US005110933A

United States Patent [19]

Berlin et al.

[11] Patent Number: 5,110,933

[45] Date of Patent: * May 5, 1992

[54] **SALTS OF 3-AZABICYCLO(3.3.1) NONANES AS ANTIARRHYTHMIC AGENTS, AND PRECURSORS THEREOF**

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[73] Assignee: **Board of Regents of Oklahoma State University**, Stillwater, Okla.

[*] Notice: The portion of the term of this patent subsequent to Jan. 28, 2009 has been disclaimed.

[21] Appl. No.: **610,428**

[22] Filed: **Nov. 7, 1990**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 435,976, Nov. 13, 1989, Pat. No. 5,084,572.

[51] **Int. Cl.**[5] **C07D 495/08**; C07D 495/10

[52] **U.S. Cl.** **546/114**; 546/112; 546/122

[58] **Field of Search** 546/114

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,581,361 4/1986 Berlin et al. 514/301

Primary Examiner—Alan L. Rotman

Attorney, Agent, or Firm—Head and Johnson

[57] **ABSTRACT**

Salts of 3-azabicyclo[3.3.1]nonanes are used in controlling antiarrhythmic processes and precursors thereof are disclosed.

4 Claims, No Drawings

SALTS OF 3-AZABICYCLO(3.3.1) NONANES AS ARTIARRHYTHMIC AGENTS, AND PRECURSORS THEREOF CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of Ser. No. 07/435,976 filed Nov. 13, 1989, now U.S. Pat. No. 5,084,572.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to antiarrhythmic compositions. Specifically, this invention relates to certain derivatives of 3-azabicyclo[3.3.1]nonanes.

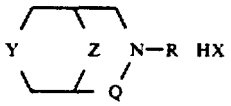
2. Description of the Prior Art

3-Azabicyclo[3.3.1]nonanes with heteroatoms such as N, S, and O at the 7-position are known and documented in the chemical literature. A review in Chemical Reviews, Volume 81, No. 2, pages 149-174 (1981), entitled "Chemistry of 3-Azabicyclo[3.3.1]nonanes" by R. Jeyaraman and S. Avila, covers the synthesis, reactions and stereochemistry of the title compounds. The review acknowledges the close resemblance of 3-azabicyclo[3.3.1]nonanes (3-ABN) to aza- and diazaadamantanes in conformation and stereochemistry, and this has caused progress in the chemistry of the title compounds. The review further acknowledges that 3-ABN systems can be obtained by a Mannich, or modified Mannich, reaction involving a condensation of ketones or aldehydes with a primary amine under relatively mild conditions. Thus, the availability of a variety of ketones or aldehydes has prompted studies on 3-ABNs.

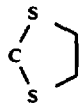
According to the chemical literature, a few derivatives of 3-ABN have exhibited useful biological properties. Potent analgesic and antitusive characteristics as well as antagonism to analgesic effects and to narcotic action have been observed, depending upon the groups attached to the basic structure. In addition, some examples have displayed sedative action as well as antipyretic and hypoglycemic activity. Simple 3-ABN has been reported to be effective against influenza infection. Some derivatives have recorded antiarrhythmic properties. Certain sulfur-substituted, as well as selenium-substituted examples, have been reported as accessible via a Mannich reaction or a modified Mannich reaction. In U.S. Pat. No. 4,581,361 and U.S. Pat. No. 4,778,892, for example, such materials are disclosed and claimed as antiarrhythmic agents.

SUMMARY OF THE INVENTION

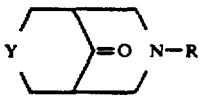
The present invention involves novel derivatives of 3-azabicyclo[3.3.1]nonanes having the basic formula:



X = ClO_4, Br, Cl, HSO_4, citrate, fumarate

Y	Z	R	Q	Number
PhC(O)N	CH_2	$(H_3C)_2CH$	CH_2	(1)
4-$ClC_6H_4C(O)N$	CH_2	$(H_3C)_2CH$	CH_2	(2)
3,4-$(H_3CO)_2C_6H_3C(O)N$	CH_2	$(H_3C)_2CH$	CH_2	(3)
3,4,5-$(H_3CO)_3C_6H_2C(O)N$	CH_2	$(H_3C)_2CH$	CH_2	(4)
$PhCH_2N$	CH_2	$(H_3C)_2CH$	CH_2	(5)
4-$ClC_6H_4CH_2N$	CH_2	$(H_3C)_2CH$	CH_2	(6)
3,4-$(H_3CO)_2C_6H_3CH_2N$	CH_2	$(H_3C)_2CH$	CH_2	(7)
S	CH_2	$(H_3C)_2CH$	CH_2	(8)
S	CH_2	3-I-$C_6H_4CH_2$	CH_2	(9)
S ⟶ O	CH_2	$PhCH_2$	CH_2	(10)
S	$C(OCH_3)_2$	$PhCH_2$	CH_2	(11)
$PhCH_2N$	$C(OCH_3)_2$	$PhCH_2$	CH_2	(12)
$C_2H_5O(O)C$	CH_2	$PhCH_2$	CH_2	(13)
$C_2H_5O(O)C$		$PhCH_2$	CH_2	(14)
S	CH_2	PhC(O)	CH_2	(15)
S ⟶ O	$C(OCH_3)_2$	$PhCH_2$	CH_2	(16)
$PhCH_2N$	CH_2	$PhCH_2$	C=O	(17)

The present invention also provides for novel intermediates of the class of 3-azabicyclo[3.3.1]nonan-9-ones having the formula:



Y	R	Number
S	CH_2Ph	(18)
NCH_2Ph	CH_2Ph	(19)
$CHCO_2Et$	CH_2Ph	(20)
$NCH(CH_3)_2$	CH_2Ph	(21)
$NCH(CH_3)_2$	$CH_2C_6H_4$-4-Cl	(22)
$NCH(CH_3)_2$	$CH_2C_6H_3$-3,4-$(OCH_3)_2$	(23)

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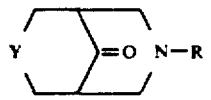
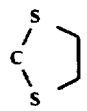


Y	R	Number
$NCH(CH_3)_2$	$CH_2C_6H_2$-3,4,5-$(OCH_3)_3$	(24)
S	$CH_2C_6H_4$-3-1	(25)
S	$CH(CH_3)_2$	(26)

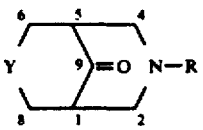
The invention further provides additional 3-azabicyclo[3.3.1]nonanes of the formula:

Y	Z	R	Number
S	CH_2	CH_2Ph	(27)
S	CH_2	H	(28)
S	CH_2	C(O)Ph	(29)
$NCH(CH_3)_2$	CH_2	CH_2Ph	(30)
$NCH(CH_3)_2$	CH_2	H	(31)
$NCH(CH_3)_2$	CH_2	C(O)Ph	(32)
$NCH(CH_3)_2$	CH_2	$C(O)-C_6H_4$-4-Cl	(33)
$NCH(CH_3)_2$	CH_2	$C(O)C_6H_3$-3,4-$(OCH_3)_2$	(34)
$NCH(CH_3)_2$	CH_2	$C(O)C_6H_2$-3,4,5-$(OCH_3)_2$	(35)
$NCH(CH_3)_2$	CH_2	$S(O)_2Ph$	(36)
NCH_2Ph	CH_2	CH_2Ph	(37)
$CHCO_2Et$	CH_2		(38)

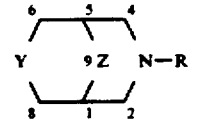
Specifically, the invention relates to the above salts (1)–(17) of certain 3-azabicyclo[3.3.1]nonanes and precursors (18)–(38) as used in controlling antiarrhythmic processes. Thus, it is the object of the present invention to provide novel compositions that display biological activity. Fulfillment of this object and the presence and fulfillment of other objects will be apparent upon complete reading of the specifications and claims.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The chemical compositions according to the preferred embodiments of this invention are heteronuclear ring organic compounds based on the 3-azabicyclo[3.3.1]nonane structures as follows:



(39)



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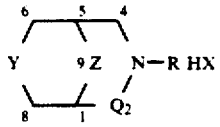


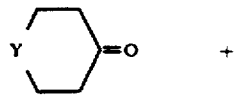
(41)

Wherein the 3-position in general structures (39-41) is nitrogen [as specifically in (1-38)], the 7-position includes nitrogen [as specifically in (1-7), (12), (17), (19), (21-24), and (30-37)], sulfur [as specifically in (8-11), (15), (16), (18), and (25-29)], and carbon [as specifically in (13), (14), (20), and (38)]. With nitrogen in the 3- or 7-position, a N—C bond is always present except for (28) and (31) which have N—H bonds and (36) which has an N—S bond. The 9-position can be preferably unsubstituted [as specifically in (1)–(10), (13), (15), (17), and (27)–(38)], 9-one [as specifically in (18)–(26)], 9,9-dimethoxy [as specifically in (11), (12), and (16)], or a 1,3-dithiolane [as specifically in (14) and (38)]. The alkylated nitrogen atom at the 3-position [as specifically in (1)–(16)] and their corresponding tertiary amine acid salts [hydroperchlorate, HCl, HBr, H_2SO_4, citrate, and fumarate] are included along with a system containing an alkylated nitrogen at the 7-position as in (17) and the corresponding salts.

These compounds are the active ingredients for potential drugs and/or intermediates for the active ingredients of potential drugs to use in the treatment of disorders of the heart. They exhibit good activity in animal models and as such are viable candidates to control life-threatening arrhythmias found in humans who experience heart attacks or major infarctions of the heart.

Typically, the 9-one systems shown by the general formula (39) [as specifically in (18)–(26)] are synthesized by the reaction of a tetrahydro-4-heteracyclohexanone in the presence of an aldehyde and amine or ammonium salt in accordance with a Mannich or Mannich type reaction. For example, and as illustrated in the following reaction scheme A, 1-isopropyl-4-piperidinone (42) [or 1-benzyl-4-piperidinone (43) or 4-thianone (44)] was allowed to react with benzylamine, 4-chlorobenzylamine, 3,4-dimethoxybenzylamine, 3,4,5-trimethoxybenzylamine, and the like with paraformaldehyde in the presence of acetic acid/methanol to produce the 3-azabicyclo[3.3.1]nonan-9-ones (39) [representative examples are (18), (19), and (21)–(24)]. The ketone (39) is then reduced with hydrazine hydrate in triethylene glycol/potassium hydroxide media to give members of (40) which could be reacted with perchloric acid, hydrochloric acid, hydrobromic acid, sulfuric acid, citric acid, or fumaric acid in benzene, ether, and/or isopropyl alcohol to yield the corresponding hydroperchlorate, hydrochloride, hydrosulfate, citrate, or fumarate derivative (41). Related examples where Y is benzyl or sulfur follow similarly. Thus the method is applicable to obtain members of (18)–(26), with the exception of (20) which was prepared from

REACTION SCHEME A



Y = $(H_3C)_2CHN$, $PHCH_2N$, S

(42) (43) (44)

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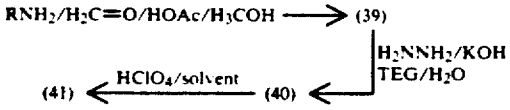
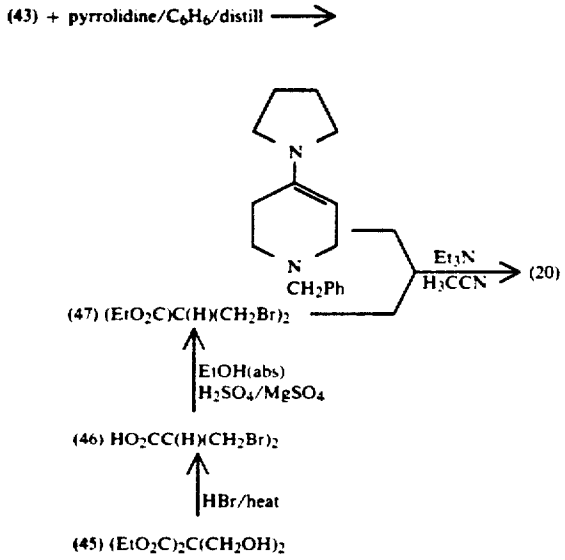
REACTION SCHEME A



the enamine in scheme B starting from (43). The co-reactant with (43) to give (20) is made by

REACTION SCHEME B

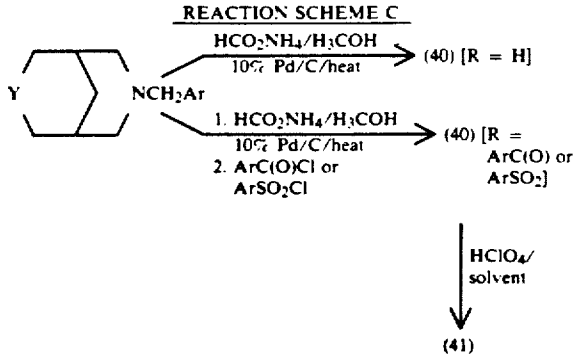


treatment of ester (45) with hydrobromic acid to give acid (46) under standard conditions. Esterification of (46) under the usual conditions produced dibromide (47) which was condensed with the enamine in the presence of triethylamine in acetonitrile to yield ketone (20) under the usual conditions.

Reduction of the ketones in scheme A, including ketone (20), via Wolff-Kishner conditions, as illustrated with hydrazine/KOH in triethylene glycol, leads to amines of general formula (40) [specifically (27), (30), and (37) are representative examples]. Addition of perchloric acid [or HCl, HBr, H_2SO_4, citric acid, or fumaric acid] in benzene or isopropyl alcohol gives members of general formula (41) [(5)–(9), and (13) are representative examples].

In reaction scheme C, members of (40) [representative examples are (28), (29), (31), and (32)–(36)] were obtained as outlined. Specific members of the family of (40) with an N—H bond [note these examples are representative starting materials for the amide systems], namely (28) and

REACTION SCHEME C



(31) as representative examples, are isolable directly from the reaction mixture after workup. Direct aroylation or sulfonation of these types of intermediates (40) in a two-phase system under modified Schotten-Baumann conditions, or phase transfer conditions, leads to amide members of (39) [(29), (32)–(35), and (36) are representative examples]. Treatment of these latter amide members of (40), such as (32)–(35) and related systems, with perchloric acid, HCl, HBr, H_2SO_4, citric acid, or fumaric acid in benzene, ether, and/or isopropyl alcohol produces salts (41) illustrated by (1)–(4) as representative examples.

Ketal formation from members of (39), using methanol or 1,2-ethanedithiol, under standard conditions, produced members of (40), such as illustrated with (38) as a representative example, or, after treatment with perchloric acid, HCl, HBr, H_2SO_4, citric or fumaric acid, produced members of (41) such as illustrated with (11), (12), (14), and (16) as representative examples.

Since oxidation products are viable candidates as potential metabolites from use of these compounds in animals, including humans, oxidation of specific sites was performed. As an example, oxidation of (37) illustrates the introduction of an oxygen atom alpha to the nitrogen when treated with $RuO_2xH_2O/NaIO_4$ in a water/carbon tetrachloride mixture to produce lactam (17). Moreover, oxidation of sulfur to give members of (41), with sulfoxides (10) and (16) as representative examples, can lead to potential metabolites. Salt formation is again effected by the method outlined previously for members of (41).

EXAMPLE I

7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one (18)

Ketone (18) was prepared by the method in U.S. Pat. No. 4,581,361.

