. *Br. J. Pharmacol.* **1991**, *102*, 13-18.

56. Taknaka, C.; Sarma, J. S. M.; Singh, B. M. Electrophysiological Effects of Ambasalide (LU47110), a Novel Class III Antiarrhythmic Agent on the Properties of Isolated Rabbit and Canine Cardiac Muscle. *J. Cardiovas. Pharmacol.* **1992**, *19*, 290-298.

57. The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the Antiarrhythmic Agent Morcizine on Survival After Myocardial Infarction. *N. Engl. J. Med.* **1992**, *327*, 227-233.

58. (a) The Cardiac Arrhythmia Suppression Pilot Study (CAPS) Investigators. The Cardiac Arrhythmia Pilot Study. *Am. J. Cardiol.* **1986**, *57*, 91-95. (b) The CAPS Investigators. Effects of Encainide, Flecainide, Impiramine, and Morcizine on Ventricular Arrhythmias During the Year After Acute Myocardial Infarction: The CAPS. *Am. J. Cardiol.* **1988**, *61*, 501-509.

59. (a) Mason, J. W., for the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) Investigators. A Comparison of Electrophysiologic Testing With Holter Monitoring to Predict Antiarrhythmic Drug Efficacy for Ventricular Tachyarrhythmias. *N. Engl. J. Med.* **1993**, *329*, 445-451. (b) Mason, J. W., for the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) Investigators. A Comparison of Seven Antiarrhythmic Drugs in Patients with Ventricular Tachyarrhythmias. *N. Engl. J. Med.* **1993**, *329*, 452-465.

60. Burkart, F.; Pfisterer, M.; Facc, W. K.; Follath, F.; Burckardt, D.; Jordi, H. Effect of Antiarrhythmic Therapy on Mortality in Survivors of Myocardial Infarction with Asymptomatic Complex Ventricular Arrhythmias: Basel Antiarrhythmic Study of Infarct Survival (BASIS). *J. Am. Coll. Cardiol.* **1990**, *16*, 1711-1718.

61. Siebels, J.; Kuck, K. H. The CASH Investigators. Implantable Cardioverter Defibrillator Compared With Antiarrhythmic Drug Treatment in Cardiac Arrest Survivors (the Cardiac Arrest Study Hamburg). *Am. Heart J.* **1994**, *89*, 2892-2907.

62. (a) Moncada, S. Nitric Oxide. *J. Hypertension* **1994**, *12(suppl 10)*, S35-S39. (b) Snyder, S. H.; Bredt, D. Biological Roles of Nitric Oxide. *Sci. Am.* **1992**, *266*, 68-77. (c) Kerwin, J. F.; Lancaster, J. R.; Feldman, P. L. Nitric Oxide: A New Paradigm for Second Messengers. *J. Med. Chem.* **1995**, *38*, 4343-4362.

63. (a) Palmer, R. M. J.; Ashton, D. S.; Moncada, S. Vascular Endothelial Cells Synthesize Nitric Oxide From *L*-Arginine. *Nature* **1988**, *333*, 664-666. (b) Furchgott, R. F. Studies of Endothelium-dependent Vasodilation and the Endothelium-derived Relaxing Factor. *Acta. Physiol. Scand.* **1990**, *139*, 257-270.

64. Moncada, S.; Higgs, A. The *L*-Arginine-Nitric Oxide Pathway. *N. Engl. J. Med.* **1993**, *329*, 2002-2012.

65. Rubanyi, G. M. Endothelium-derived Relaxing and Contracting Factors. *J. Cell. Biochem.* **1991**, *46*, 27-36.

66. Palmer, R. M.; Ferrige, A. G.; Moncada, S. Nitric Oxide Release Accounts for the Biological activity of Endothelium-Derived Relaxing Factors. *Nature* **1987**, *327*, 524-526.

67. Rhodes, P. M.; Leone, A. M.; Francis, P. L.; Strthers, A. D.; Moncada, S. *Biochem. Biophys. Res. Commun.* **1995**, *209*, 590-596.

68. Hondeghem, L. M.; Snyder, D. J. Class III Antiarrhythmic Agents Have a Lot of Potential But a Long Way to Go. Reduced Effectiveness and Dangers of Reverse Use Dependence. *Circulation* **1990**, *81*, 686-690.

69. Morgan, T. M.; Randall, L.; Lumma, W. C.; Nickisch, K.; Wohl, R. A.; Phillips, G. B.; Gomez, R. P.; Lind, J. M.; Lampe, J. W.; DiMeo, S. V. Synthesis and Cardiac

Electrophysiological Activity of *N*-Substituted-4-(1*H*-imidazole-1-yl)benzamides: New Selective Class III Agents. *J. Med. Chem.* **1990**, *33*, 1091-1097.

70. Bristol, J. A., Ed., *Cardiovascular Drugs*, John Wiley and Sons: New York, 1986.

71. Couch, K. M.; Berlin, K. D.; Scherlag, B. J.; Patterson, E. Unpublished Results.

72. Majerus, P. W.; Broze, G. J.; Miletich, J. P.; Tollefsen, D. M. in Goodman and Gilman's The Pharmacological Basis of Therapeutics, Gilman, G.; Rall, T. W.; Nies, A. S.; Taylor, P., Eds., 8th ed., McGraw Hill: New York, 1993, pp 1311-1331.

