STUDIES ON THE SYNTHESIS AND THE CHEMISTRY OF 7,8-DIHYDRO-5(6H)-QUINOLINONE, 6-CETYLOXY-1-TETRALONE AND 7-AMINO-1-TETRALONE

By

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STUDIES ON THE SYNTHESIS AND THE CHEMISTRY OF
7,8-DIHYDRO-5(6H)-QUINOLINONE, 6-CETYLOXY-
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To

My Daughter Tina

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CHAPTER I

HISTORICAL

Structure-Activity Parameters

Drug transport across cell membranes is quite likely of extreme importance in any design of compounds for chemotherapeutic use.[6,20,22,32] Consequently, lipophilicity and hydrophilicity properties of a medicinal agent could be crucial with respect to rate of passage across the membrane barrier.[51,52] Correlation of biological activity with partition coefficients for compounds in polar and nonpolar solvents has led to somewhat more accurate prediction of activity for untested chemicals.[28,33] Similarly, studies of Eger and collaborators revealed a good correlation between minimal alveolar concentrations of general anesthetics and solubilities of these compounds in olive oil.[16]

Hansch elected to start with a compound of known biological activity and determine whether analogs with various substituents could exhibit predictable activity on the basis of their partition between water and 1-octanol.[21] A parent compound, for example, was compared with a carboxylic acid derivative via the difference in the logarithms of the distribution coefficients, which is called π.

$$\pi_{CO_2H} = \log P_{CO_2H} - \log P_H$$

π = hydrophobicity constant (a measure of the contribution of a substituent to the nonaqueous solubility in a

series of partitions)

P_{CO_2H} = partition coefficient of the carboxylic acid derivative

P_H = partition coefficient of the parent compound

A positive value of π means a substituent increases solubility in non-polar solvents. A negative value implies an increase in solubility in polar solvents.

Hansch recognized that the above equation could be related to the Hammett equation[19] shown below

$$\log (k/k_o) = \rho\sigma$$

which in turn could be related to equilibrium constants.

$$\log (K/K_o) = \rho\sigma$$

Since σ is related to the ionization constant of the parent compound, an evaluation of σ is permitted.

$$\sigma = \log (K_{CO_2H}/K_H)$$

By neglecting steric factors, Hansch and coworkers were able to derive the following equation:

$$\log (1/C) = -k\pi^2 + k'\pi + \sigma\rho + k''$$

C = Drug concentration necessary to produce a biological effect

k, k', k'' : Constants for the system under study, determined through regression analysis of the equations corresponding to the derivative being tested in the series

Although Hansch and others have applied this equation to several well known families of drugs and have often obtained correlations of 0.8-0.9 or better, the method is still semiempirical. Cammarata has derived a modified equation introducing a parameter for electronic polarizability f and dividing the σ term into inductive and resonance parameters for groups.[8]

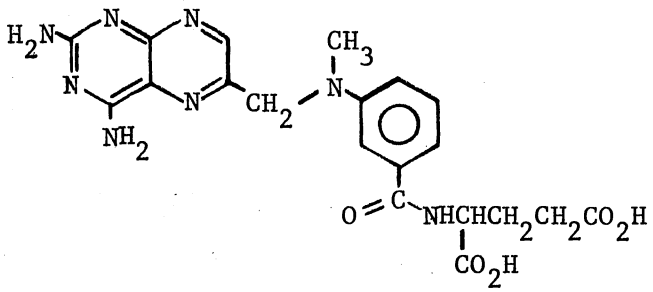
$$\log A = a\pi^2 + b\pi + c\sigma_I + d\sigma_R + f$$

Correlations of 0.99 were realized for activities of chloroamphenicol derivatives. In spite of partial successes of these equations and others for drug activity-structure correlations, some severe limitations have always been observed. A spin-off from these efforts to quantify the design process for new compounds has been to focus attention of the biomedical researcher on the importance of lipophilicity and hydrophilicity of chemicals being planned for synthesis.

Compounds carrying such groups as $-SO_3Na$, $-CO_2Na$, $-SO_3H$, and -ONa are highly hydrophilic or lipophobic. To a lesser degree, the following constituents behave similarly: -OH, -SH, -O-, $-C(O)H$, $-NO_2$, $-NH_2$, -CN, $-CO_2H$, $-CO_2R$, $-OPO_3H_2$, and the halogens. Lipophilic or hydrophobic (nonpolar) groups are exemplified by alkyl groups, aralkyl groups, and groups derived from polycyclic hydrocarbons. If both hydrophilic and lipophilic groups are in the same molecule, a surfactant property may manifest itself. Surfactants often have a marked influence on cellular membrane permeability either by disintegrating or lysing it or, according to some current theories, by enfolding it in such a manner so as to alter cell uptake of nutrients.[6,32] Thus, there appears to be an optimum size and critical electronic environment required for maximum

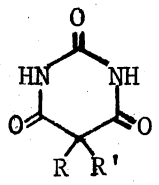
beneficial effect of substituents on biological activity in a series of compounds. The general subject of quantitative drug design has been reviewed recently and the reader is referred to the article for additional references.[47] Although the derivation of mathematical equations to predict biological properties of unknown compounds is in its infancy and is not likely to lead to an all-encompassing expression, the finding of even a semiquantitative relationship could result in an increase in rate of preparation of useful compounds for a specific malady. Increased rates of occurrence of cancer have been so large that the U. S. National Cancer Institute recently indicated a screening target rate of one thousand compounds per week.[36]

Since the movement of molecules across membranes is likely crucial for most forms of chemotherapy,[55] in vitro studies have devoted increased attention to possible mechanisms of drug-membrane-interaction. Assumptions must still be made in nearly all instances that the data are at least partially applicable to in vivo processes.[7] For example, methotrexate (1) is thought to be transported into leucocytes by facilitated diffusion.[29] This acid 1 is a clinically used anticancer agent (NSC-740).



1

Another example is acetylcholine, which may exert its influence by altering membrane permeability to cations and perhaps anions.[32] Insulin affects membrane penetration of hexoses and amino acids by presumably causing a change in the conformation of lipoproteins, a situation that is postulated to result in interstices being formed.[39] Barbiturates 2 and related compounds 3 have shown a strong correlation between



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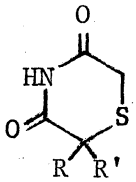
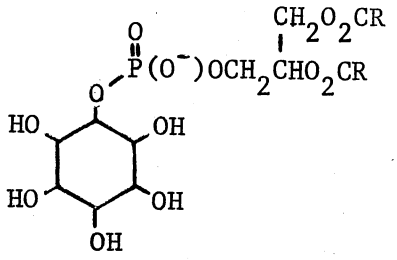
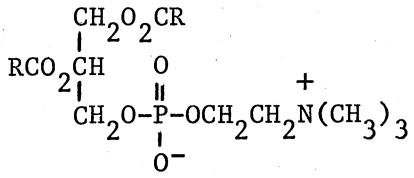


3

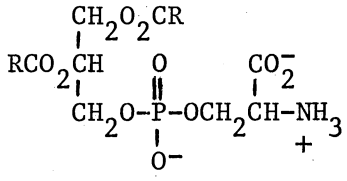
hypnotic activity and the amount of relative lipophilic character as defined by the respective octanol-water partition coefficients.[22] Since membranes generally have a high lipid content (for example, 30% of the dry weight of the membrane in certain systems[18]) and proteins can attach to lipids, drugs with hydrocarbon chains can potentially penetrate into membranes. Some of the common lipids in cellular membranes are given below:[32]



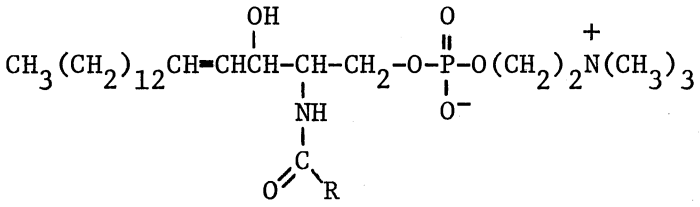
Phosphatidylinositols



Lecithins

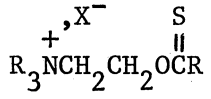


Phosphatidylserines



Sphingomyelins

In contrast, certain drugs with highly charged atoms could well compete for essential anionic groups within a cell. For example, in a series of homologous parasympathomimetics of the general formula $R\overset{+}{N}(CH_3)_3$, the drugs have maximum activity when the carbon atoms in R are greater than five.[26] Some compounds of type 4 have antibacterial[7] properties, possibly because they are ionic and therefore poorly soluble in lipids, and not quickly absorbed at the pH of the gastrointestinal tract.[32] Thus, the drugs remain in that area for an extended time.



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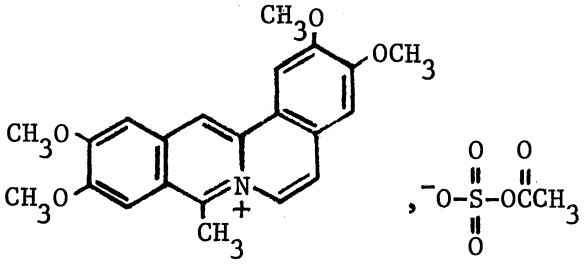
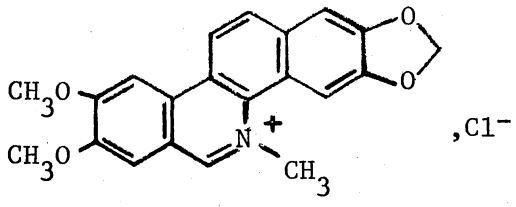
Recent interest by the National Cancer Institute in large azasteroid type molecules such as 5 and 6 clearly reflects the therapeutic potential of incorporating charged groups into large, relatively nonpolar, hydrocarbon units. A similar situation exists with 7.



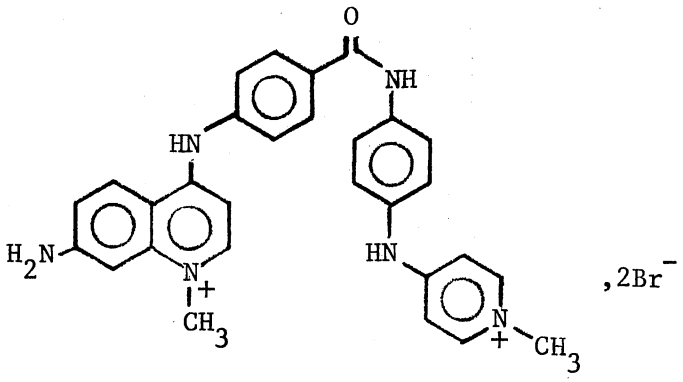
Coralyne sulfoacetate (NSC-154890)

5



Nitidine chloride (NSC-146397)

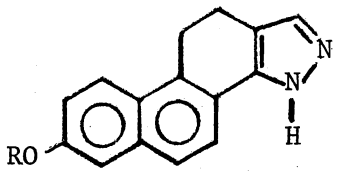
6



(NSC-176319)

7

It has been observed in our Laboratory that a variety of azasteroid-type molecules and related model compounds containing a pyrazole ring have antimicrobial activity[11,25] and, in some cases, inhibit growth of KB cells.[25,46] Members such as 8,[41] 9, and 10 have demonstrated inhibition of growth in Bacillus subtilis (the primary screen) to varying degrees.



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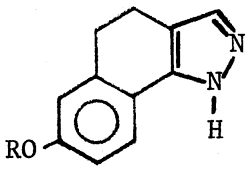

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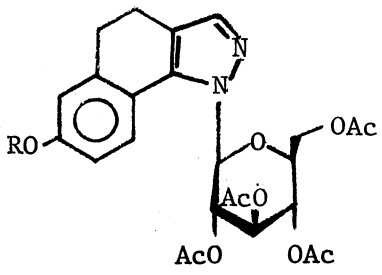
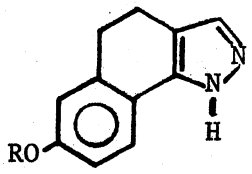


10

Particularly interesting was the inhibition of growth of B. subtilis, Pseudomonas fluorescens, Staphylococcus aureus, and KB cells by 10, where R = CH_3. This compound is being investigated as an antitumor agent by the National Cancer Institute.