EXAMPLE II

7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonane (27)

This amine (27) was prepared from ketone (18) by the method of Bailey, III, et. al. J. Med. Chem., vol. 27(6) pp. 758–767 (1984).

EXAMPLE III

7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonane Hydroperchlorate (48)

This amine salt was prepared from amine (27) by the method of Bailey, III, et. al. J. Med. Chem., vol. 27(6) pp. 758–767 (1984).

EXAMPLE IV

3-Thia-7-azabicyclo[3.3.1]nonane (28)

A 50-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a standard condenser with a N_2 inlet and two glass stoppers. In one portion, anhydrous HCO_2NH_4 (1.11 g, 17.1 mmol) was added under N_2 to a mixture of the amine (27, 0.90 g, 3.86 mmol) and 10% Pd/C (0.90 g) in anhydrous CH_3OH (25 mL). With stirring, the mixture was brought to reflux for 30 min, filtered through a Celite pad on a fritted funnel (which was washed thoroughly with CH_2Cl_2), and then concentrated to give a gummy oil with suspended solid. This material was again dissolved in CH_2Cl_2 (~15 mL), and the suspension was filtered to remove any unreacted ammonium formate. The filtrate was then concentrated to near saturation and placed in a diffusion chamber of ether overnight. Crude amine (28) became an oil; however, the mother liquor, containing predominantly starting material, could be decanted. Chromatography of the oil employed a gradient elution of CH_3OH/CH_2Cl_2 (300 mL of 10% CH_3OH/CH_2Cl_2, 50 mL of 20% CH_3OH/CH_2Cl_2, 100 mL of 50% CH_3OH/CH_2Cl_2, and 100 mL of CH_3OH) on silica gel (35 g, 1.5 cm×62 cm) and afforded 0.32 g (56.9%) of amine (28) (R_f=0.11, 10% CH_3OH/CH_2Cl_2) as a light, gummy solid which was used without further purification. ^1H NMR ($DCCl_3$) δ1.84, 2.04 [two bd, 2H, H(9)], 2.31 [bs, 2H, H(1,5)], 2.80 [bd, 2H, $H(2,4)_{ax}$, J=12.3 Hz], 3.20 [bd, 2H, $H(2,4)_{eq}$, J=13.7 Hz], 3.45 [m, 2H, $H(6,8)_{ax}$], 3.73 [bd, 2H, $H(6,8)_{eq}$, J=13.2 Hz], 7.59 (bs, 1H, N-H); ^{13}C NMR ($DCCl_3$) ppm 24.88 [d, C(1,5)], 29.79 [t, C(9)], 32.17 [t, C(2,4)], 47.8 [t, C(6,8)].

EXAMPLE V

7-Benzoyl-3-thia-7-azabicyclo[3.3.1]nonane (29)

A 10-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer, an ice bath, a standard condenser with a N_2 inlet, and a glass stopper. To a chilled (5° C.) solution of NaOH pellets (0.1 g, 2.38 mmol) in H_2O (1.7 mL) was added a solution of the amine (28, 0.17 g, 1.19 mmol) in CH_2Cl_2 (1 mL). This was followed by the dropwise addition of a solution of benzoyl chloride (0.2 g, 1.43 mmol) over ~5 min. After stirring for 30 min at 0°-5° C., 30 min at RT, and then 15 min over a steam bath, the mixture was diluted with H_2O (15 mL), and the mixture was extracted (CH_2Cl_2, 3×15 mL). Combining the extracts, drying (Na_2SO_4, overnight), filtering, and concentrating the solution gave a viscous yellow oil. Chromatography of the oil on alumina (38 g, 2.4 cm×17 cm) employed ethyl acetate as eluant and afforded amide (29) (R_f=0.47) as white crystals (157 mg, 53.3%); mp 95°-96° C. IR (KBr) cm^{-1} 3065, 3045 (Ar C—H), 3000, 2985, 2940, 2910, 2855, 2835 (C—H), 1635 (C=O), 745, 720 (C—H out of plane, mono); ^1H NMR ($DCCl_3$) δ1.78-1.93 [m, 3H, H(9) and H(1)], 2.15 [bs, 1H, H(5)], 2.39 [d, 1H, $H(4)_{ax}$, J=13.9 Hz], 2.77 [d, 1H, $H(6)_{ax}$, J=12.3 Hz], 3.12-3.21 [m, 3H, $H(4)_{eq}$ and $H(6)_{eq}$], 3.41 [d, 1H, $H(2)_{ax}$, J=12.8 Hz], 3.89 [d, 1H, $H(2)_{eq}$, J=13.4 Hz), 4.98 [d, 1H, $H(8)_{eq}$, J=13.1 Hz], 7.38-7.44 [m, 5H, Ar—H]; ^{13}C NMR ($DCCl_3$) ppm 26.53 [C(1)], 26.87 [C(5)], 31.73 [C(2)], 31.78 [C(9)], 32.34 [C(4)], 46.07 [C(8)], 52.12 [C(6)], 126.46, 128.41, 128.83, 137.35 (Ar—C), 170.38 [C=O]. Anal. Calcd. for $C_{14}H_{17}NOS$: C, 67.98; H, 6.93. Found: C, 68.01; H, 7.07.

EXAMPLE VI

7-Benzyl-3-isopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (21)

A 500-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a 250-mL addition funnel, a standard condenser with a N_2 inlet and a glass stopper. A mixture of benzylamine (10.71 g, 100 mmol), HCl (37%, 9.86 g, 100 mmol), glacial acetic acid (3.0 g, 50 mmol) and paraformaldehyde (6.31 g, 210 mmol) in deoxygenated (N_2 bubbled in for 1 h) CH_3OH (100 mL) was stirred at reflux for 15 min under N_2. A solution of 1-isopropyl-4-piperidinone (42, 14.12 g, 100 mmol) and glacial acetic acid (6.0 g, 100 mmol) in CH_3OH (100 mL) was then added dropwise to the mixture over 30 min, followed by stirring at reflux for an additional 18.5 h. Concentration of the solution gave an oil which was redissolved in H_2O (100 mL). An ether extract (100 mL) of this acidic solution was discarded. Basicification (pH~13) of the water layer was achieved by the addition of 10% NaOH, resulting in the formation of a milky suspension which was extracted (ether, 4×60 mL). Combined extracts were dried (Na_2SO_4, 1 h), filtered, and concentrated to a viscous red oil, which, when distilled (175°-185° C./10^{-5} mm Hg), afforded a light yellow oil (15.6 g, 57.2%) that solidified when refrigerated at −10° C.; mp 46°-47.5° C. This solid could be recrystallized (pentane) to give an analytical sample of ketone (21); mp 49°-50° C. IR (KBr) cm^{-1} 3095, 3070, 3035 (Ar—H), 2975, 2900, 2820 (C—H), 1745 (C=O), 1605, 1495 (C=C), 740, 700 (C—H out of plane, mono); ^1H NMR ($DCCl_3$) δ1.02 (d, 6H, CH_3), 2.58 [bs, 2H, H(1,5)], 2.87 [m, 5H, ring protons and $CH(CH_3)_2$], 3.03 (dd, 4H, ring protons), 3.53 (s, 2H, $ArCH_2$), 7.30 (m, 5H, Ar—H); ^{13}C NMR ($DCCl_3$) ppm 18.25 (CH_3), 46.93 [C(1,5)], 53.41 [$CH(CH_3)_2$], 53.71 [C(2,4)], 58.07 [C(6,8)], 61.25 ($ArCH_2$), 127.09, 128.25, 128.69, 138.67 (Ar—C), 215.20 (C=O); ^{15}N NMR ($DCCl_3$) ppm 39.25 [N(7)], 40.80 [N(3)]. Anal. Calcd. for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.28. Found: C, 75.18; H, 8.61; N, 10.24.

EXAMPLE VII

7-Benzyl-3-isopropyl-3,7-diazabicyclo[3.3.1]nonane (30)

To a mixture of KOH pellets (85%, 11.62 g, 176 mmol) and the ketone (21) (6.0 g, 22 mmol) in triethylene glycol (100 mL) was added hydrazine (95%, 2.97 g, 88 mmol) in one portion in a 200-mL, jacketed flask equipped with a magnetic stirrer, a heating mantle, a standard condenser, a lower take-off condenser with a N_2 inlet, and two glass stoppers. A heating temperature of 200°-210° C. for 4 h under N_2 was produced by boiling tetralin (bp 207° C.) in the jacket. Cooling of the solution to RT was followed by the addition of chilled water (125 mL). Combined extracts (ether, 4×50 mL) of the suspension were washed with 10% NaOH (50 mL) and saturated NaCl (50 mL), dried (Na_2SO_4, 1 h), filtered, and concentrated (rotary evaporator then vacuum pump, overnight, RT/0.2 mm Hg) to a yellow oil (5.53 g, 97.3%). Analysis of the very slight crude amine (30) showed no carbonyl stretch in the IR spectrum, and thus it was used without further purification.

EXAMPLE VIII

7-Benzyl-3-isopropyl-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (5)

A 125-mL Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. To a stirred, chilled (5° C.) solution of the amine (30, 0.84 g, 3.25 mmol) in dry ether (50 mL) was added dropwise a solution of $HClO_4$ (60%, 1.08 g, 6.50 mmol) in isopropyl alcohol (3 mL) over 20 min. After the mixture was stirred an additional hour, a white powdery material was filtered, and then dissolved in CH_3OH. Decolorizing with Norit, filtering, and concentrating the solution gave a solid that was recrystallized (CH_3OH) to give 0.65 g (49.4%) of salt (5); mp 152.0°-152.5° C. IR (KBr) cm^{-1} 3050, 3030 (Ar C—H), 2970, 2940, 2910, 2810 (C—H), 1090 (Cl—O); ^1H NMR (DMSO-d_6) δ1.18 (d, 6H, CH_3), 1.62 [d, 1H, H(9), J=12.4 Hz], 1.82 [d, 1H, H(9), J=12.7 Hz], 2.14 [bs, 2H, H(1,5)], 2.47 [d, 2H, $H(6,8)_{ax}$, J=11.4 Hz], 3.11 [m, 4H, $H(2,4)_{ax}$ and $H(6,8)_{eq}$], 3.32 [d, 2H, $H(2,4)_{eq}$, J=11.8 Hz], 3.47 [h, 1H, $CH(CH_3)_2$], 3.52 (s, 2H, $ArCH_2$), 7.30-7.46 (m, 5H, Ar—H); ^{13}C NMR (DMSO-d_6) ppm 16.11 (q, CH_3), 27.24 [d, C(1,5)], 29.67 [t, C(9)], 52.85 [t, C(2,4[, 56.00 [d, $CH(CH_3)_2$], 56.85 [t, C(6,8)], 61.15 (t, $ArCH_2$), 127.65, 128.35, 129.38, 136.35 (Ar—C); ^{15}N NMR (DMSO-d_6) ppm 50.90 [N(7)], 60.47 [N(3)]. Anal. Calcd. for $C_{17}H_{27}ClN_2O_4$: C, 56.90; H, 7.58; N, 7.81. Found: C, 56.70; H, 7.45; N, 7.84.

EXAMPLE IX

3-Isopropyl-3,7-diazabicyclo[3.3.1]nonane (31)

A 200-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. To a stirred mixture of amine (30) (5.53 g, 21.4 mmol) and 10% Pd/C (0.64 g, 30 mg/mmol of amine) in CH_3OH (80 mL) was added anhydrous HCO_2NH_4 (3.37 g, 53.5 mmol) in one portion. Stirring the mixture at reflux under N_2 for 30 min, cooling the new mixture to RT, and filtering through a celite pad was followed by concentration of the resulting solution to give a viscous oil. The oil was then dissolved in H_2O (80 mL) and the pH was adjusted to ~12 by the addition of 10% NaOH. Combined extracts (CH_2Cl_2, 4×40 mL) of the aqueous solution were dried, filtered, and concentrated (rotary evaporator then vacuum pump, 10 min, RT/0.2 mm Hg) to give amine (31) as a light oil (3.35 g, 93.0%) which was used without further purification. IR (film) cm^{-1} 3315 (N—H), 2965, 2900, 2850, 2790, 2760, 2725 (C—H); ^1H NMR ($DCCl_3$) δ1.01 (d, 6H, CH_3, J=6.7 Hz), 1.60-1.67 [m, 3H, H(1,5) and H(9)], 2.53-2.59 [m, 3H, ring protons and $CH(CH_3)_2$], 2.90-3.06 [m, 6H, ring protons], 3.56 (bs, 1H, N—H); ^{13}C NMR ($DCCl_3$) ppm 18.12 (CH_3), 30.04 [C(1,5)], 33.62 [C(9)], 52.86 [C(6,8)], 54.59 [$CH(CH_3)_2$], 54.65 [C(2,4)].

EXAMPLE X

3-Benzoyl-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (32)

A three-necked, 50-mL, round-bottomed flask was equipped with a magnetic stirrer, an ice bath, a standard condenser with a N_2 inlet, and two glass stoppers. To a solution of 10% NaOH (8.94 g, 22.3 mmol) was added the amine (31, 1.14 g, 6.77 mmol) in CH_2Cl_2 (15 mL) in one portion. Dropwise addition of a solution of benzoyl chloride (1.05 g, 7.45 mmol) in CH_2Cl_2 (5 mL) to the mixture over 15 min under N_2 was followed by stirring an additional 2.75 h at RT. After the addition of H_2O (30 mL), the organic layer was separated. Additional extracts (CH_2Cl_2, 3×25 mL) were combined with the initial organic layer, dried (Na_2SO_4, 1 h), filtered, and concentrated (aspirator followed by vacuum pump, 1 h, RT/0.2 mm Hg) to give an orange oil. Chromatography of the oil was performed over neutral alumina (200 g, 2.1 cm×33 cm) with ethyl acetate as eluant. Fractions (R_f=0.70) were combined and concentrated (rotary evaporator then vacuum pump, overnight, RT/0.2 mm Hg) to yield 1.52 g (82.4%) of the amide (32) as an oil which was used without further purification. IR (film) cm^{-1} 3085, 3065, 3035 (Ar C—H), 2970, 2925, 2865, 2805, 2780, 2750 (C—H), 1635 (C=O), 730, 710 (C—H out of plane, mono); ^1H NMR ($DCCl_3$) δ0.96 (d, 3H, CH_3, J=6.4 Hz), 1.07 (d, 3H, CH_3, J=6.6 Hz), 1.65-1.78, [m, 3H, H(5) and H(9)], 1.97 [bs, 1H, H(1)], 2.41 [d, 1H, $H(4)_{ax}$, J=10.3 Hz], 2.50 [d, 1H, $H(6)_{ax}$, J=11.0 Hz], 2.62 [m, 1H, $CH(CH_3)_2$, J=6.5 Hz], 2.72 [d, 1H, $H(6)_{eq}$, J=10.6 Hz], 3.04-3.07 [m, 2H, $H(2)_{ax}$ and $H(4)_{eq}$], 3.30 [d, 1H, $H(8)_{ax}$, J=13.2 Hz], 3.74 [d, 1H, $H(8)_{eq}$, J=12.8 Hz], 4.77 [d, 1H, $H(2)_{eq}$, J=13.9 Hz], 7.28-7.41 (m, 5H, Ar—H); ^{13}C NMR ($DCCl_3$) ppm 16.30 (CH_3), 19.33 (CH_3), 29.06 [C(1)], 29.76 [C(5)], 32.29 [C(9)], 46.55 [C(2)], 52.19 [C(4)], 52.62 [C(8)], 54.34 [$CH(CH_3)_2$], 54.75 [C(6)], 126.75, 128.24, 128.67, 137.75 (Ar—C), 170.09 (C=O).