73. (a) Drago, R. S.; Paulik, F. E. The Reaction of Nitrogen (II) Oxide with Diethylamine. *J. Am. Chem. Soc.* **1960**, *82*, 96-98. (b) Drago, R. S.; Karstetter, B. R. The Reaction of Nitrogen (II) Oxide with Various Primary and Secondary Amines. *J. Am. Chem. Soc.* **1961**, *83*, 1819-1822. (c) Drago, R. S.; Ragsdale, R. O.; Eyman, D. P. A Mechanism for the Reaction of Diethylamine with Nitric Oxide. *J. Am. Chem. Soc.* **1961**, *83*, 4337-4339. (d) Longhi, R.; Ragsdale, R. O.; Drago, R. S. Reactions of Nitrogen (II) Oxide with Miscellaneous Lewis Bases. *Inorg. Chem.* **1962**, *1*, 768-770. (e) Ragsdale, R. O.; Karstetter, B. R.; Drago, R. S. Decomposition of the Adducts of Diethylamine and Isopropylamine with Nitrogen (II) Oxide. *Inorg. Chem.* **1965**, *4*, 420-422.

74. Hrabie, J. A.; Klose, J. R.; Wink, D. A.; Keefer, L. K. New Nitric Oxide-Releasing Zwitterions Derived from Polyamines. *J. Org. Chem.* **1993**, *58*, 1472-1476.

75. (a) Arend, M.; Westermann, B; Risch, N. Modern Variants of the Mannich Reaction. *Angew. Chem. Int. Ed.* **1998**, *37*, 1044-1070. (b) Ruenitz, P. C.;

Smissman, E. E. Use of the Mannich Reaction in the Synthesis of Bispidines. *J. Het. Chem.* **1976**, *13*, 1111-1113.

76. Zisman, S. A.; Berlin, K. D.; Scherlag, B. J. The Preparation of Amide Derivatives of 3-azabicyclo[3.3.1]nonanes as New Potential Antiarrhythmic Agents. *Org. Prep. Proc. Int.* **1990**, *22*, 255-264.

77. Hatch, R. P. ; Shringarpure, J.; Weinreb, S. M. Studies on Total Synthesis of the Olivomycins. *J. Org. Chem.* **1978**, *43*, 4172-4177.

78. Ram, S.; Ehrenkaufer, R. E. Ammonium Formate in Organic Synthesis: A Versatile Agent in Catalytic Hydrogen Transfer Reductions. *Synthesis* **1988**, 91-95.

79. Somei, M.; Kato, K; Inour, S. Titanium (III) Chloride for the Reduction of Heteroromatic and Aromatic Nitro Compounds. *Chem. Pharm. Bull.* **1980**, *28*, 2515-2518.

80. Rawal, V. H.; Jones, R. J.; Cava, M. P. Photocyclization Strategy for the Synthesis of Antitumor Agent CC-1065: Synthesis of Dideoxy PDE-I and PDE-II. Synthesis of Thiophene and Furan Analogues of Dideoxy PDE-I and PDE-II. *J. Org. Chem.* **1987**, *52*, 19-28.

81. Bonnat, M.; Hercouet, A.; Corre, L. M. Effect of the Temperature on the Stoichiometry of Borane Dimethyl Sulfide Reduction of Secondary and Tertiary Amides. *Syn. Comm.* **1991**, *21*, 1579-1582.

82. Magid-Abdel, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. Reductive Amination of Aldehydes and Ketones with Sodium

Triacetoxyborohydride. Studies on Direct and Indirect Reductive Amination Procedures. *J. Org. Chem.* **1996**, *61*, 3849-3862.

83. Mandel, W. J., Ed., *Cardiac Arrhythmias*: *Their Mechanisms, Diagnosis, and Managements*, J. P. Lippincott: Philadelphia, Pennsylvania, 1987.

84. (a) Arjunan, P.; Berlin, K. D.; Barnes, C. L.; van der Helm, D. Synthesis and a Conformational Study of Certain Selected 3-Oxa-7-azabicyclo[3.3.1]nonan-9-ones. Single crystal X-Ray Diffraction Analysis of 6,8-Bis(2-Chlorophenyl-1,3-oxa-7-azabicyclo[3.3.1]nonan-9-one. *J. Org. Chem.* **1981**, *46*, 3196. (b) Bailey, B. R.; Berlin, K. D.; Holt, E. M. Isolation and Single Crystal X-Ray Diffraction Analysis of *N*-Benzyl-3-thia-7-azabicyclo[3.3.1]nonan-9,9-diol Perchlorate, A Novel Hydrate Formed from Reaction of *N*-Benzyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one with Hydroperchloric Acid. *Phosphorus and Sulfur* **1984**, *20*, 131-137. (c) Mulekar, S. V.; Berlin, K. D. Correlation of Stereochemistry and Heteroatom Configurations with ^{17}O Chemical Shifts in Substituted 1-Hetera-4-cyclohexanones. *J. Org. Chem.* **1989**, *54*, 4758-4767. (d) Tyagi, S.; Berlin, K. D.; Hossain, M. B.; Sinars, C.; van der Helm, D.; Sangiah, S. Novel 9,9-Diol Systems Starting from a 3,7-Diazabicyclo[3.3.1]nonan-9-one Nucleus-Single Crystal X-Ray Diffraction Analysis of 3-(2-Propyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonan-9,9-diol Hydrobromide, 3-(2-Propyl)-7-[3,4-dimethoxybenzyl]-3,7-diazabicyclo[3.3.1]nonan-9,9-diol Hydrobromide, and 3,7-Diisopropyl-3,7-diazabicyclo[3.3.1]nonan-9,9-diol Dihydrobromide. *Phosphorus and Sulfur* **1997**, *123*, 385-406.