To study the lipophilic properties of these chemicals, a comparison was made of the biological activities of compounds having various-sized alkyl chains.[46,62] For example, a series of compounds 9a-c have been prepared. Pyrazole 9b[46] completely inhibited growth of B. subtilis for 24 hours (at 45 μg/ml) but had no effect on Pseudomonas fluorescens. (Compounds 9a[23,41] and 9c[62] are currently being evaluated.)



9a-c

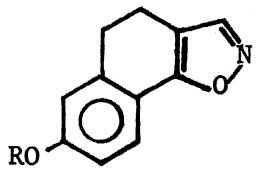
R

a. CH_3

b. n-C_6H_{13}

c. n-$C_{16}H_{33}$

Compounds 11a-c have also been synthesized and partially screened.



11a-c

R

a. CH_3

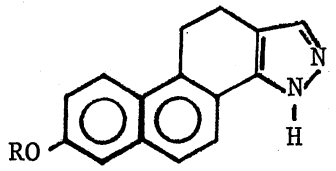
b. n-C_6H_{13}

c. n-$C_{16}H_{33}$

To illustrate, 11a[41] showed complete growth inhibition of B. subtilis for 24 hours (at 91 μg/ml), but had no effect on growth of P. fluorescens. With respect to growth of KB tissue-culture cells, 11a showed

moderate inhibition (0% plating efficiency at 150-250 μg/ml, 38% at 50 μg/ml, 67% at 25 μg/ml and 100% at 0-12.5 μg/ml.) Isoxazole 11b[46] inhibited growth of B. subtilis for 11 hours (at 91 μg/ml), but the microorganisms grew out in 24 hours. No inhibition was observed with P. fluorescens. At 45 μg/ml, 11b showed no activity toward B. subtilis nor P. fluorescens. (Data for 11c[62] are currently being gathered.)

The larger steroid-type systems 8a-b have been prepared and partially screened also. Indazole 8b[46] showed complete inhibition of growth of B. subtilis at 91 μg/ml for 24 hours, but had no effect against P. fluorescens. (Data for 8a[41] are also currently being obtained.)



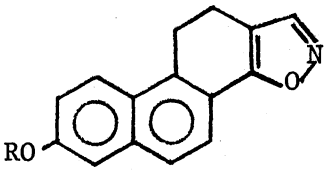
8a,b

R

a. CH_3

b. n-C_6H_{13}

Related isoxazoles 12a-b are now available and some biological results



12a,b

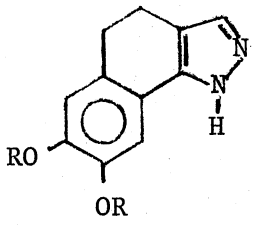
R

a. CH_3

b. n-C_6H_{13}

are available. Compound 12b[46] provided complete growth inhibition of B. subtilis at 91 μg/ml for 24 hours, but the bacteria partially grew out at 24 hours. No growth inhibition was detected with P. fluorescens. (Data on 12a[41] are now being tabulated.)

There are data available which indicate that certain vicinal polyhydroxy- and polymethoxy-substituted steroids have a variety of biological activities.[49] Growth inhibition of B. subtilis and KB cells have been observed for some of the polyhydroxy- and polymethoxy-pyrazoles synthesized in our Laboratory.[23,37] For instance, with compound 13a, complete growth inhibition of B. subtilis was observed at

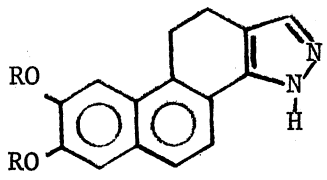


13a,b

R
a. H
b. CH_3

91 μg/ml, and this inhibition persisted when the compound was titrated down to a concentration of 2 μg/ml. Indazole 13a was screened with KB tissue-culture cells, showing complete inhibition at 6-12.5 μg/ml for 24 hours. Similarly, 13b also showed complete growth inhibition of B. subtilis but the KB plating efficiency was only 31% at 50 μg/ml over 24 hours.

For the larger steroid-type system containing polyhydroxy and polymethoxy substituents, however, the activities were somewhat reduced. For example, 14a had no effect on growth of B. subtilis or of P. fluorescens.

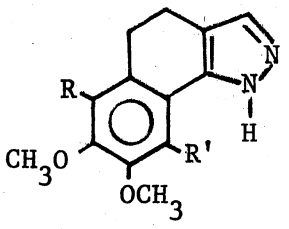


14a,b

R
a. H
b. CH_3

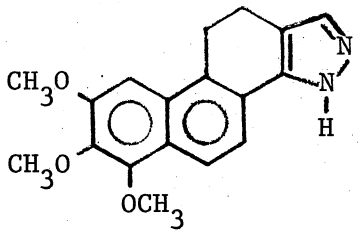
Likewise, 14b only showed complete growth inhibition of B. subtilis (at 91 μg/ml) but had no effect on the growth of P. fluorescens.

For the trimethoxy-substituted pyrazoles 15-17, analogous situations were observed.[10] Compound 15 showed growth inhibition on B. subtilis at 91 μg/ml for 24 hours, but caused a 4-hour lag in growth. Isomeric 16 showed complete inhibition for 24 hours, while 17 exhibited growth inhibition for 12 hours, but the bacteria grew out overnight. None of the three compounds had any effect on P. fluorescens.



15 R = OCH_3, R' = H

16 R = H , R' = OCH_3



17

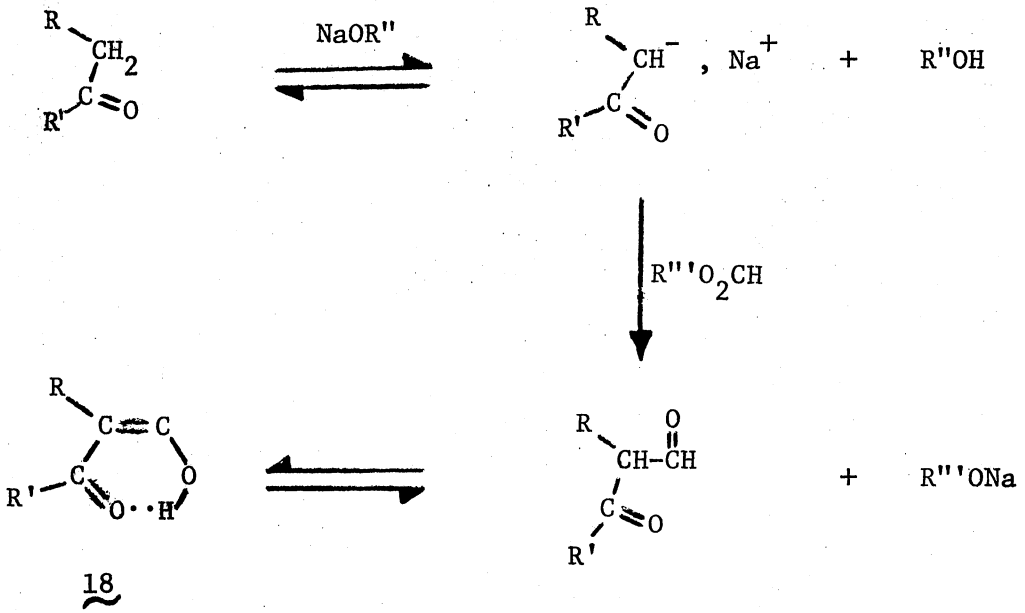
With the KB tissue-culture cells, 15 showed only very modest inhibition with regard to plating efficiency: 0% at 150-250 μg/ml, 91% at 50 μg/ml and 100% at 0-25 μg/ml. On the other hand, 16 showed a higher effect on plating efficiency: 0% at 250 μg/ml, 3% at 150 μg/ml, and 75% at 25 μg/ml. Interestingly, 17 showed only modest results: 0% at 250 μg/ml, 15% at 150 μg/ml, and 70% at 50 μg/ml.

The structure-activity correlation of heterosteroids having various-sized alkyl chains specificity positioned is a comparatively new area.[15,58] It has been suggested that one member of a homologous series may possess exceptional activity, not because of a fixed balance of orthodox physico-chemical properties, but because of a proper fit into a macromolecule involved in a complex biochemical situation.[6,32] Much

exploration in this area is sorely needed.

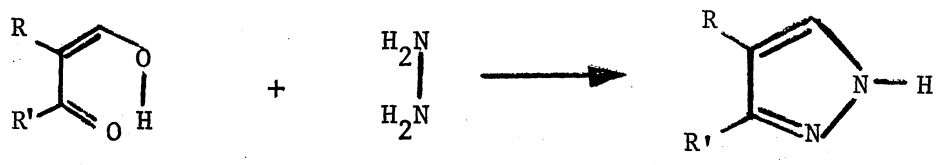
Pyrazoles

Because of the nature of our work, a brief synopsis of synthetic approaches and some physical properties of pyrazole-containing systems will be presented. Preparative methods for pyrazoles have been reviewed.[23] For our purposes, the condensation of alkyl formates with carbonyl compounds provided key precursors, namely hydroxymethylene compounds[27] such as 18.



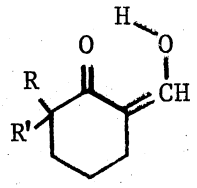
18

The hydroxymethylene compound 18 can then be condensed with hydrazine to yield the pyrazole 19.



18 19

There has been very little investigation of physical properties for the hydroxymethylene compounds, partly because in some cases they are difficult to isolate and purify. Much pioneering work was done in the 1940s on this class of compounds and therefore IR and NMR data are lacking. In fact, Johnson and Posvic[27] characterized the hydroxymethylene compound 20 by the positive violet color test with ferric chloride and by the formation of a crystalline precipitate with sodium bisulfite solution.

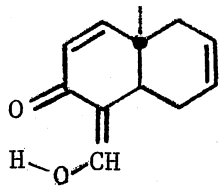


20a,b

a. R = H, R' = CH_3

b. R = R' = CH_3

Fortunately, in 1952, Woodward[64] and coworkers synthesized compound 21 and were able to characterize the molecule by IR and UV spectral analysis.



21

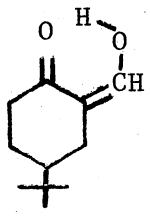
λ_{max} 229 nm (ε 10,000)

361 nm (ε 7,600)

[In 0.1 N alcoholic $NaOC_2H_5$]

Thus, as expected from examintion of the general structure for hydroxymethylene ketone 18, IR analysis[37] reveals an absorption band about 3300 cm^{-1} for the O-H stretch, and one about 1650 cm^{-1} for the C=O stretching frequency. Because of the conjugated system in 18, it is reasonable to find absorption in the UV spectrum.

More recently, NMR spectra have been obtained for this type of hydroxymethylene compound. For example, Corey and Cane[12] characterized 2-(hydroxymethylene)-4-tert-butylcyclohexanone (22) via complete IR and NMR analysis. In the PMR spectrum, the chemical shift for the



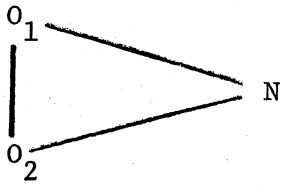
22

hydroxylic proton occurred at δ 14.0 with the signal for the vinylic proton at about δ 8.0. These shifts were in accordance with those observed for certain hydroxymethylene compounds prepared in our Laboratory [37] and examined in either deuterated chloroform ($DCCl_3$)[37] or carbon tetrachloride (CCl_4).[12] However, the chemical shift for the signal for the hydroxylic proton is undoubtedly highly solvent-dependent.

New Approaches to Structure-Activity Parameters

There has been a great deal of interest in correlating novel chemical structural features with biological activity. C. C. Cheng[65] reported that a common feature may exist among a wide variety of antileukemic agents of both synthetic and natural origin (i.e., aminopterin, anthramycin, 5-azacytidine, methotrexate, nitidine, tylocrebine, and many other compounds). This characteristic consisted of a possible

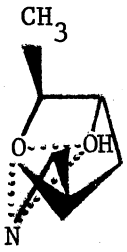
unique structural relationship between one N atom and two O atoms with the following approximate interatomic distances:



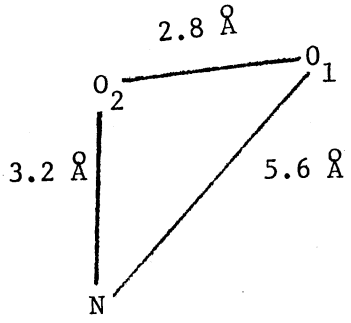
$O_1 - O_2$	3 - 4 Å
$O_2 - N$	6.5 - 9 Å
$N - O_1$	6 - 7.5 Å

The disposition of these atoms might very well be critical for binding to receptor sites on an enzyme, certain proteins, etc., in vivo.