EXAMPLE XI

3-Benzoyl-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (1)

A 250-mL Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. To a chilled (5° C.), stirred solution of the amide (32, 1.52 g, 5.58 mmol) in ether (60 mL) was added dropwise $HClO_4$ (60%, 1.17 g, 6.98 mmol) over 10 min. Filtration gave salt (1) as a white solid which was washed with dry ether (50 mL), stirred in hot CH_3OH (30 mL), cooled to −10° C. overnight, filtered, and dried (vacuum pump, 61° C./0.2 mm Hg, overnight) to afford 1.90 g (91.3%) of pure salt (1); mp 226°-227° C. (dec): IR (KBr) cm^{-1} 3150 (N—H), 2990, 2960, 2935, 2920, 2885 (C—H), 1635 (C=O), 1100 (Cl—O), 740, 710 (C—H out of plane, mono): ^1H NMR [$(D_3C)_2C$=O] δ1.55 (d, 6H, CH_3, J=6.6 Hz), 1.97 [bd, 1H, H(9), J=13.0 Hz], 2.18 [bd, 1H, H(9), J=13.2 Hz], 2.51 [bs, 2H, H(1,5)], 3.30 [bd, 2H, $H(2,4)_{ax}$, J=13.2 Hz], 3.65 [m, 2H, $H(6,8)_{ax}$], 3.83 [h, 1H, —$CH(CH_3)_2$, J=6.8 Hz], 3.94 [bd, 2H, $H(2,4)_{eq}$, J=12.3 Hz], 4.23 [bd, 2H, $H(6,8)_{eq}$, J=13.2 Hz], 7.45-7.50 (m, 5H, Ar—H), 7.85 (bs, 1H, N—H); ^{13}C NMR (DMSO-d_6, 80° C.) ppm 16.34 (CH_3), 26.69 [C(1,5)], 27.62 [C(9)], 48.80 [C(2,4)], 52.31 [C(6,8)], 59.91 [$CH(CH_3)_2$], 127.05, 128.30, 129.40, 136.40 (Ar—C), 172.86 (C=O). Anal. Calcd. for $C_{17}H_{25}ClN_2O_5$: C, 54.76; H, 6.76. Found: C, 54.43; H, 6.78.

EXAMPLE XII

3-(3',4'-Dimethoxybenzyl)-7-isopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (23)

A 200-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a standard condenser with a N_2 inlet, a 50-mL addition funnel, and a glass stopper. A mixture containing 3,4-dimethoxybenzylamine (8.36 g, 50 mmol), paraformaldehyde (3.15 g, 105 mmol) and CH_3OH (35 mL) was made acidic with the addition of glacial acetic acid (3.0 g, 50 mmol). Stirring the mixture under N_2 for 20 min

was followed by the dropwise addition of 1-isopropyl-4-piperidinone (42, 7.06 g, 50 mmol) and glacial acetic acid (3.0 g, 50 mmol) in CH_3OH (25 mL) over 1.25 h. Boiling of the mixture was continuous for an additional 23 h. This new mixture was evaporated to give a red viscous oil. After dissolving the oil in H_2O (100 mL), the solution was extracted (ether, 2×100 mL), the latter being discarded. Chilling (ice water bath) of the water layer below 10° C., followed by basification (pH ~ 12) with KOH pellets (6.6 g, 100 mmol), produced an orange suspension which was extracted (CH_2Cl_2, 4×80 mL). Combined extracts were dried (Na_2SO_4, overnight), filtered, and concentrated to give a crude oil. This oil was digested in 250 mL of Skelly B (bp 60°-68° C.) for 0.5 h and the supernatant was decanted. Evaporation of the solvent gave an oil which, when distilled (175°-205° C./10^{-4} mm Hg), afforded a yellow oil. Adding Skelly B induced crystallization to give 4.32 g (26%) of off white ketone (23); mp 79.5°-80.5° C. IR (KBr) cm^{-1} 3095, 3015 (Ar—H), 2980, 2955, 2920, 2855, 2810 (C—H), 1745 (C=O), 1620, 1605 (C=C); ^1H NMR ($DCCl_3$) δ1.03 (d, 6H, CH_3, J = 6.6 Hz), 2.59 [bs, 2H, H(1,5)], 2.81-2.90 [m, 5H, ring protons and $CH(CH_3)_2$], 2.98 (dd, 2H, ring protons, J = 10.7 Hz, J' = 3.2 Hz), 3.08 (dd, 2H, ring protons, J = 10.7 Hz, J' = 2.99 Hz), 3.47 (s, 2H, $ArCH_2$), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.80-6.92 (m, 3H, Ar—H); ^{13}C NMR ($DCCl_3$) ppm 18.17 (CH_3), 46.85 [C(1,5)], 53.40 [$CH(CH_3)_2$], 53.86 [C(2,4)], 55.76, 55.86 (OCH_3), 58.01 [C(6,8)], 60.93 ($ArCH_2$), 110.60, 111.46, 120.68, 131.30, 148.04, 148.90 (Ar—C), 215.27 (C=O); ^{15}N NMR ($DCCl_3$) ppm 39.66 [N(7)], 40.93 [N(3)]. Anal. Calcd. for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49. Found: C, 68.70; H, 8.53.

EXAMPLE XIII

7-(3',4'-Dimethoxybenzyl)-3-isopropyl-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (7)

To a mixture of KOH pellets (85%, 2.38 g, 36 mmol) and the ketone (23, 1.0 g, 3 mmol) in triethylene glycol (25 mL) was added hydrazine (95%, 1.01 g, 30 mmol) in one portion in a 70-mL, jacketed flask equipped with a magnetic stirrer, a heating mantle, a standard condenser, a lower take-off condenser and two glass stoppers. A heating temperature of 150°-160° C. for 3.5 h was achieved by using tetralin (bp 207° C.) in the jacket. After cooling to RT, the solution was diluted with cold H_2O (50 mL) and extracted with ether (3×40 mL). Combined extracts were washed with 10% NaOH (50 mL) and saturated NaCl (50 mL), dried (Na_2SO_4, overnight), filtered, and concentrated to afford a yellow oil (0.78 g). Dissolution of the oil in ether (50 mL) with magnetic stirring and cooling (5° C., via ice water bath) in a 125-mL Erlenmeyer flask (equipped with an external ice bath) was followed by the dropwise addition of a solution of $HClO_4$ (60%, 0.51 g, 3.06 mmol) over 10 min. Filtering the precipitate, washing the latter with ether (~50 mL), and then recrystallizing (95% EtOH) gave 0.79 g (62.9%) of white salt (3); mp 127.5°-128.0° C. (dec). IR (KBr) cm^{-1} 3020 (Ar C—H), 2955, 2930, 2840, 2815, 2790 (C—H), 1610 (C=C), 1090 (Cl—O); ^1H NMR (DMSO-d_6) δ1.15 (d, 6H, CH_3, J = 6.7 Hz), 1.64 [d, 1H, H(9), J = 12.1 Hz], 1.80 [d, 1H, H(9), J = 13.0 Hz], 2.14 [bs, 2H, H(1,5)], 2.50 [d, 2H, $H(6,8)_{ax}$, J = 10.4 Hz], 3.05-3.14 [m, 4H, $H(6,8)_{eq}$ and $H(2,4)_{ax}$], 3.28 [d, 2H, $H(2,4)_{eq}$, J = 11.6 Hz], 3.39 [m, 1H, $CH(CH_3)$, J = 6.7 Hz], 3.49 (s, 2H, $ArCH_2$), 3.75, 3.76 (two s, 6H, OCH_3), 6.86-7.08 (m, 3H, Ar—H); ^{13}C NMR (DMSO-d_6) ppm 16.25 (CH_3), 27.23 [C(1,5)], 29.79 [C(9)], 52.74 [C(2,4)], 55.31, 55.36 (OCH_3), 55.78 [$CH(CH_3)_2$], 56.85 [C(6,8)], 60.89 ($ArCH_2$), 111.23, 113.01, 122.02, 128.00, 148.38, 148.66 (Ar—C); ^{15}N NMR (DMSO-d_6) ppm 52.22 [N(7)], 59.43 [N(3)]. Anal. Calcd. for $C_{19}H_{31}ClN_2O_6$: C, 54.48; H, 7.46. Found: C, 54.76; H, 7.61.

EXAMPLE XIV

7-(4'-Chlorobenzyl)-3-isopropyl-3,7-diazabicyclo[3.3.1-]nonan-9-one (22)

A 200-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a standard condenser with a N_2 inlet, a 50-mL, an addition funnel and a glass stopper. A mixture of 4-chlorobenzylamine (7.08 g, 50 mmol), paraformaldehyde (3.15 g, 105 mmol), glacial acetic acid (3.0 g, 50 mmol), and CH_3OH (35 mL) was brought to gentle reflux with stirring under N_2 for 15 min. To the mixture was added dropwise a solution of 1-isopropyl-4-piperidinone (42, 7.06 g, 50 mmol) and glacial acetic acid (3.0 g, 50 mmol) in CH_3OH (25 mL) over 1 h. Boiling of the mixture was continued for an additional 24 h. After concentrating to a viscous red oil, the reaction mixture was then diluted with H_2O (100 mL) and extracted (ether, 3×100 mL), the latter being discarded. Chilling (via ice water bath) of the aqueous layer to below 10° C. was followed by basification (pH ~ 13) with KOH pellets (85%, 6.6 g, 100 mmol). Combined extracts (ether, 3×60 mL) were dried (Na_2SO_4, 4 h), filtered, and concentrated to give a viscous red oil. This oil was digested in pentane (100 mL) for 20 min and the supernatant was decanted and concentrated Distillation of the resulting oil (195°-205° C./10^{-5} mm Hg) gave 5.25 g of a yellow oil which solidified upon standing. Recrystallization (pentane) of the solid gave 3.46 g (22.6%) of white crystalline (22); mp 68°-69° C. IR (KBr) cm^{-1} 3030 (Ar C—H), 2955, 2880, 2800 (C—H), 1730 (C=O), 800 (C—H out of plane, para); ^1H NMR ($DCCl_3$) δ1.03 (d, 6H, CH_3, J = 6.3 Hz), 2.58 [bs, 2H, H(1,5)], 2.80-3.05 [m, 9H, ring protons and $CH(CH_3)_2$], 7.27 (s, 4H, Ar—H); ^{13}C NMR ($DCCl_3$) ppm 18.25 (CH_3), 46.85 [C(1,5)], 53.40 [$CH(CH_3)_2$], 53.76 [C(2,4)], 57.92 [C(6,8)], 60.48 ($ArCH_2$), 128.40, 129.95, 132.74, 137.21 (Ar—C), 215.04 (C=O); ^{15}N NMR ($DCCl_3$) ppm 39.18 [N(3)], 40.31 [N(7)]. Anal. Calcd. for $C_{17}H_{23}ClN_2O$: C, 66.55; H, 7.56. Found: 66.47; H, 7.52.

EXAMPLE XV

7-(4'-Chlorobenzyl)-3-isopropyl-3,7-diazabicyclo[3.3.1-]nonane Hydroperchlorate (6)

To a mixture of KOH pellets (85%, 1.72 g, 26.1 mmol) and the ketone (22, 1.0 g, 3.26 mmol) in triethylene glycol (30 mL) was added hydrazine (95%, 0.44 g, 13.0 mmol) in one portion in a 150-mL, jacketed flask equipped with a magnetic stirrer, a heating mantle, a standard condenser, a lower take-off condenser with a N_2 inlet, and three glass stoppers. A heating temperature of 200°-210° C. for 4 h under N_2 was produced by boiling tetralin (bp 207° C.) in the jacket. Cooling of the solution to RT was followed by the addition of chilled water (40 mL). Combined extracts of the resulting suspension (ether, 4×30 mL) were washed with 10% NaOH (30 mL) and saturated NaCl (30 mL), dried (Na_2SO_4, 4 h), filtered and concentrated to a light yellow oil which displayed no carbonyl stretch in the IR

spectrum and was used without further purification. Dissolution of the oil in ether (60 mL) at ~5° C. (via ice water bath) was followed by the dropwise addition of a solution of $HClO_4$ (60%, 0.68 g, 4.08 mmol) in $(H_3C)_2CHOH$ (1 mL) over 5 min. The resulting, precipitated solid was filtered and recrystallized (95% EtOH) to give 0.81 g (63.3%) of white crystals of (6); mp 140°-141° C. IR (KBr) cm^{-1} 3060, 3020 (Ar C—H), 2970, 2920, 2830 (C—H), 1485 (C=C), 1085 (Cl—O), 790 (C—H out of plane, para); ^1H NMR (DMSO-d_6) δ1.19 (d, 6H, CH_3, J=6.7 Hz), 1.61 [d, 1H, H(9), J=12.7 Hz], 1.82 [d, 1H, H(9), J=12.2 Hz], 2.14 [bs, 2H, H(1,5)], 2.41 [bd, 2H, $H(6,8)_{ax}$, J=11.2 Hz], 3.04 [bd, 2H, $H(6,8)_{eq}$, J=11.1 Hz], 3.16 [bd, 2H, $H(2,4)_{ax}$, J=11.2 Hz], 3.34 [bd, 2H, $H(2,4)_{eq}$, J=11.7 Hz], 3.44-3.52 [m, 3H, $CH(CH_3)_2$ and $ArCH_2$], 7.44 [s, 4H, Ar—H]; ^{13}C NMR (DMSO-d_6) ppm 16.10 (CH_3), 27.25 [C(1,5)], 29.60 [C(9)], 52.77 [C(2,4)], 56.25 [$CH(CH_3)_2$], 56.75 [C(6,8)], 60.42 ($ArCH_2$), 128.28, 131.27, 132.14, 135.72 (Ar—C); ^{15}N NMR (DMSO-d_6) ppm 50.34 [N(7)], 60.57 [N(3)]. Anal. Calcd. for $C_{17}H_{20}Cl_2N_2O_4$: C, 51.92; H, 6.66. Found: C, 51.74; H, 6.57.