85. (a) Arias, M. S.; Galvez, E.; Del Castillo, J. C.; Chicharro, J. J. Structural and Conformational Study of 3,7-Disubstituted 3,7-Diazabicyclo[3.3.1]nonan-9-ones. *J.*

Mol. Struct. **1987**, *156*, 239-246. (b) Galvez, E.; Arias, M.; Bellanato, J.; Garcia-Ramos, J. V.; Florencio, F.; Smith-Verdier, P.; Garcia-Blanco, S. Structural and Conformational Study of Diazabicyclanones and Diazabicyclanols. *J. Mol. Struct.* **1985**, *127*, 185-201. (c) Smith-Verdier, P.; Florencio, F.; Garcia-Blanco, S. Structure of 3-Benzyl-7-methyl-3,7-diazabicyclo[3.3.1]nonan-9-one, $C_{15}H_{20}N_2O$. *Acta Cryst.* **1983**, *39c*, 101-103.

86. Wasylishen, R. E.; Friesen, K. J. Carbon-13 NMR Spectra of Solid Bicyclo[3.3.1]nonan-9-one. Conformational Studies in the Solid State. *Org. Magn. Reson.* **1980**, *13*, 343-344.

87. Raber, D. J.; Janks, C. M.; Johnston, M. D.; Raber, N. K. Structure Elucidation with Lanthanide Induced Shifts. 9-Bicyclo[3.3.1]nonan-9-one. *Tetrahedron Lett.* **1980**, *21*, 677-680.

88. Takeuchi, Y.; Scheiber, P.; Takada, K. Direct Observation of Boat-Chair Chair-Boat Equilibrium in the 3,7-Diazabicyclo[3.3.1]nonane Ring. *J. C. S. Chem. Comm.* **1980**, 403.

89. (a) Marchand, A. P. *Stereochemical Applications of NMR Studies in Rigid Bicyclic Systems,* Verlag: Deerfield Beach, FL, 1982. (b) Macomber, R. S., *A Complete Introduction to Modern NMR Spectroscopy*, Ch 9, Wiley-Interscience: New York, 1998.

90. Yu, C.; Levy, G. C. Two-Dimensional Heteronuclear NOE (HOESY) Experiments: Investigation of Dipolar Interactions Between Heteronuclei and Nearby Protons. *J. Am. Chem. Soc.* **1984**, *106*, 6533.

91. GAUSSIAN 94 (Revision D. 1), Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheesman, J. R.; Keith, T. A.; Peterson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, J. D.; Binkely, S.; Degrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzales, C.; Pople, J. A., Gaussion, Inc., Pittsburgh, PA, 1995.

92. Unpublished Results of Garrison, G. L.; Zisman, S. A.; Berlin, K. D.

93. Johnson, R. A. Conformations of Alkylpiperidine Amides. *J. Org. Chem.* **1968**, *33*, 3627-3632.

94. Hirsch, J. A.; Augustine, R. L.; Koletar, G.; Wolf, H. G. Barriers to Amide Rotation in Piperidines and Related Systems. Unambiguous Assignments Using Carbon-13 Magnetic Resonance. *J. Org. Chem.* **1975**, *40*, 3547-3552.

VITA

Sameer Tyagi

Candidate for the Degree of

Doctor of Philosophy

Thesis: SYNTHESIS, CONFORMATIONAL, AND ANTIARRHYTHMIC PROPERTIES OF SELECTED DERIVATIVES OF THE 3,7-DIHETERABICYCLO[3.3.1]NONANE FAMILY

Major Field: Chemistry

Biographical:

Personal Data: Born in Meerut, Uttar Pradesh, India, June 8, 1969, the son of Ved Prakash and Santosh Tyagi

Education: Received Bachelor of Science (B.Sc.) Degree in Chemistry from University of Bombay, Bombay, India, in May, 1990; Master of Science (M.S.) from Oklahoma State University, Stillwater, OK, in July, 1995; completed requirements for the Doctor of Philosophy Degree at Oklahoma State University in May, 1999.

Professional Experience: Teaching Assistant, Department of Chemistry, Oklahoma State University, August, 1992, to December, 1998.

Professional Memberships: American Chemical Society, Phi Lambda Upsilon, Sigma Xi