Muscarinic activity[30] of acetylcholine, muscarine, and muscarone seems to be related to a triangulation property.



L(+)-Muscarine

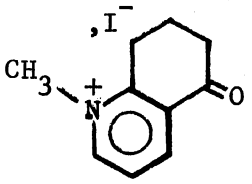


Cheng indicated that a CH_3O group was needed for reactivity (perhaps for improved lipophilicity). However, angle size ($\angle O_1O_2N$, $\angle O_2NO_1$, or $\angle NO_1O_2$) did not seem to be critical. This suggested another role for the hetero atoms besides binding, perhaps for a charge-transfer, complex-formation mechanism.

CHAPTER II

RESULTS AND DISCUSSION

Several objectives of this research have been accomplished. In view of the antimicrobial activity found for several pyrazoles prepared in our Laboratory,[11,24] it was of interest to obtain heterocyclic systems containing a water-solubilizing function (and/or a lipophilic group) in addition to the pyrazole group. Thus, we have developed syntheses for 23-25. Related molecules 26 and 9c with lipophilic groups have also been prepared and completely characterized. Biological screening is still in progress on these compounds in the Microbiology Department.



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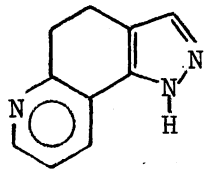

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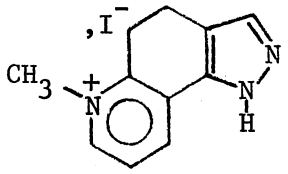

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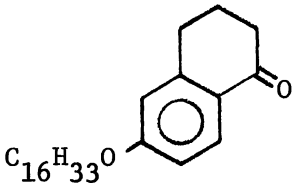

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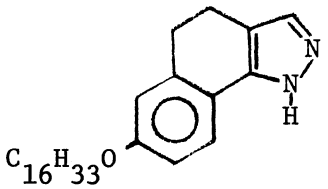
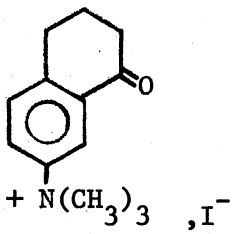


9c

In addition, a small study on the preparation of 27 was undertaken and successfully completed from the key intermediate 28.[31,48,61]



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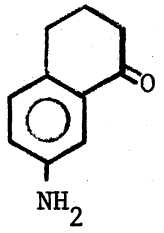

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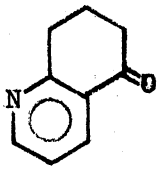
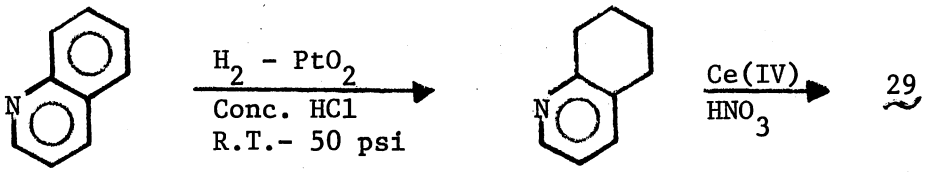


29

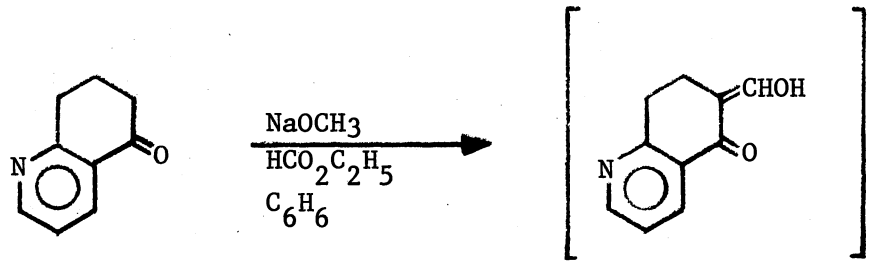
Early in the project, several attempts were made to synthesize one of the key starting materials, 7,8-dihydro-5(6H)-quinolinone (29). The benzene moiety in quinoline 30 was reported by Vierhapper and Eliel[59] to be selectively reduced in strongly acidic medium using platinum oxide as the catalyst to give the 5,6,7,8-tetrahydro compound 31. Once 5,6,7,8-tetrahydroquinoline (31) was obtained, it was reasoned that it could be oxidized to 7,8-dihydro-5(6H)-quinolinone (29) by ceric ammonium nitrate in 3.5 N nitric acid, in analogy with the oxidation of tetralin to 1-tetralone.[56] Unfortunately, all efforts provided



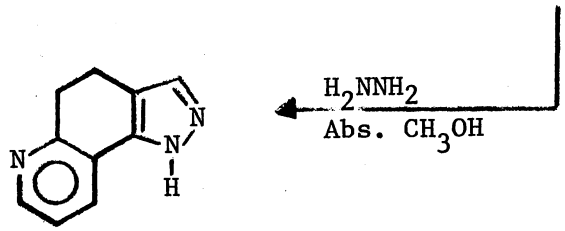
30 31

mixtures when the conversion of 30 → 31 was tried. Dr. Eliel has informed us that his method has not been consistently reproducible.

Interestingly, 29 became commercially available from Aldrich Chemical Company, milwaukee, Wisconsin, in March, 1975. The dihydroquinolinone 29 was characterized by IR [(Plate I), ν_{ArC-H}, 2880 (ms); $\nu_{C=O}$, 1665 cm^{-1} (s); $\nu_{C-N(3^o)}$, 1330 cm^{-1} (ms)]; and by NMR analysis [(Plate II), δ 2.12 (pentet), 2.64 (t), 3.80 (t), 7.25 (dd), 8.06 (d), 8.61 (d)]. The starting ketone 29 was treated with methyl iodide in absolute methanol and boiled to give the methyl iodide salt 23 in satisfactory yield (73%). The salt 23 gave a yellowish precipitate with alcoholic silver nitrate and showed a sharp singlet at δ 4.2 in the NMR spectrum (Plate IV) corresponding to three protons of the N-methyl group. The starting ketone 29 reacted with sodium methoxide and ethyl formate in dry benzene to give the hydroxymethylene intermediate 32.[1,27,40,57] Crude 32 was treated directly with hydrazine in absolute methanol to give indazole 24 (61%).



29 32

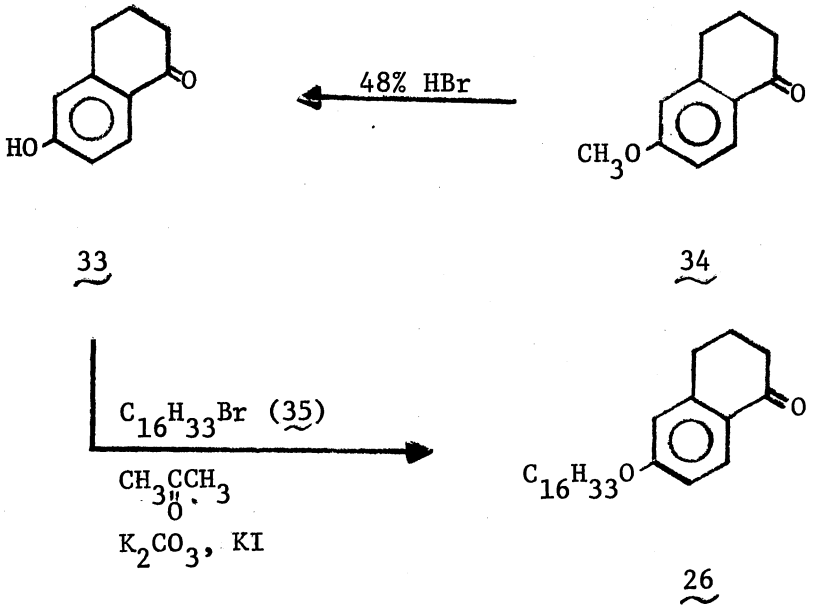


24

Indazole 24, m.p. 209-210.5° was characterized by IR (Plate V), ν_{N-H}, 3020 cm^{-1} (s); ν_{ArC-H}, 2620 (vs) and by NMR analysis (Plate VI), which showed the characteristic pyrazolic C=N-H proton[35] (broad singlet) at δ 12.82 in addition to the sharp singlet at δ 7.54 corresponding to the vinylic proton -C(H)=N-NH- and the other expected signals.

The indazole 24 was boiled with methyl iodide in absolute methanol to give ammonium salt 25 which, in alcohol, gave a yellowish precipitate upon treatment with silver nitrate solution. The salt 25, m.p. 222.5-224°, showed a sharp singlet at δ 4.34 in the NMR spectrum (Plate VIII) for the $N-CH_3$ group and the usual signals. In the IR spectrum (Plate VII) of 25, a medium-strong peak at 3170 cm^{-1} was seen as the characteristic N-H stretching band in the pyrazole ring.

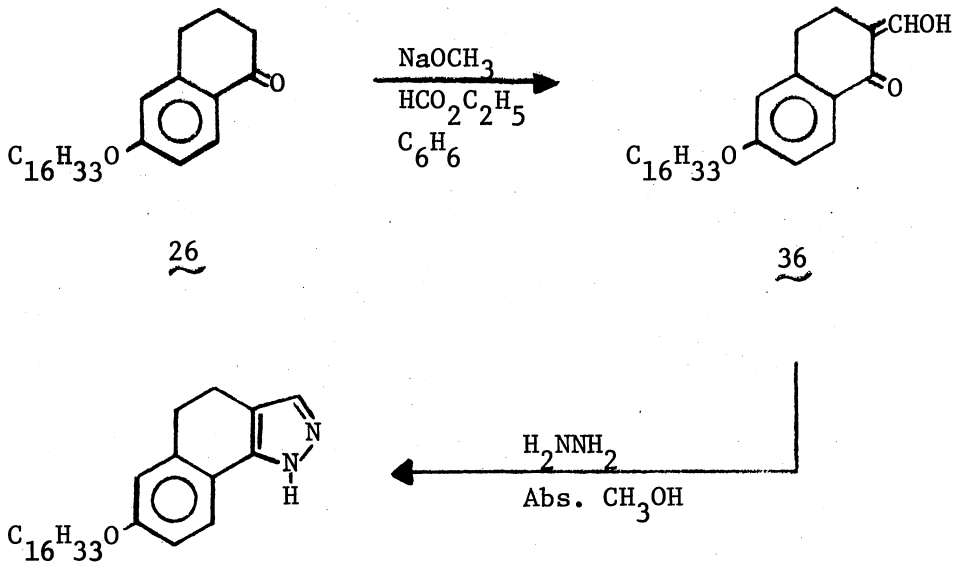
For the synthesis of compounds 26 and 9c containing a lipophilic moiety, the key starting material was 6-hydroxy-1-tetralone[45] (33). Ketone 33 was obtained in our Laboratory through an improved procedure,[2,3] i.e., via the demethylation of 6-methoxy-1-tetralone (34) with 48%



aqueous hydrobromic acid. The IR spectrum (Plate IX) of 33 showed a strong, broad O-H absorption (phenolic) at 3210 cm^{-1}, indicating there could be intermolecular bonding existing. In addition, a strong $\nu_{C=O}$ absorption appeared at 1650 cm^{-1}. The NMR spectrum (Plate X) of 33 showed a distinct singlet at δ 9.02 for the phenolic O-H, together with other expected signals for the tetralone. When 33 was then boiled with cetyl bromide 35 in dry acetone in the presence of potassium iodide and potassium carbonate (heterogeneous mixture), hexadecyloxy ketone 26 (84%) resulted, m.p. 48-50°. The NMR spectrum (Plate XII) of 26 showed a singlet at δ 1.26 which integrated to 28 protons, corresponding to the 28 methylene protons of the cetyl group. In addition, a peak at δ 0.88 (3H) for the terminal methyl group of the cetyl moiety and a triplet at δ 4.00 were clearly visible. The methylene group bonded to oxygen in the cetyl function along with the rest of the spectrum fitting the structure of the 6-substituted 1-tetralone nucleus was also displayed. An IR analysis (Plate XI) was also consistent, showing strong absorption at 2850 cm^{-1} and 2800 cm^{-1} for the aliphatic C-H stretching in the cetyl group and a strong $\nu_{C=O}$ peak at 1650 cm^{-1}.