EXAMPLE XVI

3-(4'-Chlorobenzoyl)-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (33)

A 25-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a standard condenser with a N_2 inlet, a 10-mL addition funnel and two glass stoppers. To a mixture of the amine (31, 0.60 g, 3.57 mmol) in CH_2Cl_2 (5 mL) and 10% NaOH (3.58 g, 8.93 mmol) was added dropwise a solution of 4-chlorobenzoyl chloride (0.69 g, 3.92 mmol) in CH_2Cl_2 (5 mL) over 15 min. Stirring of the mixture was continued for an additional 3 h under N_2. An aqueous mixture, formed upon addition of H_2O (30 mL), was extracted (CH_2Cl_2, 4×25 mL). Combined extracts were dried (Na_2SO_4, 2 h), filtered, and concentrated to give a viscous yellow oil. Chromatography of the oil was performed by adding an ether solution of the oil to a neutral alumina column (69 g, 1.7 cm×30 cm) and then using 60:40 hexanes/ethyl acetate as eluant. Fractions (R_f=0.41) were saved and concentrated (rotary evaporator then vacuum pump, overnight, RT/0.2 mm Hg) to give 0.86 g (80.4%) of off-white solid (33); mp 97°-98° C. IR (KBr) cm^{-1} 3085, 3070 (Ar C—H), 2965, 2935, 2865, 2800, 2770 (C—H), 1630 (C=O); ^1H NMR ($DCCl_3$) δ0.95 (d;, 3H, CH_3, J=6.5 Hz), 1.05 (d, 3H, CH_3, J=6.4 Hz), 1.63-1.75 [m, 3H, H(5) and H(9)], 1.97 [bs, 1H, H(1)], 2.41 [bd, 1H, $H(4)_{ax}$, J=10.6 Hz], 2.50 [bd, 1H, $H(6)_{ax}$, J=11.2H], 2.59 [heptet, 1H, $CH(CH_3)_2$, J=6.5 Hz], 2.71 [bd, 1H, $H(6)_{eq}$, J=11.0 Hz], 3.03-3.06 [m, 2H, $H(2)_{ax}$ and $H(4)_{eq}$], 3.31 [bd, 1H, $H(8)_{ax}$, J=12.8 Hz], 3.71 [bd, 1H, $H(8)_{eq}$, 13.1 Hz], 4.77 [bd, 1H, $H(2)_{eq}$, J=13.2 Hz], 7.27-7.37 (m, 4H, Ar—H); ^{13}C NMR ($DCCl_3$) ppm 16.37, 19.35 (CH_3), 29.07 [C(1)], 29.07 [C(1)], 29.80 [C(5)], 32.29 [C(9)], 46.68 [C(2)], 52.22 [C(4)], 52.56 [C(8)], 54.38 [$CH(CH_3)_2$], 54.79 [C(6)], 128.35, 128.51, 134.67, 136.11 (Ar—C), 169.03 (C=O). Anal. Calcd. for $C_{17}H_{23}ClN_2O$: C, 66.55; H, 7.56. Found: C, 66.45; H, 7.71.

EXAMPLE XVII

β,β'-Dibromoisobutyric Acid (46)

Into a 500-mL, single necked, round-bottomed flask equipped with a heating mantle, a magnetic stirrer, a Claisen distillation head, a standard condenser and a receiver were placed diethyl bis(hydroxymethyl)malonate (45, 37 g, 0.17 mol), and hydrobromic acid (48%, 280 mL, 2.5 mol). The resulting homogeneous solution was distilled for 2.5 h (35°-126° C.), and 100 mL of distillate was collected. Heating was momentarily stopped, and the distillation head, condenser and receiver were removed and replaced with a condenser. The mixture was heated at reflux for 6 h. A brown reaction mixture was poured into a 250 mL Erlenmeyer flask which was allowed to cool to RT (1 h) and then was placed in an ice bath (1 h) to yield acid (46) as a white solid. This white solid was filtered off using a Buchner funnel under suction (aspirator) and was then washed with cold H_2O (50 mL) to afford, after drying (Abderhalden, 78° C., 12 h/0.2 mm Hg, P_2O_5), acid (19.1 g, 46.3%); mp 96°-97° C. The mother liquor was concentrated to about 75 mL and then cooled to RT (0.5 h) [followed by an ice bath (0.5 h)] to yield a second crop of the acid (46) (3.7 g, 9.0%); mp 95°-97° C. IR (KBr) cm^{-1} 3500-2500 (CO_2H), 1700 (C=O); ^1H NMR ($DCCl_3$) δ3.27 (m, 1H, CH), 3.79 (m, 4H, CH_2Br), 10.91 (bs, 1H, CO_2H); ^{13}C NMR ($DCCl_3$) ppm 29.80 (t, CH_2Br), 48.38 (d, CH), 175.30 (s, CO_2H).

EXAMPLE XVIII

Ethyl β,β'-Dibromoisobutyrate (47)

Into a 250-mL, single necked, round-bottomed flask equipped with a soxhlet extractor, standard condenser, magnetic stirrer and heating mantle were placed the dibromo acid (46, 27 g, 0.11 mol), benzene (125 mL), absolute ethanol (50 mL) and conc H_2SO_4 (0.5 mL). Into the Soxhlet extractor was placed a thimble containing anhydrous $MgSO_4$ (20 g). The reaction mixture was heated at reflux for 24 h. Solvent was distilled off until about 50 mL remained. The concentrated reaction mixture was cooled to RT (0.5 h), and H_2O (50 mL) was added followed by slow addition of solid $NaHCO_3$ with stirring until the pH was 7. The resulting suspension was transferred to a separatory funnel and the organic layer was separated. The aqueous layer was extracted with ether (3×50 mL). The organic layers were combined and washed with H_2O (50 mL) and saturated NaCl (50 mL). This was followed by drying (anhydrous $MgSO_4$, 2 h), filtration, and evaporation (rotary evaporator, aspirator) to yield a pale brown liquid which was distilled under reduced pressure to yield the ester (47, 3 g, 94.9%), bp 60°-62° C./0.2 mm Hg. IR (film) cm^{-1} 1735 (C=O); ^1H NMR ($DCCl_3$) δ1.30 (t, 3H, CH_3), 3.20 (m, 1H, CH), 3.78 (m, 4H, CH_2Br), 4.25 (q, 2H, OCH_2); ^{13}C NMR ($DCCl_3$) ppm 14.18 (q, CH_3), 30.75 (t, CH_2Br), 48.52 (d, CH), 61.66 (t, OCH_2), 169.32 (s, CO_2Et).

EXAMPLE XIX

Ethyl 3-Benzyl-3-azabicyclo[3.3.1]nonan-9-one-7-(endo)-carboxylate (20)

As the starting point for the preparation of (20), the preparation of 1-benzyl-4-pyrrolidinyl-1,2,3,6-tetrahydropyridine was required. Into a 250-mL, single-necked, round-bottomed flask equipped with a Dean-Stark trap, standard condenser, magnetic stirrer, heating mantle, and a N_2 inlet were placed 1-benzyl-4-piperidinone (43, 10.2 g, 55 mmol), benzene (125 mL) and pyrrolidine (6.0 g, 85 mmol). The resulting mixture was heated at reflux for 24 h. The Dean-Stark trap was removed and a simple distillation apparatus was in-

stalled. Distillation of the solvent was completed at atmospheric pressure followed by another distillation under reduced pressure to yield the enamine as a pale yellow oil (12.7 g, 97.0%), bp 167°-169° C./0.2 mm Hg. IR (film) cm^{-1} 1650 (C=C—N); ^1H NMR ($DCCl_3$) δ1.79 [bs, 4H, H(9,10)], 2.30 [bs, 2H, H(3)], 2.56 [t, 2H, H(2)], 3.00 [bs, 2H, H(8,11)], 3.05 [bs, 2H, H(6)], 3.54 (s, 2H, CH_2Ph), 4.16 [bs, 1H, H(5)], 7.26-7.33 (m, 5H, Ar—H); ^{13}C NMR ($DCCl_3$) ppm 24.69 [t, C(9,10)], 28.31 [t, C(3)], 47.10 [t, C(8,11)], 50.07 [t, C(2)], 52.94 [t, C(6)], 62.68 (t, CH_2Ph), 90.24 [d, C(5)], 126.64, 127.88, 128.92, 138.61 (Ar—C), 141.29 [s, C(4)].

Into a 250-mL, three-necked, round-bottomed flask equipped with a heating mantle, magnetic stirrer, standard condenser, dropping funnel and a N_2 inlet were placed a solution of the above enamine [9.9 g, 40 mmol in CH_3CN (50 mL)] and triethylamine (11.6 g, 9.1 g, 90 mmol). The resulting mixture was heated at reflux, and, to the boiling solution was added dropwise a solution of the dibromo ester (47, 11.1 g, 40 mmol) in CH_3CN (20 mL) over a period of 0.5 h. During addition, triethylammonium bromide precipitated as a white solid, and the reaction mixture turned brown. Heating was continued for 3.5 h after the addition was complete. Solvent was removed (rotary evaporator) to yield a dark brown oil to which was added H_2O (50 mL). The mixture was extracted with $HCCl_3$ (4×50 mL). The organic layers were combined and washed successively with HCl (1N, 2×50 mL), $NaHCO_3$ (saturated aqueous, 2×50 mL) and NaCl (saturated, 2×50 mL). After drying (anhydrous Na_2SO_4), the solution was filtered and evaporated (rotary evaporator) to yield the crude ketone (20) as a dark brown oil. This dark brown oil was purified by column chromotography over silica gel (150 g, 3.8 cm×61 cm; 1 mL/min) using 10% EtOAc in hexanes as the eluant to yield ketone (20) as a pale yellow, viscous oil (4.1 g, 33.0%). R_f=0.49 in 9:1 hexanes:EtOAc. IR (film) cm^{-1} 1730 (C=O); ^1H NMR ($DCCl_3$) δ1.30 (t, 3H, CH_3), 2.18 [dd, 2H, $H(6,8)_{ax}$, J=6.9, 15.9 Hz], 2.29 [bs, 2H, H(1,5)], 2.44 [m, 3H, $H(6,8)_{eq}$ and $H(7)_{exo}$], 2.82 [dd, 2H, $H(2,4)_{ax}$, J=6.0, 14.4 Hz], 3.04 [d, 2H, $H(2,4)_{eq}$, J=10.6 Hz], 3.56 (s, 2H, CH_2Ph), 4.22 (q, 2H, OCH_2), 7.17-7.30 (m, 5H, Ar—H); ^{13}C NMR ($DCCl_3$) ppm 14.35 (q, CH_3), 33.21 [t, C(6,8)], 37.75 [d, C(7)], 46.61 [d, C(1,5)], 58.06 (t, CH_2Ph), 60.34 (t, OCH_2), 127.26, 128.09, 129.50, 135.10 (Ar—C), 172.40 (s, CO_2Et), 215.92 (C=O). The oil, very slightly crude (20), was used without further purification for succeeding steps since the oil decomposed upon attempted distillation.

EXAMPLE XX

Ethyl 3-Benzyl-9,9-(1,3-dithiolan-2-yl)-3-azabicyclo[3.3.1]nonane-7-(endo)-carboxylate (38)

Into a 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, standard condenser, dropping funnel, N_2 inlet and an ice-bath were placed the ketone (20, 3.01 g, 10 mmol), 1,2-ethanedithiol (2 mL, 2.25 g, 24 mmol), and dry $HCCl_3$ (50 mL). The resulting mixture was cooled to 0°-5° C. in an ice bath. Freshly distilled BF_3 etherate (4 mL, 2.2 g, 15 mmol) was added dropwise over a period of 0.5 h. The reaction mixture was stirred at 0°-5° C. for 1 h and then at RT for 8 h. To the resulting mixture was added $HCCl_3$ (25 mL), and the solution was successively washed with NaOH (1N, 3×50 mL) and NaCl (saturated, 50 mL). After drying (anhydrous Na_2SO_4), the solution was filtered and evaporated (rotary evaporator, aspirator) to yield the crude thioketal (38) as a pale yellow, viscous oil, which was purified by column chromatography over silica gel (105 g) using 10% EtOAc in hexanes as the eluant. The thioketal was obtained as a colorless oil which crystallized out as a white solid upon standing at RT (12 h). This white solid was recrystallized (hexanes) to yield solid thioketal (38) as white needles (1.6 g, 42.0%, mp 76°-78° C.). IR (KBr) cm^{-1} 1715 (CO_2Et); ^1H NMR ($DCCl_3$) δ1.30 (t, 3H, CH_3), 1.90 [bs, 2H, H(1,5)], 2.34 [bd, 2H, $H(6,8)_{ax}$], 2.47 [m, 1H, H(7)], 2.68-2.83 [m, 6H, $H(6,8)_{eq}$, $H(2,4)_{ax}$ and $H(2,4)_{eq}$], 3.10-3.17 (m, 4H, SCH_2), 3.44 (s, 2H, CH_2Ph), 4.19 (q, 2H, OCH_2), 7.12-7.33 (m, 5H, Ar—H); ^{13}C NMR ($DCCl_3$) ppm 14.36 (q, CH_3), 30.25 [t, C(6,8)], 36.71 [d, C(7)], 38.21, 38.64 (t, SCH_2), 42.10 [d, C(1,5)], 54.92 [t, C(2,4)], 60.14 (t, CH_2Ph), 60.27 (t, OCH_2), 127.00, 127.84, 129.91, 134.21 (Ar—C), 172.35 (CO_2Et). Anal. Calcd. for $C_{20}H_{27}NO_2S_2$: C, 63.66; H, 7.16; S, 16.97. Found: C, 63.99; H, 7.08; S, 17.23.

EXAMPLE XXI

Ethyl 3-Benzyl-9,9-(1,3-dithiolan-2-yl)-3-azabicyclo[3.3.1]nonane-7-(endo)-carboxylate Hydroperchlorate (14)

Into a 250-mL Erlenmeyer flask equipped with a magnetic stirrer were placed the thioketal (38, 1.5 g, 4 mmol), anhydrous ether (150 mL), and absolute ethanol (5 mL). The resulting solution was cooled in an ice bath for 0.5 h. To this cooled solution was added dropwise $HClO_4$ (60%, 0.85 g, 5 mmol) over a period of 0.5 h. During the addition a white solid precipitated. The resulting mixture was stirred in an ice bath for another 1 h, after the addition was complete, and then for 2 h at RT. The white solid obtained by filtration was recrystallized (isopropyl alcohol) to yield the thioketal hydroperchlorate (14) as white needles (1.7 g, 90.0%); mp 153°-154° C. IR (KBr) cm^{-1} 3400 (N—H), 1700 (CO_2Et), 1100 (Cl—O); ^1H NMR ($DCCl_3$) δ1.30 (t, 3H, CH_3), 2.05 [d, 2H, $H(6,8)_{ax}$, J=16.1 Hz], 2.36 [bs, 2H, H(1,5)], 2.71 [m, 2H, $H(6,8)_{eq}$], 3.33 (m, 4H, SCH_2), 3.50 [m, 2H, $H(2,4)_{ax}$], 3.68 (d, 2H, CH_2Ph), 7.43-7.60 (m, 5H, Ar—H), 10.30 (bs, 1H, N—H); ^{13}C NMR ($DCCl_3$) ppm 13.79 (q, CH_3), 28.42 [t, C(6,8)], 29.53 [d, C(7)], 39.18 [d, C(1,5)], 39.51, 39.88 (t, SCH_2), 56.60 [t, C(2,4)], 61.81 (t, CH_2Ph), 63.67 (t, OCH_2), 68.96 [s, C(9)], 127.84, 129.93, 130.31, 131.57 (Ar—C), 183.05 (s, CO_2Et). Anal. Calcd. for $C_{20}H_{28}ClNO_6S_2$: C, 50.26; H, 5.86; N, 2.93. Found: C, 50.24; H, 6.12; N, 2.94.

EXAMPLE XXII

Ethyl 3-Benzyl-3-azabicyclo[3.3.1]nonane-7-(endo)-carboxylate Hydroperchlorate (13)

Ester (38) (1.89 g, 0.005 mol), ethanol (200 mL), and Raney nickel (about 20 mL of a wet solid) were heated together at reflux for 18 hours, and the mixture was allowed to cool. After the mixture was filtered, the solvent was evaporated to a viscous oil. The oil was treated with a saturated brine solution, and the resulting mixture was extracted with chloroform (3×50 mL). Evaporation of the solvent gave a colorless oil (0.97 g, 68.0%). Thus, slightly crude ethyl 3-benzyl-3-azabicyclo[3.3.1]nonane-7-(endo)-carboxylate was used in the next step without further purification.

Into a 250 mL Erlenmeyer flask equipped with magnetic stirrer were placed the above ester (0.95 g, 3

mmol), anhydrous ether (150 mL), and absolute ethanol (5 mL). The resulting solution was cooled in ice bath and to the chilled solution was added dropwise $HClO_4$ (60%, 0.75 g, 4.5 mmol) over a period of 0.5 h. During the addition, a white solid precipitated. The resulting mixture was stirred in ice bath for 1 h, after the addition was complete, and then for 2 h at RT. Filtration and recrystallization (isopropyl alcohol) yielded the hydroperchlorate (13) as colorless platelets (0.87 g, 68.0%); mp 130°-131° C. IR (KBr) cm^{-1} 3440 (N—H), 1700 (CO_2Et), 1100 (Cl—O); ^1H NMR ($DCCl_3$) δ1.30 (t, 3H, CH_3), 1.61 [bd, 1H, $H(9)_{endo}$], 1.87 [d, 2H, $H(6,8)_{ax}$, J=12 Hz], 2.05 [bd, 1H, $H(9)_{exo}$], 2.16-2.31 [m, 4H, H(1,5) and $H(6,8)_{eq}$], 2.91-2.98 [m, 1H, H(7)], 3.35-3.48 [m, 4H, $H(2,4)_{ax}$ and $H(2,4)_{eq}$], 4.32 (q, 2H, OCH_2), 4.50 (d, 2H, CH_2Ph), 7.38-7.68 (m, 5H, Ar—H); ^{13}C NMR ($DCCl_3$) ppm 13.79 (q, CH_3), 25.74 [d, C(1,5)], 27.85 [t, C(6,8)], 31.91 [d, C(7)], 55.96 [t, C(2,4)], 61.68 (t, CH_2Ph), 63.05 (t, OCH_2), 128.60, 129.98, 131.25, (Ar—C), 182.93 (s, CO_2Et). Anal. Calcd. for $C_{18}H_{26}ClNO_6$: C, 55.75; H, 6.71. Found: C, 56.11; H, 6.82.

EXAMPLE XXIII

7-Isopropyl-3-(3',4',5'-trimethoxybenzoyl)-3,7-diazabicyclo[3.3.1]nonane (35)

A 25-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a standard condenser with N_2 inlet, a 10-mL addition funnel and two glass stoppers. To a mixture of the amine (31, 0.60 g, 3.57 mmol) in CH_2Cl_2 (5 mL) and 10% NaOH (3.58 g, 8.93 mmol) was added dropwise a solution of 3,4,5-trimethoxybenzoyl chloride (0.92 g, 3.92 mmol) in CH_2Cl_2 (5 mL) over 15 min. Stirring of the mixture was continued for an additional 3 h under N_2. An aqueous mixture, upon addition of H_2O (30 mL), was extracted (CH_2Cl_2, 4×25 mL). Combined extracts were dried (Na_2SO_4, 2 h), filtered, and concentrated to give a viscous yellow oil. Chromatography of the oil was performed on neutral alumina (74 g, 1.7 cm×32 cm) using 60:40 ethyl acetate/hexanes as eluant. Fractions (R_f=0.34) were saved and concentrated (rotary evaporator then vacuum pump, overnight, RT/0.2 mm Hg) to give 1.02 g (79.1%) of off-white solid (35); mp 67.5°-69.5° C. IR (KBr) cm^{-1} 3055 (Ar C—H), 2985, 2955, 2910, 2890, 2780 (C—H), 1620 (C=O); ^1H NMR ($DCCl_3$) δ0.96 (d, 3H, CH_3, J=6.5 Hz), 1.09 (d, 3H, CH_3, J=6.7 Hz), 1.64-1.79 [m, 3H, H(5) and H(9)], 2.05 [bs, 1H, H(1)], 2.44 [bd, 1H, $H(4)_{ax}$, J=10.6 Hz], 2.57 [bd, 1H, $H(6)_{ax}$, J=10.8 Hz], 2.66 [heptet, 1H, $CH(CH_3)_2$, J=6.6 Hz], 2.71 [bd, 1H, $H(6)_{eq}$, J=11.0 Hz], 3.02-3.07 [m, 2H, $H(4)_{eq}$ and $H(2)_{ax}$], 3.31 [bd, 1H, $H(8)_{ax}$, J=13.2 Hz], 3.80-3.92 [m, 10H, $H(8)_{eq}$ and OCH_3], 4.77 [bd, 1H, $H(2)_{eq}$, J=13.5 Hz], 7.29 (s, 2H, Ar—H); ^{13}C NMR ($DCCl_3$) ppm 15.87, 19.42 (CH_3), 29.02 [C(1)], 29.78 [C(5)], 32.35 [C(9)], 46.64 [C(2)], 51.73 [C(4)], 52.48 [C(8)], 54.39 [$CH(CH_3)_2$], 54.95 [C(6)], 56.13, 60.86 (OCH_3), 103.83, 133.32, 133.21, 138.22, 153.21 (Ar—C), 169.66 (C=O). Anal. Calcd. for $C_{20}H_{30}N_2O_4$: C, 66.27; H, 8.34. Found: C, 66.04; H, 8.32.

EXAMPLE XXIV

3-(3',4'-Dimethoxybenzoyl)-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (34)

A 25-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a standard condenser with a N_2 inlet, a 10-mL addition funnel, and two glass stoppers. To a mixture of the amine (31, 0.60 g, 3.57 mmol) in CH_2Cl_2 (5 mL) and 10% NaOH (3.58 g, 8.93 mmol) was added dropwise a solution of 3,4-dimethoxybenzoyl chloride (0.80 g, 3.92 mmol) in CH_2Cl_2 (10 mL) over 15 min. Stirring of the mixture was continued for an additional 3 h under N_2. An aqueous mixture, formed upon addition of H_2O (30 mL), was extracted (CH_2Cl_2, 4×25 mL). Combined extracts were dried (Na_2SO_4, 2 h), filtered and concentrated to give a viscous yellow oil. Chromatography of the oil was performed on neutral alumina (74 g, 1.7 cm×32 cm) using 60:40 ethyl acetate/hexanes as eluant. Fractions (R_f=0.31) were saved and concentrated (rotary evaporator then vacuum pump, overnight, RT/0.2 mm Hg) to give 0.87 g (73.1%) of off-white solid (34); mp 67.5°-69.5° C. IR (KBr) cm^{-1} 3055 (Ar C—H), 2950, 2915, 2845, 2820, 2770, 2750, 2710 (C—H), 1625 (C=O); ^1H NMR ($DCCl_3$) δ0.96 (d, 3H, CH_3, J=6.4 Hz), 1.06 (d, 3H, CH_3, J=6.5 Hz), 1.62-1.75 [m, 3H, H(5) and H(9)], 1.96 [bs, 1H, H(1)], 2.43 [bd, 1H, $H(4)_{ax}$, J=9.7 Hz], 2.51 [bd, 1H, $H(6)_{ax}$, J=10.5 Hz], 2.62 [heptet, 1H, $CH(CH_3)_2$, J=6.4 Hz], 2.74 [bd, 1H, $H(6)_{eq}$, J=9.9 Hz], 3.00-3.09 [m, 2H, $H(4)_{eq}$ and $H(2)_{ax}$], 3.32 [bd, 1H, $H(8)_{ax}$, J=13.2 Hz], 3.83-3.94 [m, 7H, $H(8)_{eq}$ and OCH_3], 4.77 [bd, 1H, $H(2)_{eq}$, J=13.3 Hz], 6.84-6.94 (m, 3H, Ar—H); ^{13}C NMR ($DCCl_3$) ppm 16.46, 19.15 (CH_3), 29.13 [C(1)], 29.86 [C(5)], 32.36 [C(9)], 46.71 [C(2)], 52.25 [C(4)], 52.65 [C(8)], 54.35 [$CH(CH_3)_2$], 54.68 [C(6)], 55.88, 55.93 (OCH_3), 110.50, 119.64, 130.23, 148.78, 149.39 (Ar—C), 169.90 (C=O). Anal. Calcd. for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49. Found: C, 68.58; H, 8.47.

EXAMPLE XXV

3-(3',4'-Dimethoxybenzoyl)-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (3)

A 50-mL Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. To a chilled (5° C.), stirred solution of the amide (34, 0.30 g, 0.90 mmol) in ether (30 mL) was added dropwise a solution of $HClO_4$ (60%, 0.18 g, 1.08 mmol) in isopropyl alcohol (1 mL) over 10 min. A white precipitate resulted which was filtered and then stirred in hot CH_3OH (10 mL) for 20 min. The mixture was filtered and dried (Abderhalden, P_2O_5, overnight, RT/0.2 mm Hg) to give 0.27 g (69.2%) of white solid (3); mp 235°-236° C. (dec). IR (KBr) cm^{-1} 3130 (N—H), 3010 (Ar C—H), 2975, 2945, 2920 (C—H), 1635 (C=O), 1095 (Cl—O); ^1H NMR (DMSO-d_6, 80° C.) δ1.33 (d, 6H, CH_3, J=6.7 Hz), 1.74 [bd, 1H, H(9), J=12.8 Hz], 1.91 [bd, 1H, H(9), J=13.2 Hz], 2.27 [bs, 2H, H(1,5)], 3.12 [bd, 2H, $H(6,8)_{ax}$, J=13.7 Hz], 3.19-3.28 [m, 2H, $H(2,4)_{ax}$], 3.42-3.56 [m, 3H, $H(6,8)_{eq}$ and $CH(CH_3)_2$], 3.78, 3.81 (two s, 6H, OCH_3), 3.97 [bd, 2H, $H(2,4)_{eq}$, J=13.6 Hz], 6.94-7.03 [m, 3H, Ar—H], 7.81 (bs, 1H, N—H); ^{13}C NMR (DMSO-d_6, 80° C.) ppm 16.34 (CH_3), 26.81 [C(1,5)], 27.80 [C(9)], 49.06 [C(2,4)], 52.40 [C(6,8)], 55.88, 55.92 (OCH_3), 59.97 [$CH(CH_3)_2$], 111.85, 112.10, 120.44, 128.68, 148.74, 150.26 (Ar—C), 172.97 (C=O). Anal. Calcd. for $C_{19}H_{29}ClN_2O_7$: C, 52.72; H, 6.75. Found: C, 52.35; H, 6.77.

EXAMPLE XXVI

3-Benzenesulfonyl-7-isopropyl-3,7-diazabicyclo[3.3.1-]nonane (36)

A 50-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a standard condenser with a N_2 inlet, an ice bath, a 10-mL addition funnel, and a glass stopper. To a stirred, ice cold (5° C.) mixture of

the amine (31, 1.03 g, 6.12 mmol) and NaOH pellets (97%, 0.76 g, 18.4 mmol) in H_2O (7 mL) and CH_2Cl_2(5 mL) was added dropwise a solution of benzenesulfonyl chloride (2.16 g, 12.2 mmol) in CH_2Cl_2(5 mL) over 30 min. Stirring of the mixture was continued for an additional 17.5 h at RT. The reaction mixture was then partioned between H_2O (30 mL) and CH_2Cl_2(30 mL) followed by basification (pH ~ 12) of the aqueous phase. Extracts (CH_2Cl_2,3×30 mL) of the remaining water layer were combined with the initial organic layer. The solution was washed with 10% NaOH (30mL) and then saturated NaCl (30 mL); it was dried (Na_2SO_4, overnight), filtered, and concentrated to give an orange viscous oil. Chromatography of the oil was performed on silica gel (39 g, 1.6 cm×62 cm) using 10% CH_3OH/CH_2Cl_2. Fractions (R_f=0.44) were saved, concentrated, and reeluted on neutral alumina (90 g, 2.5 cm×18 cm) employing ethyl acetate as eluant. Fractions (R_f=0.53) were saved and concentrated. A colored impurity persisted which was removed by again eluting over silica gel (21 g, 1.6 cm×33 cm) using 5% CH_3OH/CH_2Cl_2 as eluant. Fractions (R_f=0.34) were combined and concentrated (rotary evaporator then vacuum pump, overnight, RT/0.2 mm Hg) to give 0.54 g (28.6%) of white solid (36); mp 85.5°-86.5° C. IR (KBr) cm^{-1}3060 (Ar C—H), 2960, 2910, 2890, 2865, 2820 (C—H), 1585 (C=C), 1340, 1170 (S=O), 760, 720 (C—H out of plane, mono); ^1H NMR (DMSO-d_6) δ0.88 (d, 6H, CH_3, J=6.5 Hz), 1.40 [bs, 2H, H(9)], 1.94 [bs, 2H, H(1,5)], 2.35 [bd, 2H, $H(6,8)_{ax}$, J=10.3 Hz], 2.53 [heptet, 1H, $CH(CH_3)_2$, J=6.5 Hz], 2.69 [bd, 2H, $H(6,8)_{eq}$, J=10.3 Hz], 2.89 [dd, 2H, $H(2,4)_{ax}$, J=11.2 Hz, J'=4.5 Hz], 3.36 [d, 2H, $H(2,4)_{eq}$, J=10.9 Hz], 7.58-7.75 (m, 5H, Ar—H); ^{13}C NMR (DMSO-d_6) ppm 17.57 (CH_3), 27.39 [C(1,5)], 28.95 [C(9)], 48.88 [C(2,4)], 52.66[C(6,8)], 53.42 [$CH(CH_3)_2$], 126.90, 129.01, 132.36, 136.79 (Ar—C). Anal. Calcd. for $C_{16}H_{24}N_2O_2S$: C, 62.31; H, 7.85. Found: C, 62.48; H, 7.69.

EXAMPLE XXVII

7-Isopropyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one (26)

A three-necked, 300-mL, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a standard condenser with a N_2 inlet, and two glass stoppers. A mixture containing isopropylamine (2.96 g, 50 mmol), paraformaldehyde (12.01 g, 400 mmol), and CH_3OH(188 mL) was made acidic with glacial acetic acid (4.5 g, 75 mmol). In one portion, 4-thianone (44, 5.81 g, 50 mmol) was added followed by stirring at reflux for 21 h. Evaporation of the solvent gave a red oil, which was diluted with H_2O (200 mL) and extracted with ether (2×100 mL), the latter being discarded. Basification (pH ~ 12) of the aqueous layer by the addition of NaOH pellets (3.0 g, 75 mmol) resulted in the formation of a yellow suspension which was extracted with CH_2Cl_2(4×100 mL). Combined extracts were dried ($MgSO_4$, overnight), filtered, and concentrated to afford a yellow oil which solidified upon standing. This solid was digested in 250 mL of Skelly B (bp 60°-68° C.) for 30 min, and the supernatant was decanted. Evaporation of the solvent, followed by heating the crude solid in vacuo (95°-110° C./0.3 mm Hg) in a sublimation apparatus gave a sticky white solid (mp 54°-57° C.). Recrystallization (Skelly B) afforded 4.15 g (41.6%) of white flakes of ketone (26); mp 59°-60° C. IR (KBr) cm^{-1}2965, 2935, 2900, 2875, 2805 (C—H), 1730 (C=O); ^1H NMR ($DCCl_3$) δ1.04 (d, 6H, CH_3, J=6.7 Hz), 2.75-2.90 [m, 5H, ring protons, $CH(CH_3)_2$, and H(1,5)], 3.05-3.13 (m, 4H, ring protons), 3.24-3.29 (m, 2H, ring protons); ^{13}C NMR ($DCCl_3$) ppm 18.30 (q, CH_3), 34.16 [t, C(2,4)], 47.52 [d, C(1,5)], 53.76 [d, $CH(CH_3)_2$], 54.16 [t, C(6,8)], 213.68 (s, C=O); ^{15}N NMR ($DCCl_3$) ppm 39.27 [N(7)]. Anal. Calcd. for $C_{10}H_{17}NOS$: C, 60.26; H, 8.60. Found: C, 60.40; H, 8.65.