Treatment of ketone 26 with sodium methoxide and ethyl formate in dry benzene gave, after acidic hydrolysis, hydroxymethylene ketone 36, m.p. 53-54.5°. The latter gave a violet color with ferric chloride. Compound 36 showed a small broad peak around δ 14.5 integrating to one proton in the NMR spectrum (Plate XIV) and demonstrating the existence of the O-H proton on the hydroxymethylene group along with other characteristic signals. In the IR spectrum (Plate XIII), a weak, broad peak at 3400 cm^{-1} was detected for the O-H stretch. In addition, strong absorptions appeared at 2900 cm^{-1} and 2820 cm^{-1} for the aliphatic C-H

stretch. A characteristic C=O absorption was also observed at 1645 cm^{-1}. Moreover, peaks for the Ar-O-CH_2 stretching were also observed at 1250 (s) and 1100 (s).[53]



26 36 9c

Crude hydroxymethylene ketone 36 was boiled with hydrazine in dry methanol and gave pyrazole 9c (68%), m.p. 91-92°. The pyrazole 9c showed a medium strong absorption at 3050 cm^{-1} for the N-H in the IR spectrum (Plate XV), together with strong peaks at 2850 cm^{-1} and 2780 cm^{-1} for the aliphatic C-H stretch. Peaks at 1270 cm^{-1} and 1240 cm^{-1} for the C=N stretch and at 1240 cm^{-1} and 1110 cm^{-1} for the Ar-O-CH_2 stretching vibration were likewise observed.

It is worthwhile to mention the method by which cetyl bromide (35) was obtained. Since cetyl bromide was not commercially available, it was synthesized from a classic procedure of boiling cetyl alcohol (37) [commercial product from Matheson, Coleman and Bell Company, m.p.

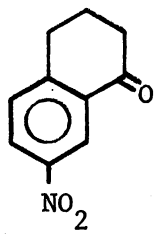
48-50°] and bromine [commercial from Fisher Scientific Company] at 235° in the presence of red phosphorus.[60] Haloalkane 35 was then purified by vacuum distillation (180-190°/7mm.)(62%). An NMR spectrum (Plate

$$C_{16}H_{33}OH \xrightarrow[\text{Bromine}\ 235^{\circ}]{\text{Red P}} C_{16}H_{33}Br$$

37 35

XVIII) of the bromide 35 showed a singlet at δ 1.30, corresponding to the 13 pairs of methylene protons in between a triplet at δ 2.30 for the 2 methylene protons adjacent to bromine, a multiplet at δ 1.80 for the 2 methylene protons β to bromine, and a triplet peak at δ 9.90 for the terminal methyl group.

For the synthesis of the ammonium salt 27, it was necessary to obtain 7-amino-1-tetralone (28) which could logically be obtained from 7-nitro-1-tetralone (38). There were few routes reported in literature for compound 38. Reppe and coworkers[48] cyclized γ-phenylbutyric acid (39) with concentrated sulfuric acid and concentrated nitric acid at 20° and nitrated the acid at the same time to give the nitro compound 38, m.p. 105°. No reaction time nor yield were given, however.



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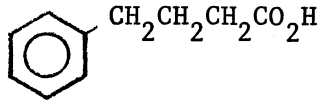
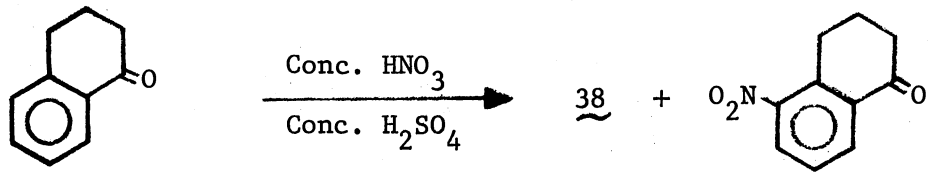


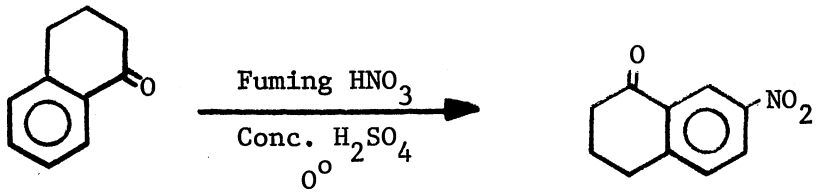
39

von Braun[61] did the same cyclization and nitration, only at -10°, and obtained a modest yield (50%). Schroeter,[50] in 1930, nitrated 1-tetralone (40) with almost anhydrous HNO_3 in concentrated H_2SO_4 with cooling and obtained a mixture of 93:7 7-nitro-1-tetralone (38):5-nitro-1-tetralone (41). No yield of the product based on the starting material



40 41

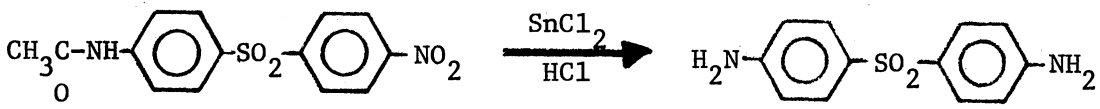
was reported. We did not succeed in obtaining the 7-nitro-1-tetralone from γ-phenylbutyric acid nor from 1-tetralone by using the nitrating mixture of concentrated HNO_3-concentrated H_2SO_4. The facile nitrating reagent, nitronium tetrafluoborate, reported to be excellent in nitrating alkylaromatics or aromatic esters by Olah and Kuhn[44] did not yield the 7-nitro-1-tetralone (38) from 1-tetralone in our hands under a variety of conditions. However, with a fuming nitric acid-concentrated sulfuric acid mixture,[13] we succeeded in nitrating 1-tetralone (40) at 0°, but only in 25% yield. The nitro compound 38, m.p. 105-106°, showed peaks totaling for three protons in the NMR



40 38

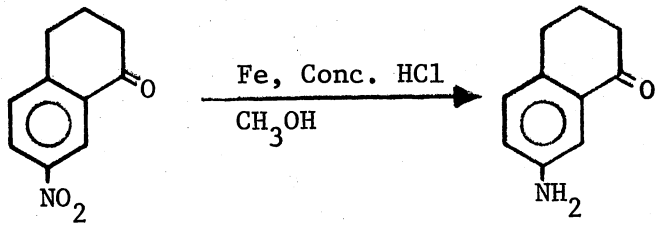
spectrum (Plate XXII) shifted downfield with respect to the corresponding four protons in 1-tetralone. Nitro compound 38 showed strong absorption at 1675 cm^{-1} for C=O stretch, which was at slightly shorter wavelength than $\nu_{C=O}$ in 1-tetralone (1650 cm^{-1}), apparently due to the electron withdrawing effect of the nitro group. There were also strong bands at 1500 cm^{-1} and 1340 cm^{-1} for the NO_2 stretch.[53]

Reduction of 38 to the amino compound 28 was then undertaken. Reppe and coworkers[48] carried out the reduction with Pd/C in methanol and obtained a product, m.p. 137°. No yield, reaction time, or temperature was given. von Braun[61] reduced 38 with stannous chloride and HCl and reported the m.p. of the amino product as 136°. Again, no reaction time, temperature or yield was recorded. A satisfactory yield (74-77%) was reported by Ferry and co-workers[17] on the reduction of the nitro sulfone (42) to the amino sulfone (43) by $SnCl_2$ and hydrochloric acid.



42 43

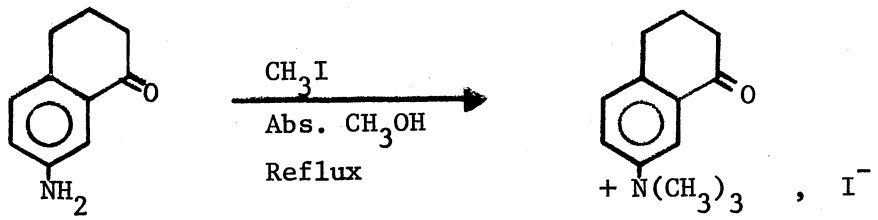
Koopman[31] observed that the reduction of nitro compounds to amino compounds by using iron and conc. HCl could be greatly facilitated by adding methanol to the mixture. In our hands, this latter general technique proved best for the conversion of 7-nitro-1-tetralone (38) to 7-amino-1-tetralone (28). A good yield (73%) was obtained, m.p. 139-141°. NMR analysis of 28 showed a sharp singlet for the 2 amino protons



38 28

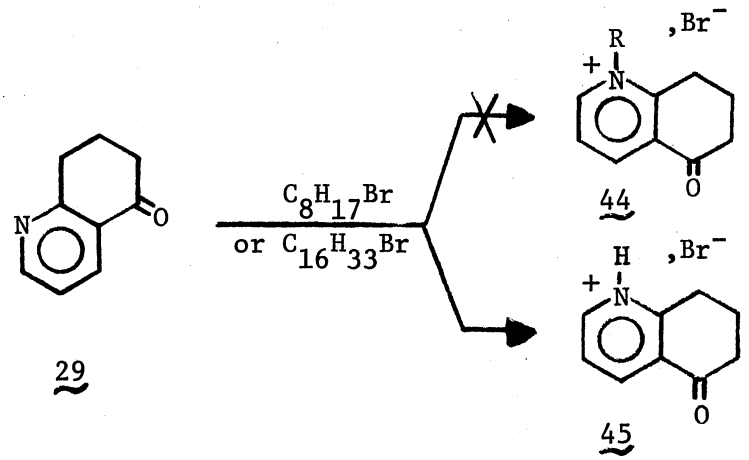
at δ 3.70 in the NMR spectrum (Plate XXIV) which contained also the usual other signals. In the IR spectrum (Plate XXIII), there were strong bands at 3260 and 3150 cm^{-1} for the $-NH_2$ stretching and a strong band at 1320-1310 cm^{-1} for the C-N stretch of aromatic amines. The $\nu_{C=O}$ occurred at 1650 cm^{-1}.

Once the amino tetralone 28 was obtained, it was boiled with excess methyl iodide in absolute methanol to give the N,N,N-trimethylammonium salt 27 which gave a yellowish precipitate in a silver nitrate test. The NMR spectrum (Plate XXVI) showed a sharp singlet at δ 3.60 corresponding to the nine protons on the 3 methyl groups along with the other expected signals.



28 27

Attempts were made to N-alkylate with the cetyl group and the octyl group on the benzindazole 24 and the aminotetralone 28 in an effort to incorporate both lipophilic (octyl and cetyl groups) and hydrophilic (quaternary ammonium salt structure) functions in one system. Unfortunately, only the hydrobromide was formed rather than the quaternary ammonium bromide. One exception resulted when 28 was treated with cetylbromide (35). An unknown solid was formed (m.p. 181.5-183°) the structure of which may be 46b but much structural work is needed to verify this. With 29, a crystalline compound was isolated



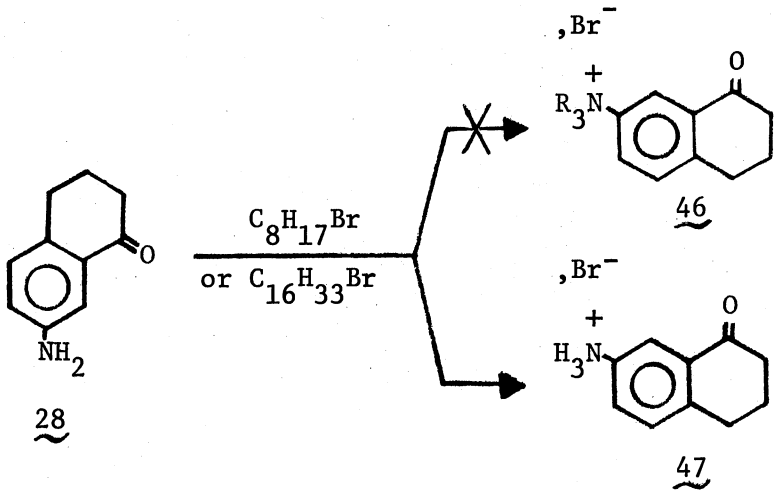
R

a. C_8H_{17}

b. $C_{16}H_{33}$

the PMR spectra of which resembled that expected for 45 except for a sharp singlet at δ 5.78 (DMSO-d_6). In D_2O, the signal changed to δ 4.72 and markedly increased in intensity, which suggests perhaps water of hydration present in a nonstoichiometric quantity. Elemental analysis does not agree for a mono or a dihydrate and thus the identity of the product is still in question.

As indicated previously, aminotetralone 28 was boiled with octyl bromide (50) [commercial from Aldrich Chemical Company, b.p. 201°] in absolute methanol for 72 hours. Again, only the hydrobromide 47 was obtained. NMR analysis (Plate XXVIII) of 47 in DMSO-d_6 showed a broad signal at δ 8.4, integrating to 3 protons. When the spectrum was taken



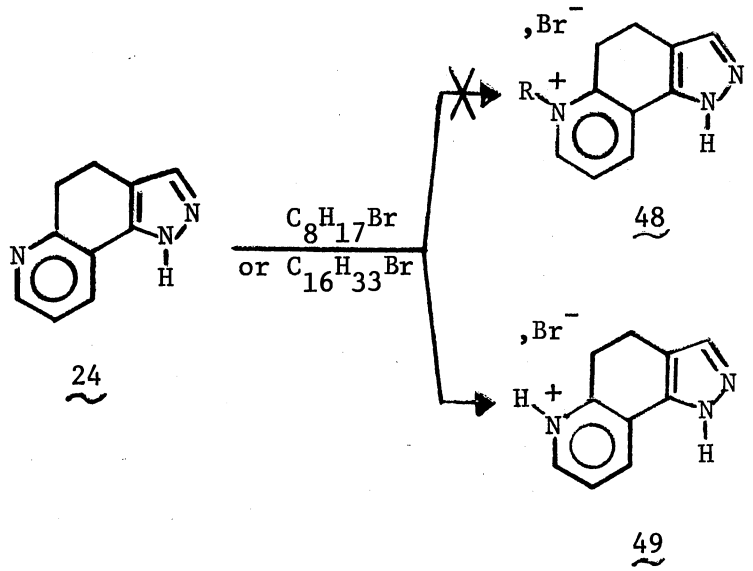
R

a. C_8H_{17}

b. $C_{16}H_{33}$

in D_2O (Plate XXIX), a sharp singlet appeared at δ 4.76 (H-O-D) while the signal at δ 8.4 was absent. Thus, there was exchange of protons between the quaternary ammonium group and D_2O, as expected. No product resembling 46 could be isolated.

In the analogous situation with pyrazole 24, boiling with octyl bromide (50) [or cetyl bromide (35)], in absolute ethanol for 72 hours (or 24 hours), gave only salt 49. Elemental analysis agreed for the hydrobromide (see Experimental data). NMR spectral data (Plate



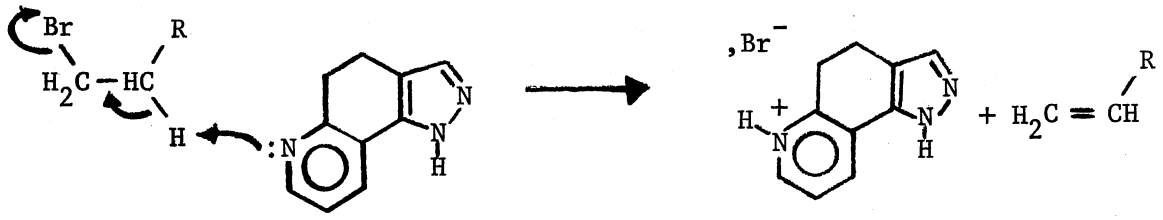
R

a. C_8H_{17}

b. $C_{16}H_{33}$

XXXI) for 49 in DMSO-d_6 displayed a broad signal at δ 11.40 integrating to 2 protons, corresponding to the quaternary ammonium proton and the pyrazolic N-H proton. Again, NMR analysis (Plate XXXII) of 49 in D_2O demonstrated proton exchange between the hydrobromide 49 and D_2O, showing a singlet at δ 4.72 with the disappearance of the signal at δ 11.40. The other expected signals were found, too.

Since pyridines are reported[5,14,34,38,43] to undergo N-alkylation, an explanation for our observations seems in order. Octyl bromide (or cetyl bromide) when boiled in ethanol, with 24 (or 28) prompted what appears to be an elimination process. For verification, a check with GLC analysis of the reaction mixture is needed to determine if an alkene is present. A very tentative mechanism can be written:

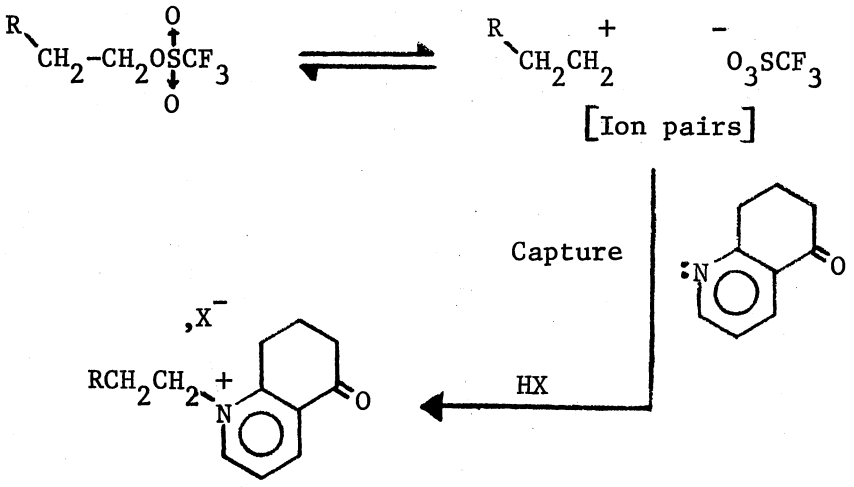


24 49

The obvious question arises as to a rationale for the proton abstraction process being heavily favored over the nucleophilic displacement by the =N- atom on the carbon holding the bromine atom (simple S_N2 displacement in the N-alkylation). With the evidence at hand, one can reasonably predict that the nucleophilicity of the nitrogen atom in 24

(or 28) may be markedly reduced via the inductive effect of the pyrazole group (or C=O group in 28). Since the reaction times for attempted alkylation were long, a slow proton abstraction process apparently is competitive with other reactions. A similar rationale may be applicable with 29 although a thorough product analysis is necessary before any predictions can be made with a degree of certainty.

It is conceivable that with a better leaving group such as a triflate (F_3C-SO_2O-), attached to the alkyl functions, one might obtain the N-alkylation product. Triflates are known to ionize at room temperature even when the product could be a primary, solvated cation.[42]



Thus, the free cation (or the cation in the ion pair) might well be captured in an alkylation reaction competitive with the β-proton abstraction. This, of course, must wait experimental trial.

Since all of the compounds are currently being screened in microorganisms, any evaluation of structure-activity relationships is premature. It is anticipated that future work in this area will be guided, in part, by the lipophilic and hydrophilic character introduced

into a potential medicinal agent, perhaps with a lethal group (lethal to normal cells) also present in the molecule. Lethal groups such as $N(CH_2CH_2Cl)_2$ and the $\triangleright N-$ are well known[63] in tumor chemotheraphy and seem worthy of investigation when strategically located in a system carrying lipophilic and hydrophilic functions.

CHAPTER III

EXPERIMENTAL[a-e]

Preparation of 4,5-Dihydro-1H-pyrazolo[3,4-f]quinoline (24)[27,40,57]

Sodium methoxide (2.42 g., 0.9448 mole) was suspended in 30 ml. of anhydrous benzene in a 200-ml., three-necked, round-bottom flask fitted with nitrogen inlet, a mechanical stirrer with a rubber sleeve, a condenser and a 60-ml, pressure-equalized addition funnel. Ethyl formate (3.40 g., 0.0448 mole) in 10 ml. of anhydrous benzene was then added dropwise to the suspension while the flask was cooled to 0° (ice bath). The addition took about 10 minutes and gave a white mixture. Spinning-band distilled 7,8-dihydro-5(6H)quinolinone (29) [commercial product from Aldrich Chemical Company] (3.352 g., 0.0228 mole; b.p. 131-132°/12mm)

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[a]Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and were uncorrected.

[b]Proton magnetic resonance spectra were taken on a Varian XL-100 (15) high resolution NMR spectrometer using tetramethylsilane (TMS) as the internal standard.

[c]Infrared spectra were taken on a Beckman IR-5A spectrophotometer with samples as films on sodium chloride plates or in potassium bromide pellets.

[d]Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

[e]Commercially available reagents were used without further purification unless otherwise stated. Sodium methoxide was obtained from Research Organic/Inorganic Chemical Corporation, Belleville, New Jersey.

was dissolved in 50 ml. of anhydrous benzene. The resulting clear solution was added dropwise to the white mixture from the same addition funnel with the round-bottom flask still in ice-bath. As ketone 29 was added, the color of the mixture turned from white to yellow in 5 minutes. By the end of the addition (about 30 minutes), the whole mixture was a bright yellow slurry. The ice-bath was removed and the bright yellow mixture was allowed to react at room temperature for 24 hours with constant stirring. After one hour, the color of the mixture turned from bright yellow to grayish-green up to 24 hours. At this end, the stirring was stopped and two layers resulted, a top clear layer and a bottom layer of a grayish-yellow solid. To this mixture was then added dropwise 40 ml. of absolute methanol [distilled over magnesium turnings (1 g. of Mg. per each 100 ml. methanol), b.p. 64°] from the same addition funnel. Stirring was resumed and as the methanol was added, the mixture became dark green. Gradually, the solids dissolved and the color changed from dark green to dark brown in 5 minutes, giving a homogeneous dark brown solution. Dry hydrazine (3.65 g., 0.114 mole) was added to the solution which was boiled (3 hours). The solution was then allowed to cool to room temperature. The solvents were evaporated off (rotary evaporator) to dryness. A yellow solid was obtained and was recrystallized from a minimum amount (ea. 40 ml.) of 50-50 2-propanol-benzene. Yellow crystals of pure 24 weighed 2.66 g. (70%, m.p., 208.5-210°). A second recrystallization gave fine yellowish crystals (2.39 g., 61%, m.p. 209-210.5°). IR and NMR spectral data (Plates V and VI) support the structure of 24.

Anal. Calcd. for $C_{10}H_9N_3$: N, 24.56.

Found: N, 24.77.

Preparation of 6-Methyl-4,5-dihydro-1H-pyrazolo [3,4-f] quinolinium Iodide (25).[4,54] A yellowish suspension of 0.513 g. (0.003 mole) of pyrazole 24 in 30 ml. of absolute 2-propanol [distilled (b.p. 82.5°) over CaO] was placed in a 100 ml. three-necked, round-bottom flask fitted with a 25 ml., pressure-equalized dropping funnel, a condenser and a rubber slip-sleeve-sealed stirrer. The whole setup was fitted with a nitrogen inlet. While the suspension was being rapidly stirred, 1.9 ml. (4.26 g., 0.03 mole) of methyl iodide [D^{15} = 2.27, commercial product from Fisher Scientific] contained in a dropping funnel was added slowly. The suspension remained cool during addition. After all the methyl iodide was added (ca. 5 minutes), the suspension cleared and a clear yellowish solution resulted. The solution was then boiled at about 85° by means of an oil bath (3 hours). After the first 30 minutes, the solution became cloudy and a white solid appeared which appeared to accumulate up to 3 hours. The mixture was then allowed to cool. The solid was filtered (0.587 g., 63%, m.p. 220-222°) and recrystallized (water-2-propanol). Yellow needles of salt 25 were obtained (0.486 g., 52%, m.p. 222.5-224°). IR and NMR spectral data (Plates VII and VIII) support the structure of 25. An alcoholic solution of 25 gave yellowish precipitate with the silver nitrate test.