EXAMPLE XXVIII

7-Isopropyl-3-thia-7-azabicyclo[3.3.1]nonane Hydroperchlorate (8)

To a mixture of KOH pellets (85%, 3.96 g, 60 mmol) and the ketone (26, 1.0 g, 5 mmol) in triethylene glycol (25 mL) was added hydrazine (95%, 1.69 g, 50 mmol) in one portion in a 70 mL, jacketed flask equipped with a magnetic stirrer, a heating mantle, a standard condenser, a lower take-off condenser with a N_2 inlet, and two glass stoppers. A heating temperature of 200°-210° C. for 5 h was produced by boiling tetralin (bp 207° C.) in the jacket. After cooling to RT, the solution was diluted with chilled water (100 mL) and extracted with ether (4×50 mL). Combined extracts were washed with 10% NaOH (50 mL) and saturated NaCl (50 mL), dried (Na_2SO_4, overnight), filtered, and concentrated to a yellow oil (0.8 g). Dissolution of the oil in ether (50 mL) via magnetic stirring and cooling (5° C.) with an external ice bath was followed by dropwise addition of a solution of $HClO_4$ (60%, 1.08 g, 6.45 mmol) in isopropyl alcohol (3 mL) over 10 min. Stirring of the mixture an additional 10 min, filtering the precipitated salt, and then washing the latter with ether (~50 mL) gave an off-white solid. Dissolving the salt in hot 95% EtOH and decolorizing the solution with Norit, followed by filtering, and cooling, afforded 0.91 g (63.6%) of salt (8) as a white solid; mp 281°-282.5° C. IR (KBr) cm^{-1}3060 (N—H), 3000, 2960, 2935 (C—H), 1090 (Cl—O); ^1H NMR (DMSO-d_6) δ1.28 (d, 6H, CH_3), 1.76 [d, 1H, H(9), J=13.3 Hz], 1.91 [d, 1H, H(9), J=12.9 Hz], 2.35 [bs, 2H, H(1,5)], 2.78 [bd, 2H, $H(2,4)_{ax}$, J=12.2 Hz], 3.14 [bd, 2H, $H(2,4)_{eq}$, J=13.6 Hz], 3.29-3.57 [m, 3H, $H(6,8)_{ax}$ and $CH(CH_3)_2$], 3.62 [d, 2H, $H(6,8)_{eq}$, J=12.7 Hz], 9.07 (bs, 1H, N—H); ^{13}C NMR (DMSO-d_6) ppm 16.19 (q, CH_3), 25.51 [d, C(1,5)], 28.35 [t, C(9)], 30.69 [t, C(2,4)], 52.36 [t, C(6,8)], 58.66 [d, $CH(CH_3)_2$]; ^{15}N NMR (DMSO-d_6) ppm 58.47 [N(7)]. Anal. Calcd. for $C_{10}H_{20}ClNO_4S$: C, 42.03; H, 7.05. Found: C, 42.10; H, 7.18.

EXAMPLE XXIX

7-(3'-Iodobenzyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-one (25)

A 100 mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a standard condenser with a N_2 inlet, and two glass stoppers. A mixture containing 3-iodobenzylamine (1.19 g, 5.10 mmol), paraformaldehyde (1.22 g, 40.8 mmol), and CH_3OH (30 mL) was made acidic with glacial acetic acid (0.46 g, 7.65 mmol). In one portion, 4-thianone (44, 0.59 g, 5.10 mmol) was added and the resulting mixture was heated under N_2 at reflux for 21 h. Evaporation of the solvent gave a reddish oil, which was dissolved in H_2O (40 mL). Basification (pH ~ 13) of the solution by the dropwise addition of 10% NaOH resulted in the formation of a milky suspension which was extracted with ether (5×40 mL). Combined extracts were dried (Na_2SO_4, overnight), filtered, and concentrated to a yellow oil. Digestion of the oil occurred in Skelly B

(125 mL, bp 60°-68° C.) for 30 min, and the supernatant was decanted. Further digestion of the residual material was effected in pentane (2×125 mL) for 30 min. Combined supernatant extracts were concentrated (rotary evaporator the vacuum pump, overnight, RT/0.2 mm Hg) to give 0.84 g (57.5%) of a slightly crude viscous oil (25) which was used without further purification in the next step. IR (film) cm^{-1}3055 (Ar C—H), 2930, 2825 (C—H), 1735 (C=O), 885, 790, 695 (C—H out of plane, meta); ^1H NMR ($DCCl_3$) δ2.72-3.18 [m, 10H, ring protons and H(1,5)], 3.51 (s, 2H, $ArCH_2$), 7.07-7.71 (m, 4H, Ar—H); ^{13}C NMR ($DCCl_3$) ppm 35.05 [C(2,4)], 46.95 [C(1,5)], 58.20 [C(6,8)], 60.69 ($ArCH_2$), 94.43, 127.98, 130.23, 136.44, 137.64, 140.63 (Ar—C), 213.00 (C=O).

EXAMPLE XXX

7-(3'-Iodobenzyl)-3-thia-7-azabicyclo[3.3.1]nonane Hydroperchlorate (9)

To a mixture of KOH pellets (85%, 0.48 g, 7.2 mmol) and the ketone (25, 0.224 g, 0.60 mmol) in triethylene glycol (10 mL) was added hydrazine (95%, 0.20 g, 6.0 mmol) in one portion in a 50-mL, jacketed flask equipped with a magnetic stirrer, a heating mantle, a standard condenser, a lower take-off condenser with a N_2 inlet, and two glass stoppers. A heating temperature of 140°-150° C. for 4 h was produced by boiling o-xylene (bp 144° C.) in the jacket. After cooling to RT, the solution was diluted with cold H_2O (30 mL) and was then extracted with ether (4×30 mL). Combined extracts were washed with 10% NaOH (30 mL) and saturated NaCl (30 mL), dried (Na_2SO_4, overnight), filtered, and concentrated to give a yellow oil (209 mg). Dissolution in ether (25 mL) via magnetic stirring and cooling (5° C.) in a 50-mL Erlenmeyer flask equipped with an external ice bath was followed by the dropwise addition of a solution of $HClO_4$ (60%, 0.15 g, 0.87 mmol) in isopropyl alcohol (1 mL) over 10 min. Filtration of the precipitate and then washing the latter with ether (~50 mL) gave a solid which changed to an oil. This oil was dissolved in 95% EtOH, and the solution was decolorized with Norit, filtered, and left to stand at RT overnight. White crystalline salt (9) was collected (77 mg, 27.7%); mp 169.5°-170° C. IR (KBr) cm^{-1}3045 (Ar C—H), 2950, 2915, 2825 (C—H), 1570 (C=C), 1085 (Cl—O), 780, 765 (C—H) out of plane, meta); ^1H NMR (DMSO-d_6) δ1.81 [m, 2H, H(9)], 2.36 [bs, 2H, H(1,5)], 2.70 [d, 2H, $H(2,4)_{ax}$, J=13.6 Hz], 3.09 [d, 2H, $H(2,4)_{eq}$, J=13.7 Hz], 3.35 [m, 2H, $H(6,8)_{ax}$], 3.58 [d, 2H, $H(6,8)_{eq}$, J=11.9 Hz], 4.22 (s, 2H, $ArCH_2$), 4.24 (s, 1H, $ArCH_2$), 7.32-8.03 (m, 4H, Ar—H), 9.20 (bs, 1H, N—H); ^{13}C NMR (DMSO-d_6) ppm 25.78 [C(1,5)], 28.48 [C(9)], 30.65, [C(2,4)], 56.53 [C(6,8)], 60.04 ($ArCH_2$), 95.40, 129.93, 131.08, 132.47, 138.18, 138.93 (Ar—C); ^{15}N NMR (DMSO-d_6) ppm 54.17 [N(7)]. Anal. Calcd. for $C_{14}H_{19}ClINO_4S$: C, 36.58; H, 4.17; N, 3.05; I, 27.60. Found: C, 36.87; H, 4.15; N, 2.99; I, 27.64.

EXAMPLE XXXI

3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]nonan-2-one (19)

A 500-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, a standard condenser with a N_2 inlet, a 250-mL addition funnel, and a glass stopper. A mixture of benzylamine (10.71 g, 100 mmol), HCl (37%, 4.93 g, 50 mmol), glacial acetic acid (6.0 g, 100 mmol) and paraformaldehyde (6.31 g, 210 mmol) in CH_3OH (100 mL) was brought to gentle reflux with stirring under N_2 over 15 min. A solution of 1-benzyl-4-piperidinone (43, 18.93 g, 100 mmol) and glacial acetic acid (6.01 g, 100 mmol) in CH_3OH (100 mL) was then added dropwise over 1 h and this was followed by a period of reflux for an additional 18 h. Upon cooling the mixture to RT, the solvent was removed and the resulting red oil was redissolved in H_2O (100 mL). Combined extracts (ether, 2×100 mL) of the acidic aqueous layer were discarded. Basification of the chilled (10° C., ice water bath) water layer to pH ~12 was effected by the addition of 10% NaOH. Combined extracts (ether, 4×60 mL) were dried (Na_2SO_4, 1 h), filtered, and concentrated to give a viscous red oil. This oil was digested (Skelly B, 2×250 mL, 20 min), and the supernatant extracts were concentrated and then distilled (190°-215° C./10^{-5} mm Hg) to give an oil. Crystallization of the oil was induced by dissolving the oil in hot pentane (800 mL) and then chilling (−10° C.) the solution to give 14.66 g (45.8%) of white, crystalline ketone (19); mp 82.5°-83.5° C. Concentration (hot plate) of the mother liquor to ~80 mL produced a second crop (0.81 g, 2.5%) of 3,7-dibenzyl-3,7-diazabicyclo[3.3.1]nonan-9-one (19); mp 81.5°-82.0° C. The total yield was (15.47 g, 48.3%).

A 70-mL, five-necked, jacketed flask was equipped with a magnetic stirrer, a heating mantle, a standard condenser, a lower take-off condenser with a N_2 inlet, a thermometer, and two glass stoppers. After the addition of the ketone (19, 2.0 g, 6.24 mmol), KOH pellets (85%, 4.94 g, 56.1 mmol) and hydrazine (95%, 2.11 g, 32.1 mmol) in triethylene glycol (40 mL) were added. The apparatus was flushed with N_2, and the mixture was heated at 140°-150° C. for 4 h using boiling o-xylene (bp 144° C.) in the jacket. Cooling the solution to RT was followed by the addition of chilled water (80 mL). Combined extracts (ether, 3×75 mL) of the suspension were washed with saturated NaCl (75 mL), dried (Na_2SO_4, overnight), filtered, and concentrated to a yellow oil (1.83 g, 95.7%) which displayed no carbonyl stretch in the IR spectrum. This oil, that is amine (37), was used without further purification.

A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser with a N_2 inlet, a 50-mL addition funnel, and a glass stopper. To a solution of $NaIO_4$ (2.49 g, 11.62 mmol) in H_2O (22.4 mL) was added $RuO_2 \times H_2O$ (0.1 g) which produced a dark green solution. After the apparatus was flushed with N_2, a solution of the amine (37, 0.89 g, 2.9 mmol) in CCl_4 (16 mL) was added in one portion to produce a black mixture. The mixture was stirred at RT for 72 h and then the organic layer was separated. Further extraction of the aqueous phase was effected with CCl_4 (20 mL) followed by $HCCl_3$ (3×20 mL). Combined extracts were treated with isopropyl alcohol (3 mL) to destroy excess oxidant and were then filtered through a celite pad. After washing the extracts with 5% sodium thiosulfate (50 mL), the extracts were dried (Na_2SO_4, overnight), filtered, and concentrated to a yellow oil. Elution of the oil on neutral alumina (84 g, 2.4 cm×19 cm) using first ether (50 mL) and then ethyl acetate (150 mL) as eluants gave a solid material (R_f=0.60, ethyl acetate). This material was recrystallized by dissolving in ether (6 mL) and then refrigerating at −10° C. for 2 h; this solution was placed in a diffusion chamber of pentane for 1 h. Filtration afforded (0.27 g, 28.9%) of the lactam (17); mp 96.0°-96.5° C. IR (KBr) cm^{-1}3070, 3050, 3020 (Ar C—H), 2945, 2920, 2855, 2785, 2760 (C—H), 1645 (C=O), 1600 (C=C) 740, 710 (C—H out of plane, mono); ^1H NMR ($DCCl_3$) δ1.69 [d, 1H, H(9),

J=12.7 Hz], 1.88 [d, 1H, H(9), J=12.7 Hz], 2.05-2.09 [m, 2H, ring proton and H(1)], 2.24 (dd, 1H, ring proton, J=10.74 Hz, J'=2.66 [m, 2H, ring proton and H(5)], 3.08 [d, 1H, ring proton, J=11.8 Hz], 3.25-3.36 [m, 3H, ring proton and H(11)], 3.59 [d, 1H, H(11), J=13.2 Hz], 4.24 [d, 1H, H(10), J=14.8 Hz], 5.06 [d, 1H, H(10), J=14.7 Hz], 7.08-7.38 (m, 10H, Ar—H); ^{13}C NMR ($DCCl_3$) ppm 27.94 [C(9)], 28.07 [C(5)], 39.07 [C(1)], 49.84 [C(10)], 51.60 [C(4)], 57.07 [C(8)], 59.03 [C(6)], 62.70 [C(11)], 126.88, 127.14, 128.17, 128.40, 128.49, 128.72, 137.39, 138.13 (Ar—C), 172.77 (C=O). Anal. Calcd. for $C_{21}H_{24}N_2O$; C, 78.72; H, 7.55. Found: C, 78.39; H, 7.78.

EXAMPLE XXXII

7-Benzyl-9,9-dimethoxy-3-thia-7-azabicyclo[3.3.1]-nonane Hydroperchlorate (11)

Caution: The use of shields, protective goggles and gloves is very strongly recommended when performing this experiment. The formation of explosive methyl perchlorate is a likely side reaction in this experiment. No difficulty was noted when the reaction was performed as described, but this may have been fortuitous. A one-necked, 100-mL, round-bottomed flask was fitted with a Soxhlet containing 3A molecular sieves (30 g), a condenser, a heating mantle, a magnetic stirrer, and a heating mantle. The effective cycling volume of the Soxhlet was approximately 15 mL. The flask was charged with a solution of the ketone (18, 1.0 g, 4 mmol) in methanol (20 mL) and benzene (20 mL). To this solution was added $HClO_4$ (60%, 2.0 g, 12 mmol) in one portion. The apparatus was flushed with N_2 and the pale yellow solution was heated at reflux with stirring and cycling through the Soxhlet for 24 h. The solution was cooled to RT and concentrated to about 5 mL. Ethyl ether (20 mL) was added, thus precipitating the salt as a powder. This was filtered, washed with ether (5 mL), and dissolved in hot methanol (20 mL, decolorizing carbon). Trituration with ether (25 mL), followed by standing for 24 h, afforded the salt (11) (0.74 g, 46.2%) as small white crystals; mp 193°-194° C. (dec); IR (KBr) cm^{-1} 2800-2600 (N—H), 1090 (Cl—O); ^1H NMR (DMSO-d_6) δ2.58 [bs, 2H, H(1,5)], 2.75 [d, 2H, $H(2,4)_{ax}$, J=14 Hz], 3.15-3.18 [m, 8H, $H(2,4)_{eq}$ and OCH_3], 3.38 [dd, or bt, 2H, $H(6,8)_{ax}$, J=12 Hz], 3.60 [d, 2H, $H(6,8)_{eq}$, J=12 Hz], 4.33 (d, 2H, CH_2Ph, J=5 Hz), 7.49-7.62 (m, 5H, Ar—H); ^{13}C NMR (DMOS-d_6) ppm 28.8 [t, C(2,4)], 32.2 [d, C(1,5)], 46.6 (q, OCH_3), 47.0 (q, OCH_3), 54.5 [t, C(6,8)], 60.2 (t, CH_2Ph), 95.1 [s, C(9)], 129.0, 129.5, 130.1, 130.2 (d, Ar—C); ^{15}N NMR (DMSO-d_6) ppm 53.5 [N(7)]. Anal. Calcd. for $C_{26}H_{24}ClNO_6S$: C, 48.79; H, 6.14; Cl, 9.00; N, 3.56; S, 8.14. Found: C, 48.73; H, 6.09; Cl, 9.39; N, 3.54; S, 8.40.