Anal. Calcd. for $C_{11}H_{12}N_3I$: C, 42.17; H, 3.83; N, 13.41.

Found: C, 41.96; H, 3.75; N, 13.31.

Attempted Preparation of 6-Octyl-4,5-dihydro-1H-pyrazolo [3,4-f]-quinolinium Bromide (48a). A yellow solution containing 0.513 g. (p.003 mole) of pyrazole 24 dissolved in 25 ml. of absolute ethanol was boiled with 1.93 g. (0.01 mole) of 1-bromooctane [commercial product from Aldrich Chemical Company, b.p. 201°, d. 1.118] with constant

stirring (magnetic) and under nitrogen (72 hours). As the reaction proceeded, the color became a deeper yellow. After 72 hours, the solution had become a homogeneous brown solution. After cooling to room temperature, the solution was poured into excess (ca. 200 ml.) of absolute ether. A milky appearing mixture formed. Filtration of the mixture gave a solid, 0.92 g. (84%), m.p. 220-230°. It was recrystallized twice [absolute methanol-absolute ether mixture (1:1)], 0.45 g. (42%), m.p. 263-266°. A silver nitrate test was also positive for active haologen. The elemental analysis indicated the product was not for 48a, but instead, the hydrobromide 49. IR and NMR spectral data (Plates XXX, XXXI and XXXII) support the structure for the salt 49.

Anal. Calcd. for $C_{18}H_{26}N_3Br$: C, 59.34; H, 7.17; N, 11.54.

Calcd. for $C_{10}H_{10}N_3Br$: C, 47.62; H, 3.97; N, 16.67.

Found: C, 48.03; H, 4.17; N, 16.28.

Attempted Preparation of 6-Hexadecyl-4,5-dihydro-1H-pyrazolo-[3,4-f]quinolinium Bromide (48b). A yellow solution containing 0.513 g. (0.003 mole) of pyrazole 24 dissolved in 25 ml. of absolute ethanol was boiled with 3.05 g. (0.01 mole) of cetyl bromide (72 hours) with constant stirring (magnetic) and under N_2. The solution was then poured into an excess (ca. 150 ml.) of absolute ether and a cloudy mixture formed. Filtration gave a white precipitate, 1.1 g. (70%), m.p. 200°. Recrystallized three times (absolute methanol-absolute ether) gave white crystals, 0.5 g. (32%), m.p. 262-265°. An alcoholic solution of 48b gave white precipitate with the silver nitrate test. IR and NMR spectral data do not support the structure of 48b, but instead, the structure of the hydrobromide 49.

Anal. Calcd. for $C_{26}H_{42}N_3Br$: C, 65.55; H, 8.83; N, 8.83.

Calcd. for $C_{10}H_{10}N_3Br$: C, 47.62; H, 3.97; N, 16.67.

Found: C, 47.23; H, 4.13; N, 16.36.

Preparation of Cetyl Bromide (35).[60] A mixture of 121 g. n-hexadecyl alcohol (cetyl alcohol, 0.5 mole, commercial from MC&B, practical, m.p. 48°) and 3.41 g. of purified red phosphorus (from Fisher) were mixed in a 500-ml., three-necked round-bottom flask equipped with an addition funnel, a mechanical stirrer and a condenser. The mixture was heated to about 235° with an oil bath. Bromine (14.5 ml., 46.23 g., 0.578 g. atom, commercial from Fisher, D = 3.188) was then added slowly from the addition funnel at this temperature. After all the bromine was added, the mixture was allowed to cool to room temperature. Ether (300 ml.) was added all at once. Excess phosphorus was filtered off and the ether was washed with 75 ml. water and then dried (K_2CO_3) overnight. Ether was evaporated to give a brown liquid which was vacuum-distilled (180-190°/7mm.) to give a pale yellow liquid. Cetyl bromide (35) weighed 95 g. (62%, m.p. 14°). IR and NMR spectral data (Plates XVII and XVIII) support the structure of the bromide.

Anal. Calcd. for $C_{16}H_{33}Br$: C, 62.95; H, 10.82.

Found: C, 62.85; H, 10.87.

Preparation of 1-Methyl-7,8-dihydro-5(6H)-oxoquinolinium Iodide (23). 7,8-Dihydro-5(6H)-quinolinone (29)(0.88 g., 0.006 mole) was dissolved in 15 ml. of absolute methanol and 3.9 ml. (8.52 g., 0.06 mole) of methyl iodide was added. The mixture was then boiled under N_2 (72 hours). A clear brownish-yellow solution was obtained. The solution was then allowed to cool. When the solvent was evaporated, yellow crystals were obtained. The yellow crystals dissolved in hot absolute

methanol (which was filtered), and absolute ether was added dropwise until a faint turbidity appeared. Upon standing, the mixture deposited yellow crystals of 23 which were filtered; 1.27 g. (73%), m.p. 226-228° . Recrystallization (absolute methanol) gave a solid; m.p. 229.5-231°. An alcoholic solution of 23 gave yellowish precipitate with the silver nitrate test. IR and NMR spectral data (Plates III and IV) support the structure for 23.

Anal. Calcd. for $C_{10}H_{12}NOI$: C, 41.52; H, 4.15; N, 4.84.

Found: C, 41.63; H, 4.20; N, 4.90.

Attempted Preparation of 1-Octyl-7,8-dihydro-5(6H)-oxoquinolinium Bromide (44a). 7,8-dihydro-5(6H)-quinolinone (29) (2.06 g., 0.014 mole) was dissolved in 25 ml. absolute ethanol and boiled with 8.11 g. (0.042 mole) octyl bromide (72 hours) under N_2. After cooling, the clear yellow solution was poured into excess (ca. 150 ml.) of absolute ether and white precipitate formed. The precipitate was filtered and washed with more dry ether (ca. 50 ml.); 3.5 g. (74%), m.p. 182-185°. The precipitate was recrystallized twice (absolute methanol-absolute ether) and melted at 191.5-193°, 2.5 g. (53%). IR and NMR spectral data (Plates XXXIII, XXXIV and XXXV) do not support the structure for 44a, but instead the structure for the hydrobromide 45.

Anal. Calcd. for $C_{17}H_{26}NOBr$: N, 4.12.

Calcd. for $C_9H_{10}NOBr$: N, 6.14.

Found: N, 5.97.

Attempted Preparation of 1-Hexadecyl-7,8-dihydro-5(6H)-oxoquinolinium Bromide (44b). Ketone 29 (2.06 g., 0.014 mole) was dissolved in 25 ml. of absolute ethanol and boiled with 12.81 g. (0.042 mole) of cetyl bromide (72 hours). A clear yellow solution resulted

and was allowed to cool. Addition of the solution to excess (ca. 200 ml.) of absolute ether gave a white precipitate. The material weighed 3.7 g. (58%), m.p. 160-165°. Recrystallized twice (absolute methanol-absolute ether) the white crystals of 44b melted at 191.5-193°. IR and NMR spectral data (Plates XXXIII, XXXIV and XXXV) do not support the structure for 44b nor that of the salt 45.

Anal. Calcd. for $C_{25}H_{42}NOBr$: C, 66.37; H, 9.29; N, 3.10.

Calcd. for $C_9H_{10}NOBr$: C, 47.37; H, 4.36; N, 6.14.

Found: C, 70.76; H, 4.31; N, 8.47.

Preparation of 7-Nitro-1-tetralone (38).[13] Concentrated sulfuric acid (50 ml.) was placed in a three-necked, round-bottom flask immersed in an ice salt bath (-10°) and fitted with a mechanical stirrer, a thermometer (so adjusted as to touch the liquid) and a 50 ml. addition funnel. When the sulfuric acid was cold (about -5°), 1-tetralone [freshly distilled over K_2CO_3, 113-116°/6 mm., commercial product from Aldrich Chemical Company] (20 g., 0.137 mole) was slowly added to the acid so as the temperature remained at 0° or below. The addition took about 5 minutes. A cold mixture (0°) of 11 ml. of fuming nitric acid and 12 ml. of concentrated sulfuric acid was added dropwise to the 1-tetralone solution with vigorous stirring. The addition rate was kept at 60 drops per minute. The addition took about 20 minutes with the temperature maintained below 3° at all times. [Caution: Addition should not exceed 45 minutes. Long exposure of 1-tetralone to the acid mixture decreased the yield sharply.] After the addition was over, the reaction was allowed to proceed for 20 minutes longer with vigorous stirring and at 0° or lower. The mixture (yellow) was then poured slowly into 500 ml. of ice water with vigorous manual stirring. As the

mixture was poured, the water became milky and a yellow gummy paste was formed. The whole aqueous mixture was allowed to stand overnight in an ice-salt bath. During that time, the yellow paste became hardened and became somewhat darkened in color. The solid was filtered and washed 3 times with 500-ml. portions of ice water and each time the solid was crushed to a mush (to facilitate leaching of the acid) and pressed dry on the filter. The solid was then washed with ice-cold alcohol (40 ml.) and filtered and pressed dry. The solid was then dissolved in 60 ml. of hot 95% alcohol and recrystallized. Brown crystals of 38 were collected: 23.9 g., 91%, m.p. 78-95°. Recrystallization three times from 60 ml. boiling alcohol-Norite gave white crystals of 38, but with considerable loss: 8.2 g. (31%), m.p. 103-105°. The white crystals, if desired, could be recrystallized from ether, giving a higher melting point: 6.44 g. (25%), 105-106°; reported m.p. in the literature was 105°.[48,61] IR and NMR spectral data (Plates XXI and XXII) support the structure for the nitro compound.

Preparation of 7-Amino-1-tetralone (28).[31] To a mixture of 7.64 g. (0.04 mole) of 7-nitro-1-tetralone (38), 20 ml. of methanol and 22 ml. of concentrated hydrochloric acid in a 100-ml., three-necked, round-bottom flask equipped with a mechanical stirrer and a condenser, 6.70 g. (0.12 mole) of iron powder (commercial from Fisher) was gradually added in small portions. The temperature rose to the b.p. of methanol (64°) and the ketone dissolved, resulting in a clear brown solution. After the addition of iron powder (about 15 minutes), the solution was allowed to react for 30 minutes. The reaction mixture was then poured into 300 ml. of ice water with stirring. The aqueous solution was then washed with three portions of 100 ml. of ether and the aqueous layer was then

basified with 10% NaOH (about 50 ml.) to pH about 7.5-8.0. (The pH should not exceed 9, otherwise heavy hydroxide complexes form and trap the amine with sharp decrease in the yield.) Green fluffy precipitate (ferrous hydroxide) formed. The mixture was then extracted with six portions of 100 ml. of ether. The combined ether extracts were dried ($MgSO_4$) overnight, filtered and evaporated. Yellow crystals of amine 28 were obtained: 5.15 g. (80%), m.p. 137.5-140°. Recrystallization from 50 ml. dry benzene gave yellow-orange crystals, 4.74 g. (73%), m.p. 139-141°; reported m.p. in the literature was 137°,[48] 136°.[61] IR and NMR spectral data (Plates XXIII and XXIV) support the structure of the amine 28.

Preparation of N,N,N-Trimethyl-5,6-dihydro-8(7H)-oxo-2-naphthyl-ammonium Iodide (27). 7-amine-1-tetralone (28) (0.8 g., 0.005 mole) was suspended in 20 ml. of absolute methanol. Methyl iodide (7.1 g., 0.05 mole) was added to the mixture which was boiled for 36 hours under nitrogen. The reaction mixture was then allowed to cool. Methanol was evaporated off to about 5 ml. volume and absolute ether (excess, about 40 ml.) was added. Yellow crystals of 27 were obtained [0.7 g. (42%), m.p. 188-192°]. The crystals were recrystallized from absolute methanol and then washed with absolute ether and air-dried, m.p. 201-202°. IR and NMR spectral data (Plates XV and XXVI) support the structure.

Anal. Calcd. for $C_{13}H_{18}NOI$: C, 47.13; H, 5.44; N, 4.23.

Found: C, 47.02; H, 4.93; N, 4.12.

Attempted Preparation of N,N,N-Trioctyl-5,6-dihydro-8(7H)-oxo-2-naphthylammonium Bromide (46a). 7-Amino-1-tetralone (28) (0.8 g., 0.005 mole) was suspended in 20 ml. of absolute methanol. 1-Bromooctane (5.8 g., 0.03 mole) was added and the mixture was boiled for 72 hours under N_2. A brown solution was allowed to cool and then it was evaporated in part which resulted in an oil left in the bottom of a brown solution. Absolute ether (100 ml.) was added and the mixture was triturated. The oil solidified to a brown solid which was filtered [1.45 g. (50%), 211-215°]. The brown solid was then dissolved in 15 ml. distilled water and boiled with Norite for 7 minutes, filtered and evaporated to dryness. Light brownish crystals were obtained. The crystals were dissolved in 15 ml. distilled water again and boiled with Norite, filtered and evaporated to dryness. White crystals were collected which were recrystallized from absolute MeOH--absolute ether (10 ml., 1:1 mixture). White needles were collected, m.p. 213-215°, 0.5 g., 17%. IR and NMR specral data (Plates XXVII, XXVIII and XXIX) indicated that the needles were the hydrobromide 47 instead of the N,N,N-trioctyl ammonium bromide (46a). Elemental analysis agreed well for the hydrobromide also instead of the alkyl ammonium bromide.

Anal. Calcd. for $C_{34}H_{60}NOBr$: C, 70.59; H, 10.38; N, 2.42.

Calcd. for $C_{10}H_{12}NOBr$: C, 49.59; H, 4.96, N, 5.78.

Found: C, 49.65; H, 5.03; N, 5.70.

Attempted Preparation of N,N,N-Trihexadecyl-5-6-dihydro-8(7H)-oxo-2-naphthylammonium Bromide (46b). 7-Amino-1-tetralone (28) (0.8 g., 0.005 mole) was suspended in 20 ml. of absolute ethanol. Cetyl bromide (9.15 g., 0.03 mole) (35) was added and the mixture was boiled for 72 hours under N_2. The reaction mixture was then cooled and solids

appeared. Absolute ether (50 ml.) was added and more crystals accumulated. The solids were filtered (pale brown in color), m.p. 112-117°, 1.34 g. (29%). The solids were dissolved in absolute alcohol (20 ml.) and absolute ether was added until slight turbidity appeared. Brownish crystals were obtained; m.p. 173-175°, 1.34 g. (29%). Recrystallization from absolute alcohol-ether gave crystals melting at 181.5-183°. Since the m.p. does not correspond to that of the hydrobromide 47, the compound must result from a usual reaction. Additional work is needed to determine the structure of the product melting at 181.5-183°.

Preparation of 6-Hydroxy-1-tetralone (33).[45] 6-Methoxy-1-tetralone (34)(17.62 g., 0.1 mole) was boiled with 250 ml. of aqueous 48% hydrobromic acid for 5 hours. The reaction mixture was cooled and filtered. A resulting pink solid was recrystallized (H_2O) to yield 12.5 g. (77%) of a white solid, m.p. 156-157°; reported m.p. in the literature was 154°.[3] IR and NMR spectral data (Plates IX and X) support the structure of 33.

Preparation of 6-(Hexadecyloxy)-3,4-dihydro-1(2H)-naphthalenone (26). 6-Hydroxy-1-tetralone (33)(6.48 g., 0.04 mole) was dissolved in 70 ml. of dry acetone, and potassium iodide (0.5 g., 0.003 mole) anhydrous potassium carbonate (5.52 g., 0.04 mole) and cetyl bromide (10.68 g., 0.035 mole) were added to the acetone solution. The mixture was boiled (12 hours) in a three-necked, 300-ml., round-bottom flask fitted with N_2 inlet, a mechanical stirrer and a condenser. When the stirring was stopped, a top clear layer and a bottom layer of white solids were obtained. The mixture was then poured into 100 ml. of water. The solids dissolved and a top yellow-brown oil was formed which soon solidified. The mixture was extracted with three 75 ml. portions of

ether. The combined ether extracts were washed twice with 50 ml. of 5% NaOH solution and then dried ($MgSO_4$) overnight. The ether was evaporated to give a yellow solid, m.p. 40-44°, 11.4 g., 84%. The white solid was recrystallized (n-pentane) and gave white leaflets of 26; m.p. 44-45.5°, 10.0g. (74%). IR and NMR spectral data (Plates XI and XII) support the structure of 26.

Anal. Calcd. for $C_{26}H_{42}O_2H_2O$: C, 77.22; H, 10.89.

Found: C, 77.09; H, 10.89.

The results of analysis indicated that the product labelled 26 might very well contain a molecule of water as shown, although the compound had been dried in the Abderhalden for 24 hours. Recrystallization from methanol gave white leaflets, m.p. 48-50°.

Anal. Calcd. for $C_{26}H_{42}O_2$: C, 80.83; H, 1095.

Found: C, 80.94; H, 10.85.

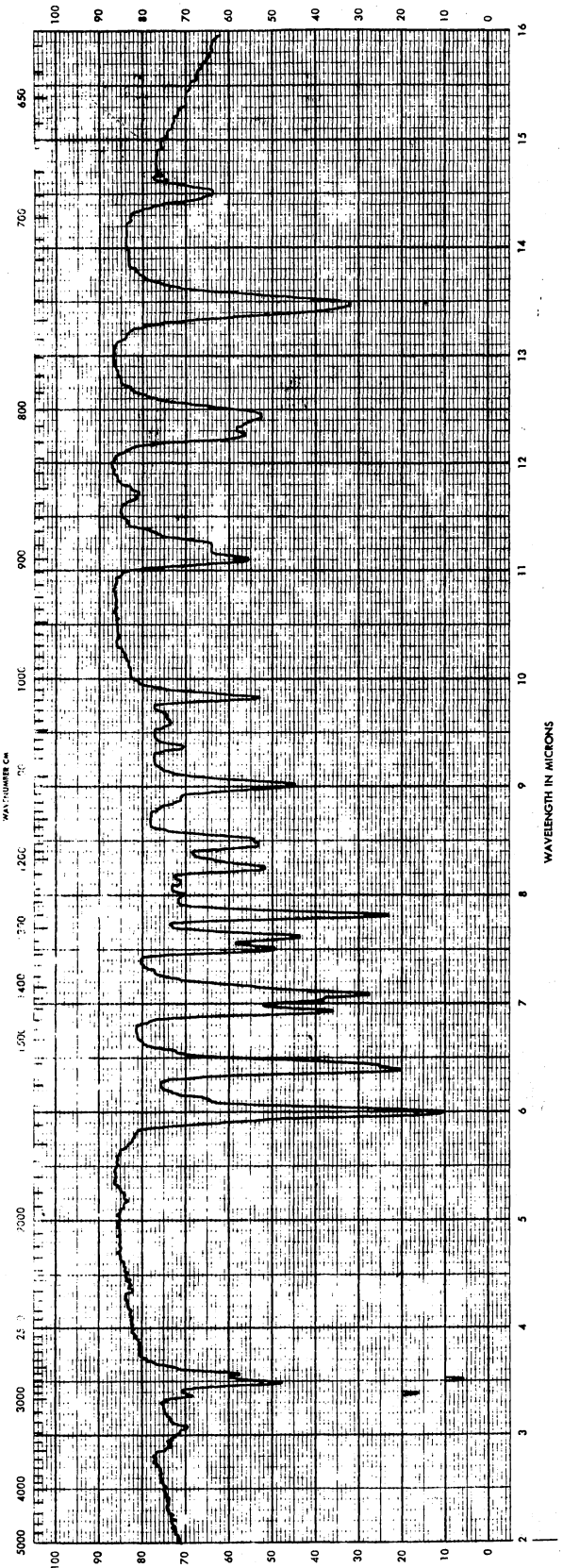
Preparation of 6-(Hexadecyloxy)-2-(hydroxymethylene)-3,4-dihydro-1-naphthalenone (36). Sodium methoxide (1.62 g., 0.03 mole) was suspended in 20 ml. of dry benzene in a 100-ml., three-necked, round-bottom flask with a mechanical stirrer, a N_2 inlet, a condenser, and an addition funnel. Ethyl formate (2.22 g., 0.03 mole), dissolved in 7 ml. of dry benzene, was added dropwise to the suspension at 0°. After all the formate was added, ketone 26 (5.78 g., 0.015 mole) dissolved in 35 ml. of dry benzene was added dropwise at 0°. The mixture became light yellow upon contact with the ketone. The color turned reddish-pink in one hour. After 20 hours at room temperature, the mixture was purple colored. Hydrolysis was effected with 200 ml. of ice water. The organic layer was separated and was washed twice with 75 ml. of 5% NaOH. The combined aqueous layers were acidified with 6N HCl to pH

about 6. A brown liquid appeared on top of the acidic solution. Four separate 75 ml. portions of ether were employed to extract the brown liquid from the mixture. Dehydration ($MgSO_4$) of the ether extracts overnight gave a clear solution which was filtered. Evaporation of the ether gave a yellow-tan solid weighing 3.13 g. (50%), m.p. 53-54.5°. The solids were recrystallized from n-pentane (Norite added) 2.33 g. (37%), 53.7-55° . IR and NMR spectral data (Plates XIII and XIV) support the structure for the hydroxymethylene compound 36 .

Preparation of 7-(Hexadecyloxy)-4,5-dihydro-1H-benz[g]indazole (9c). The hydroxymethylene compound 36 (1.035 g., 0.0025 mole), dry hydrazine (0.16 g., 0.005 mole) and 20 ml. of absolute methanol were boiled under N_2 (3 hours). The solution was then permitted to cool and a yellow solid precipitated. The mixture was then poured into 200 ml. of ice water. After being stirred briefly by hand, the mixture was filtered. Recrystallization of the solid from 20 ml. of ethanol (Norite added) and then from ethanol-water (trace) gave light yellow crystals. The weight was 0.7 g. (68%); m.p. 88-90°. The crystals were again recrystallized from 8 ml. of 95% alcohol and dried in the Abderhalden (12 hours). White crystals of 9c were obtained, m.p. 91-92°. IR and NMR spectral data (Plates XV and XVI) confirmed the structure for the benzindazole 9c.

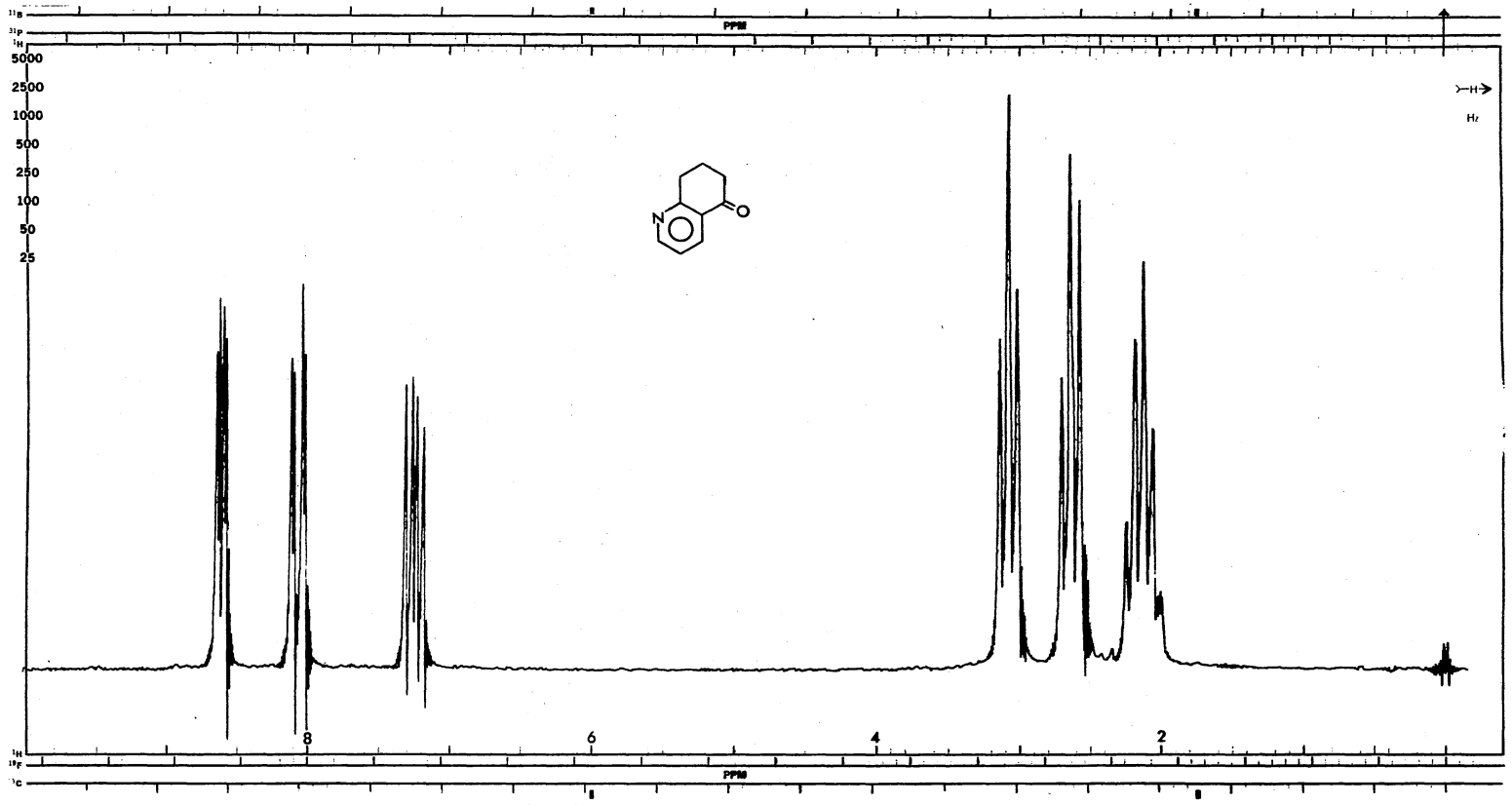
Anal. Calcd. for $C_{27}H_{42}N_2O$: C, 78.97; H, 10.31; N, 6.82.
Found: C, 79.13; H, 10.26; N, 6.65.