EXAMPLE XXXIII

3,7-Dibenzyl-9,9-dimethoxy-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (12)

Caution: The use of shields, protective goggles and gloves is very strongly recommended when performing this reaction. The formation of explosive methyl perchlorate is a likely side reaction in this experiment. No difficulty was noted when the experiment was performed as described, but this may have been fortuitous. A one-necked, 100-mL, round-bottomed flask was equipped with a Soxhlet containing 3A molecular sieve (30 g), a condenser with a N_2 inlet, a magnetic stirrer, and a heating mantle. The effective cycling volume of the Soxhlet was approximately 20 mL. The flask was charged with a solution of the ketone (19, 1.0 g, 3.12 mmol) in CH_3OH (25 mL) and benzene (25 mL) to which was added $HClO_4$ (60%, 1.5 g, 8.96 mmol) in one portion. The apparatus was flushed with N_2 and the colorless solution was heated to reflux with cycling through the Soxhlet. After 24 h, the now pale yellow solution was cooled to RT and concentrated to a white solid which was filtered, washed with C_6H_6 (10 mL), and recrystallized (CH_3OH, 80 mL) to afford the monoperchlorate (0.91 g) as small white crystals, mp 223.6°-224.0° C. (dec). The mother liquor was concentrated to approximately 10 mL. Upon cooling to a −10° C. overnight, a second crop of salt (12) was obtained (89.4 mg, 68.6% total), mp 219°-220° C. (dec). The spectral data were as follows: IR (KBr) cm^{-1} 2800-2600 (N-H), 1100 (Cl—O); ^1H NMR (DMSO-d_6) δ2.35 [bs, 2H, H(1,5)], 2.90 [d, 4H, $H(2,4,6,8)_{ax}$, J=13 Hz], 3.08 [d, 4H, $H(2,4,6,8)_{eq}$, J=13 Hz], 3.14 (s, 6H, OCH_3), 3.88 (s, 4H, CH_2Ph), 7.38-7.54 (m, 10H, Ar—H), 9.84 (bs, 1H, N-H); ^{13}C NMR (DMSO-d_6) ppm 33.0 [d, C(1,5)], 47.0 (q, OCH_3), 53.8 [t, C(2,4,6,8)], 59.6 (t, CH_2Ph), 95.4 [C(9)], 128.2, 128.4, 129.6, 133.5 (Ar—C); ^{15}N NMR (DMSO-d_6) ppm 52.9 [N(3,7)]. Anal. Calcd. for $C_{23}H_{31}ClN_2O_6$: C, 59.16; H, 6.69; Cl, 7.59; N, 6.00. Found: C, 58.98; H, 6.81; Cl, 7.86; N, 6.28.

EXAMPLE XXXIV

7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonane 3-Oxide (49)

A 200-mL flask was equipped with a magnetic stirrer, an ice bath, and a condenser with nitrogen inlet. To a stirred, chilled (5° C.) solution of the amine (27, 1.4 g, 6 mmol) in methanol (60 mL) was added dropwise a solution of $NaIO_4$ (1.35 g, 6.3 mmol) in water (15 mL) over 30 min. After stirring for one hour, the suspension was filtered and washed with methanol (50 mL); the washings and filtrate were combined and concentrated to a residue which was partitioned between H_2CCl_2 and water (40 mL each). Additional extracts ($HCCl_3$, 3×40 mL) of the aqueous layer were combined with the initial extract, and the solution was dried (Na_2SO_4) and concentrated to afford an oil which solidified upon standing. Recrystallization ($HCCl_3$/pentane) of the solid gave 1.15 g (76.9%) of crystalline (49); mp 140°-141° C. IR (KBr) cm^{-1} 3085, 3065, 3030, 2955, 2920, 2895, 2815, 1495, 1020, 740, 705; ^1H NMR ($DCCl_3$) δ1.59 [bd, 1H, H(9), J=13.3 Hz], 1.86 [bd, 1H, H(9), J=13.2 Hz], 2.20 [d, 2H, $H(2,4)_{ax}$, J=11.7 Hz], 2.37 bs, 2H, H(1,5)], 2.62 [d, 2H, $H(6,8)_{ax}$, J=12.0 Hz], 2.78 [d, 2H, $H(2,4)_{eq}$, J=11.8 Hz], 3.51 [d, 2H, $H(6,8)_{eq}$, J=11.7 Hz], 3.55 [s, 2H, $ArCH_2$], 7.26-7.39 (m, 5H, Ar—H); ^{13}C NMR ($DCCl_3$) ppm 31.86 [t, C(9)], 32.59 [d, C(1,5)], 57.42 [t, C(2,4)], 58.59 [C(6,8)], 62.88 ($ArCH_2$), 127.20, 128.39, 129.12, 137.67; ^{15}N NMR ($DCCl_3$) ppm 49.37 [N(7)]. Anal. Calcd. for $C_{14}H_{19}NOS$: C, 67.43; H, 7.68. Found: C, 67.61; H, 7.73.

EXAMPLE XXXV

7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonane 3-Oxide Hydroperchlorate (10)

A 50-mL Erlenmeyer flask was equipped with a magnetic stirrer and an ice bath. To a stirred, chilled (5° C.) solution of the sulfoxide (49, 0.47 g, 1.88 mmol) in ether (20 mL) and isopropyl alcohol (3 mL) was added dropwise a solution of $HClO_4$ (60%, 0.63 g, 3.75 mmol) in isopropyl alcohol (3 mL) over 30 min. Filtering of the precipitate followed, and latter was washed with ether

(50 mL) and then recrystallized (95% ethanol) to give a crystalline salt (10) (0.51 g, 78.1%); mp 137°-138° C. IR (KBr) cm^{-1} 3090, 2970, 2950, 1465, 1095, 745, 705; ^1H NMR (D_3COD) δ1.70 [bd, 1H, H(9), J=14.0 Hz], 2.01 [bd, 1H, H(9), J=13.9 Hz], 2.61 [bd, 2H, $H(2,4)_{ax}$, J=11.8 Hz], 2.69 [bs, 2H, H(1,5)], 3.06 [bd, 2H, $H(2,4)_{eq}$, J=11.8 Hz], 3.36 [bd, 2H, $H(6,8)_{ax}$, J=13.1 Hz], 3.94 (s, 2H, $ArCH_2$), 4.19 [bd, 2H, $H(6,8)_{eq}$, J=12.9 Hz], 7.35-7.42 (m, 5H, Ar—H); ^{13}C NMR (D_3COD) ppm 30.80 [C(9)], 36.27 [C(1,5)], 53.94 [C(2,4)], 58.56 [C(6,8)], 61.07 [$ArCH_2$], 129.43 129.78, 131.49, 135.29; ^{15}N NMR (DMSO-d_6) ppm 56.45 [N(7)]. Anal. Calcd. for $C_{14}H_{20}ClNSO_5$: C, 48.06; H, 5.76. Found: C, 47.84; H, 5.74.

EXAMPLE XXXVI

7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one 6,8,10-$^{14}C_3$ (18)*

Caution: Special precautions should be taken when handling radioactive chemicals. All reactions should be carried out in a well ventilated hood with protective shields to prevent possible contamination of the lab area. Protective safety goggles as well as quality rubber gloves should also be worn at all times since exposure to the ^{14}C materials could be dangerous. A 50-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. To a mixture containing benzylamine (0.43 g, 4 mmol), [^{14}C] benzylamine HCl [1 mg, 7×10^{-3} mmol, 0.5 mCi (minimum activity, ICN)] in H_2O (2.5 mL), and deoxygenated methanol (15 mL) was added HCl (37%, 0.1 g, 1 mmol) followed by glacial acetic acid (0.36 g, 6 mmol). Addition in one portion of paraformaldehyde (0.96 g, 32 mmol) and [^{14}C] paraformaldehyde [1 mg, 3.3×10^{-2} mmol, 0.5 mCi (minimum activity, ICN)] was followed by subsequent addition of 4-thianone (43, 0.47 g, 4 mmol) all at once with stirring. After the mixture was heated at reflux under N_2 for 6 h, the solution was concentrated to 2-3 mL and then diluted with H_2O (30 mL). The aqueous solution was extracted with ether (2×30 mL), and the latter was discarded. Chilling (via ice water bath) of the aqueous layer to below 5° C. was followed by basification (pH ~ 12) with NaOH pellets (97%, 0.29 g, 7 mmol) which resulted in the formation of a cloudy suspension. Combined extracts (ether, 4×30 mL) were dried (Na_2SO_4, overnight), filtered, and concentrated (rotary evaporator) to give a viscous oil, which was then digested in 200 mL of Skelly B (bp 60°-68° C.) for 0.5 h. Concentration of the supernatant afforded a yellow oil which was subjected to heating at high vacuum (110° C./0.1 mm Hg) in a sublimation apparatus to give 0.13 g of ketone (18)*; mp 91°-93° C. The residue which remained was again dissolved in ether (~50 mL), and the latter solution was dried (Na_2SO_4, overnight), filtered, and concentrated to an oil. Digestion of the oil was effected in 50 mL of Skelly B for 0.5 h, and the supernatant was concentrated to a viscous oil. This material was heated under vacuum (110° C./0.1 mm Hg) in a sublimation apparatus and gave 0.05 g of slightly crude ketone (18)*; mp 78°-80° C. A mixture melting point determination with the first crop was 86°-88° C. without significant depression. This gave a total yield of 0.18 g (17.7%) of ketone (18)* which was used without further purification in the next step.

EXAMPLE XXXVII

7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonane Hydroperchlorate 6,8,10-$^{14}C_3$ (48)*

Caution: Special precautions should be taken when handling radioactive chemicals. All reactions should be carried out in a well ventilated hood with protective shields to prevent possible contamination of the lab area. Protective safety goggles as well as quality rubber gloves should also be worn at all times since exposure to the ^{14}C materials could be dangerous. To a mixture of KOH pellets (85%, 0.48 g, 8.5 mmol) and the ketone (18)* (0.18 g, 0.71 mmol) in triethylene glycol (5 mL) was added hydrazine (95%, 0.23 g, 7.1 mmol) in one portion in a 50-mL, jacketed flask equipped with a magnetic stirrer, a condenser, a lower take-off condenser and two glass stoppers. A heating temperature of 140°-150° C. for 4 h was produced by boiling o-xylene (bp 144° C.) in the jacket. After cooling to RT, the solution was diluted with chilled H_2O (30 mL) and extracted with ether (4×20 mL). Combined extracts were dried (Na_2SO_4, overnight) and filtered. Cooling of the ethereal solution to below 5° C. was followed by the dropwise addition of $HClO_4$ (60%, 1 mL) over 10 min with stirring, which resulted in the formation of a white precipitate. Crude salt (48)* was filtered, recrystallized (95% EtOH), and dried over P_2O_5 (78° C./0.1 mm Hg) to give 0.14 g (58.6%) of white crystals of salt (48)*; mp 154.5°-155.0° C.; (lit 155°-156° C.). A stock solution (3.49 mg/mL) of salt (48)* was prepared using DMSO, H_2O, and 0.1N HCl (40:53.5:6.5 by volume). Samples were made by diluting 4 μL of the stock solution with 10 mL of Aquasol 2 scintillation cocktail (New England Nuclear Research Products). Measurements of activity were obtained at room temperature using a TRI-CARB liquid scintillation analyzer, model 1900 CA (Packard Instrument Company). An average count of 19,800 DPM was observed for each sample and the specific activity was determined to be 0.64 μCi/mg. In similar fashion, samples were prepared from stock solution of the salt (48)* in methanol and the specific activity was determined to be 0.63 μCi/mg.

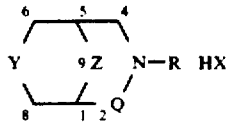
To illustrate the useful biological properties of the compounds described in this invention, selected derivatives were screened for antiarrhythmic activity using dog models. The clinically used agent lidocaine and 7-benzyl-3-thia-7-azabicyclo[3.3.1]nonane hydroperchlorate (48) [U.S. Pat. No. 4,581,361] were employed as standards as basis for comparison. A small infarction was created in an area of the dog heart and thereafter electrical pacing was initiated to generate a sustained ventricular tachycardia (VT). This irregular beating pattern of the heart results in a reduction of the pumping capability of the heart in a manner now accepted as resembling symptoms observed in humans during a heart attack (see: Scherlag, B. J. et. al., *Am. J. Cardiol.* 1983, 51, 207; Bailey, B. R. et. al., *J. Med. Chem.* 1984, 27, 759; Thompson, M. D. et. al., *J. Med. Chem.* 1987, 30, 780; U.S. Pat. No. 4,581,361; and U.S. Pat. No. 4,778,892 for further details, said references incorporated herein for such purposes). The effects of the selected compounds in terms of ability to reduce the rate of the induced VT or to eliminate the same (abolish the VT completely or at least not allow it to be sustained) is then evaluated and compared to lidocaine or to 7-benzyl-3-thia-7-azabicyclo[3.3.1]nonane hydroperchlorate (48). Since the latter hydroperchlorate proved superior

to lidocaine in most of the studies, data in Table A are compared to that obtained for the salt (48) cited herein. In Table A, it is clear that salts (1), (3), (5), (11), (13), and (14) are extremely effective in eliminating the induced VT as was the standard 7-benzyl-3-thia-7-azabicyclo[3.3.1]nonane hydroperchlorate (48) at 3 mg/kg as well as at 6 mg/kg. Salts (10), (12), (15), and (17) reduced the rates of the induced VT but did not abolish them. In contrast, salt (8) exhibited little effect on the dog model which suggests there exists a high degree of specificity of action of these molecules in terms of antiarrhythmic activity. Thus, these heterocyclic molecules claimed in this application have electrocardiology properties equal or superior to those of the standard 7-benzyl-3-thia-7-azabicyclo[3.3.1]nonane hydroperchlorate (48) which is known to have such superior properties to those of lidocaine (see: U.S. Pat. Nos. 4,581,361 and 4,778,891) which is a clinically used agent for the treatment of victims of heart attacks.

In principle, it is felt that the compositions of the present invention can be employed separately or incombination with each other or in combination with other drugs to achieve either individually or in combination the desired antiarrhythmic properties. It is expected that the composition can be utilized and administered via a variety of methods including by way of an example, but not limited thereto, intravenously, orally, by suppository, by inhalation, and the like. Furthermore, it is generally felt that the compositions as claimed either specifically possess antiarrhythmic activity or generally are broad biologically active or the respective compositions are intermediates to antiarrhythmic and biologically active species that are released or created in situ as the result of administration of the drug.

TABLE A

ANTIARRHYTHMIC PROPERTIES
OF REPRESENTATIVE 3-AZABICYCLO[3.3.1]NONANE SALTS



Comp[a]	R	Y	Z	(Effect on SVT[b]) 3mg/kg	6mg/kg
(1)	$CH(CH_3)_2$	NC(O)Ph	CH_2	NSVT	NSVT
(3)	$CH(CH_3)_2$	$NCH_2C_6H_4$-3,4(OCH_3)$_2$	CH_2	NSVT	NSVT
(5)	$CH(CH_3)_2$	NCH_2Ph	CH_2	NSVT	NSVT
(8)	$CH(CH_3)_2$	S	CH_2	No action	No action
(Stand.-48)	CH_2Ph	S	CH_2	NSVT[c]	NSVT
(10)	CH_2Ph	S ⟶ O	CH_2	Reduced rate of VT	Reduced rate of VT
(11)	CH_2Ph	S	$C(OCH_3)_2$	NSVT	NSVT
(12)	CH_2Ph	NCH_2Ph	$C(OCH_3)_2$	Reduced rate of VT	Reduced rate of VT
(13)	CH_2PH	$CHCO_2Et$	CH_2	NSVT	NSVT
(14)	CH_2Ph	$CHCO_2Et$	$C(SCH_2)_2$	NSVT	NSVT
(15)	NC(O)Ph	S	CH_2	Reduced rate of VT	Reduced rate of VT
(17)[d]	CH_2Ph	NCH_2Ph	CH_2	Reduced rate of VT	Reduced rate of VT

[a]X = ClO_4, Cl, Br, citrate, fumarate, HSO_4
[b]SVT = Sustained ventricular tachycardia induced by electrical pacing of infarcted dog heart
[c]NSVT = Nonsustained ventricular tachycardia (or abolished ventricular tachycardia)
[d]All compounds have Q is CH_2 except (17) where Q is C=O

In order to determine the potential viability of members of the above family to act as useful antiarrhythmic agents in vivo, a pharmacokinetic and metabolism study was undertaken using a representative example from the above compounds. The techniques employed in these preliminary studies are well documented, but a summary of pharmacokinetic procedures can be found in: J. D. Baggot, "Principals of Drug Disposition in Domestic Animals: The Basis of Veterinary Clinical Pharmacology", W. B. Saunders Company, Philadelphia, 1977. These studies were conducted using ^{14}C-labelled (48)* [Prepared by the method of Zisman, Berlin, et al. *J. Labelled Compounds and Radiopharmaceuticals*, In Press (1989)] in Sprague-Dawley rats.

Radioactivity-time data obtained by analysis of blood samples collected after intracardiac or oral administration are recorded in Tables B and C so designated. Coefficients and exponents of the disposition curves which best described changes in blood radioactivity with time after administration were obtained using a microcomputer program [R. D. Brown et al. *J. Pharmaceutical Sciences*, 67, 1687 (1978)]. The disposition of (48)* after intracardiac administration was well described by a two-compartment open model and the pharmacokinetic parameters derived from the analysis of individual blood radioactivity data are presented in Table D so designated. The median half-life of elimination ($T_{\frac{1}{2}(\beta)}$) of radioactivity was 5.7 hours, which suggested that a moderate to reasonably long dosage interval might be appropriate for therapeutic use. The median apparent volume of distribution, based on total area under the disposition curve ($V_{d(area)}$), was high (4070 ml/kg) indicating extensive distribution into body tissues. The high total body clearance value (Cl_B=470) confirms the presence of efficient drug elmination pathways.

Pharmacokinetic terms describing changes in blood radioactivity after oral administration are presented in Table D so designated. Compartmental analysis showed that the data fitted a one-compartment pharmacokinetic

model. Oral dosing resulted in rapid and extensive absorption and peak concentrations within 30 minutes after administration. The ratio of the areas under the radioactivity-time curves obtained after oral and intracardiac administration (AUC_{po}/AUC_{ic}) indicates a high bioavailability (±81%). Thus, the oral route of administration may be suitable for therapeutic management of patients suffering from cardiac arrhythmias.

TABLE B

Kinetics of appearance of radioactivity [dpm/ml] in blood after intracardiac administration of a bolus dosage (10 mg/kg) of (48)*(1332000dpm/mg).

Time after administration	Individual rats								
(hours)	#2	#3	#8	#9	#10	#15	#16	Mean	SD
0.0333	—	6802	6732	6419	6173	6595	7140	6644	333
0.0833	5482	5424	—	5496	5661	6106	7262	5905	710
0.1667	4741	5520	6087	4903	4780	5752	6435	5460	674
0.3333	4807	4225	—	4261	4768	5219	6197	4913	731
0.5	—	5294	3233	4210	4228	5152	3938	4343	773
1	2911	3619	4182	4343	3002	3433	3873	3623	551
2	1862	2004	2495	2451	2721	2463	1907	2272	340
3	—	1307	2357	2369	2314	—	—	2087	520
4	1374	1382	2316	2429	2379	1578	1438	1842	504
6	—	1719	2089	1905	2186	1690	1377	1828	295
10	1005	1113	1123	1191	903	1040	900	1039	112
16	—	534	332	515	353	395	349	413	89
24	242	308	71	60	178	197	144	171	89

TABLE C

Kinetics of appearance of radioactivity [dpm/ml] in blood after oral administration of a bolus dosage (10 mg/kg) of (48)*(1332000dpm/mg).

Time after administration	Individual rats								
(hours)	#4	#6	#7	#11	#12	#13	Mean	SD
0.1667	1928	802	1026	1601	479	967	1134	534
0.3333	2153	1723	2311	3265	754	1946	2025	818
0.5	4281	2086	2659	4421	1025	2151	2771	1335
1	3895	1911	2272	3154	958	2106	2383	1022
2	2208	1545	1618	2896	991	2043	1884	654
4	1786	2034	2114	2017	1767	1713	1905	169
6	1601	1502	1224	1594	1714	1138	1462	230
10	893	662	885	1118	1613	984	1026	324
16	418	245	302	140	586	390	347	154
24	300	89	79	66	197	75	134	95

TABLE C-continued

Kinetics of appearance of radioactivity [dpm/ml] in blood after oral administration of a bolus dosage (10 mg/kg) of (48)*(1332000dpm/mg).

Time after administration	Individual rats								
(hours)	#4	#6	#7	#11	#12	#13	Mean	SD
2	2208	1545	1618	2896	991	2043	1884	654
4	1786	2034	2114	2017	1767	1713	1905	169
6	1601	1502	1224	1594	1714	1138	1462	230
10	893	662	885	1118	1613	984	1026	324
16	418	245	302	140	586	390	347	154
24	300	89	79	66	197	75	134	95

TABLE D

Pharmacokinetic values derived from each rat's (48)* blood disposition curves.

	I. Intracardiac administration: Inidividual rats								
Determinant	2	3	8	9	10	15	16	Mean	SD
A (dpm/ml)	3670	3924	2583	2532	2350	3852	5097	3330	966
B (dpm/ml)	2192	2152	4333	4647	3659	2972.	2652	1616	1808
α (hr^{-1})	1.36	0.86	1.93	11.49	2.18	1.48	1.62	1.55	2.96
β (hr^{-1})	0.090	0.080	0.163	0.164	0.131	0.115	0.121	0.124	0.035
K_{21} (hr^{-1})	0.568	0.359	1.276	7.499	1.380	0.710	0.636	1.775	2.551
K_{el} (hr^{-1})	0.217	0.194	0.248	0.252	0.207	0.241	0.310	0.238	0.038
K_{12} (hr^{-1})	0.673	0.394	0.578	3.908	0.726	0.646	0.800	1.103	1.243
$t_{\frac{1}{2}(\beta)}$ (hr)	7.67	8.60	4.23	4.20	5.28	5.99	5.70*		
$t_{\frac{1}{2}(\alpha)}$ (hr)	0.50	0.79	0.35	0.06	0.31	0.46	0.42*		
C_o (dpm/ml)	5863	6077	6917	7179	6010	6824	7750	6660	701
V_c (ml/kg)	2271	2191	1925	1855	2216	1951*	1718		
$V_{d(area)}$ (ml/kg)	5471	5291	2926	2843	3504	4070*	4390		
$V_{d(ss)}$ (ml/kg)	4963	4596	2798	2822	3381	3725*	3879		
Cl_B (ml/hr · kg)	494	426	478	468	459	470*	533		
AUC_{ic}	25282	27480	29169	30489	28444	27126	24104	27442	2205

	I. Oral administration: Individual rats							
Determinant	4	6	7	11	12	13	Mean	SD
β (hr^{-1})	0.107	0.138	0.143	0.181	0.149	0.137	0.143	0.023
$t_{\frac{1}{2}(\beta)}$ (hr)	6.42	5.00	4.81	3.80	4.63	5.04	4.90*	
AUC_{po}	25306	18755	20243	24510	24383	20555	22292	2760
AUC_{po}/AUC_{ic}							0.81233	

*Values represent medians

Tissue distribution of (48)* was studied by measuring the radioactivity in selected organs collected from rats sacrificed at several time intervals after oral administration. Data obtained from these studies is reported in Table E so designated. High levels of radioactivity

were measured in liver and kidney which is consistent with the extensive metabolism and excretion of metabolites commonly encountered with highly lipid soluble xenobiotics [agent (48)* has both polar and nonpolar structural features]. These observations correlate well with the high volume of distribution calculated from pharmacokinetic data. Reasonably high concentrations of radioactivity in the heart confirm that (48)* achieves good penetration into the target organ. Radioactivity in the brain and perirenal fat were low in comparison with other tissues and decreased steadily with time after administration. This suggests that central neurotoxicity may not limit the therapeutic use of these agents and that long-term accumulation in fat depots may not present a toxicological hazard.

Thin layer chromatographic analysis of urine samples collected after oral administration of ^{14}C-labelled (48)* to rats indicated that most of the dose was excreted in the form of metabolites. Using mass spectrometry, the major metabolite was identified as ^{14}C-labelled (15)*, the structure of which was confirmed by comparison with an authenticated sample of unlabelled (15). Consequently, amide (15) is an active metabolite of (48) and is therefore a potentially viable agent in its own right.

TABLE E

Concentration of radioactivity in selected organs and tissues after oral administration of a bolus dosage (10 mg/kg) of (48)*(1332000dpm/mg).

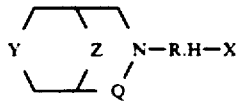
Time after administration (hr)	Experimental units I	II	III	Mean	SD
I. Blood concentrations (dpm/ml):					
0.083	2330	1970	3975	2758	1069
0.25	5170	6755	4615	5513	1111
0.5	6020	6010	4935	5655	624
0.75	4370	3335	4245	3983	565
1.5	2840	2790	3300	2977	281
4	2060	2580	1800	2147	397
8	740	650	740	710	52
16	276	219	295	263	40
I. Kidney concentrations (dpm/g):					
0.083	11320	5425	21341	12695	8047
0.25	27222	34142	20528	27297	6807
0.5	31622	39516	28700	33279	5595
0.75	26793	19249	24987	23676	3939
1.5	18881	16254	21566	18900	2656
4	15219	17715	12217	15050	2753
8	4963	4835	5296	5031	238
16	2591	1761	2285	2212	420
24	1250	2489	1004	1581	796
I. Liver concentrations (dpm/g):					
0.083	49025	37302	33768	40032	7986
0.25	77479	86705	53662	72615	17050
0.5	82327	81324	68846	77499	7510
0.75	40648	16117	46449	34405	16101
1.5	14156	18970	21791	18306	3861
4	14430	17811	15814	16018	1700
8	10272	9195	9855	9774	543
16	6886	4065	4948	5300	1443
24	3427	4709	2563	3566	1080
I. Heart concentrations (dpm/g):					
0.083	4813	1236	4292	3447	1932
0.25	5402	5647	3890	4980	952
0.5	5071	4903	4107	4694	515
0.75	3442	2785	3608	3278	435
1.5	2415	2511	2736	2554	165
4	1820	2114	1676	1870	223
8	826	668	790	761	83
16	336	273	412	340	70
24	221	320	184	242	70
Perirenal fat concentrations (dpm/g):					
0.083	2583	647	4670	2633	2012
0.25	16771	1925	926	6541	8874

TABLE E-continued

Concentration of radioactivity in selected organs and tissues after oral administration of a bolus dosage (10 mg/kg) of (48)*(1332000dpm/mg).

Time after administration (hr)	Experimental units I	II	III	Mean	SD
0.5	1606	2068	2145	1940	292
0.75	1070	1866	2599	1845	765
1.5	718	933	745	799	117
4	610	508	562	560	51
8	577	172	558	436	229
16	216	138	271	208	67
24	77	119	97	98	21
I. Brain concentrations (dpm/g):					
0.083	1280	296	1496	1024	640
0.25	1562	1980	1028	1523	477
0.5	824	971	643	813	164
0.75	711	1051	551	771	255
1.5	477	506	626	536	79
4	399	343	399	380	32
8	248	232	274	251	21
16	108	106	92	102	9
24	70	96	79	82	13

The 3-azabicyclo[3.3.1]nonane compounds described herein may be generally characterized by the formula:

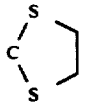


wherein

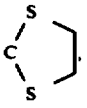
H-X represents a pharmacologically acceptable acid,

Q represents CH_2, or CO,

Z represents CH_2, CO, $C(OCH_3)_2$, or



R represents hydrogen, lower alkyl, or a benzyl- or benzoyl group wherein the phenyl ring is unsubstituted or is substituted by halogen or by 1 to 3 methoxy groups, a benzene sulfonyl group, or



and

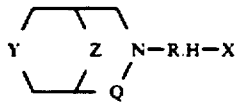
Y represents S, S→O, CH—$CO_2C_2H_5$, or a group N—R' wherein R' is lower alkyl or a benzyl- or benzoyl group, in which group the phenyl ring is unsubstituted or is substituted by halogen or by 1 to 3 methoxy groups.

The claims and the specification describe the invention presented and the terms that are employed in the claims draw their meaning from the use of such terms in the specification. The same terms employed in the prior art may be broader in meaning than specifically employed herein. Whenever there is a question between the broader definition of such terms used in the prior art and the more specific use of the terms herein, the more specific meaning is meant.

While the invention has been described with a certain degree of particularity it is manifest that many changes may be made in the details of construction and the arrangement of components without departing from the spirit and scope of this disclosure. It is understood that the invention is not limited to the embodiments set forth herein for purposes of exemplification, but is to be limited only by the scope of the attached claim or claims, including the full range of equivalency to which each element thereof is entitled.

What is claimed is:

1. A 3-azabicyclo [3.3.1]nonane compound having the following formula:

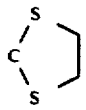


wherein

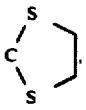
H-X represents a pharmacologically acceptable acid,

Q represents CH_2, or CO,

Z represents CH_2, CO, $C(OCH_3)_2$, or



R represents hydrogen, lower alkyl, or a benzyl- or benzoyl group wherein the phenyl ring is unsubstituted or is substituted by halogen or by 1 to 3 methoxy groups, a benzene sulfonyl group, or



and

Y represents S→O.

2. A compound according to claim **1** wherein Q represents CH_2.

3. A compound according to claim **1** wherein Z represents CH_2.

4. A compound according to claim **1** wherein R represents C_1–C_4-alkyl or an optionally substituted benzyl- or benzoyl group.

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