PLATE I



7,8-Dihydro-5(6H)-quinoline (29), Film

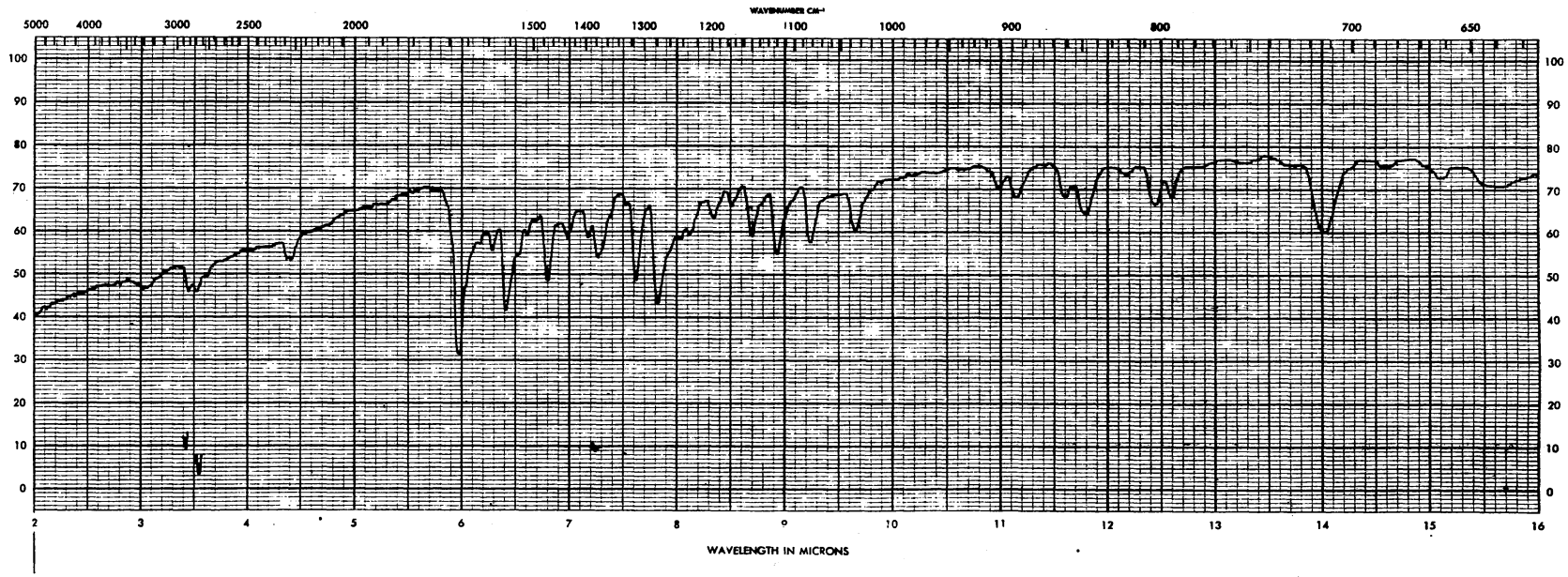
PLATE II



7,8-Dihydro-5(6H)-quinolinone (29)

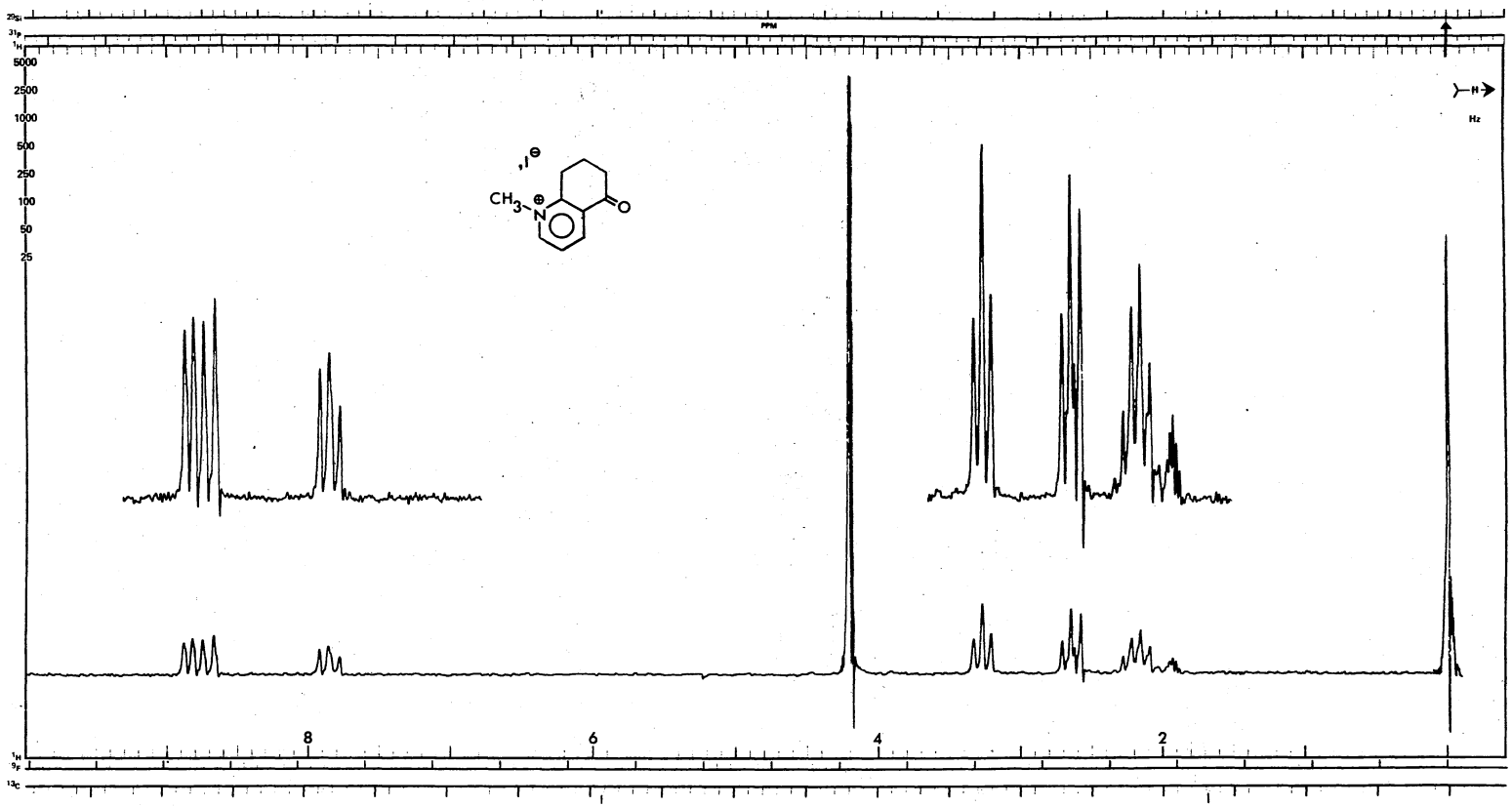
Solvent. . . Neat O.F. . . . 100.1 MHz F.B. . . . . 4 Hz R.F. . . 61 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . . 1 Lock. .HOMO

PLATE III



1-Methyl-7,8-dihydro-5(6H)-oxo quinolinium Iodide (23), KBr Pellet

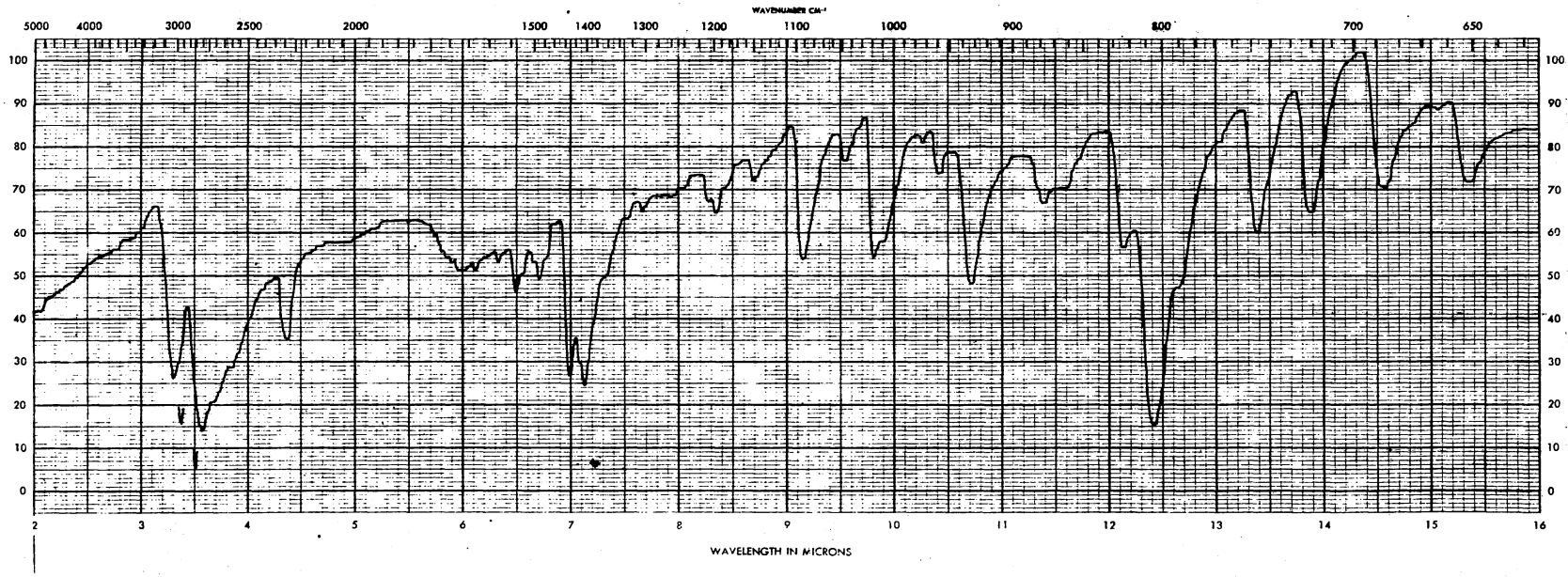
PLATE IV



1-Methyl-7,8-dihydro-5(6H)-oxoquinolinium Iodide (23)

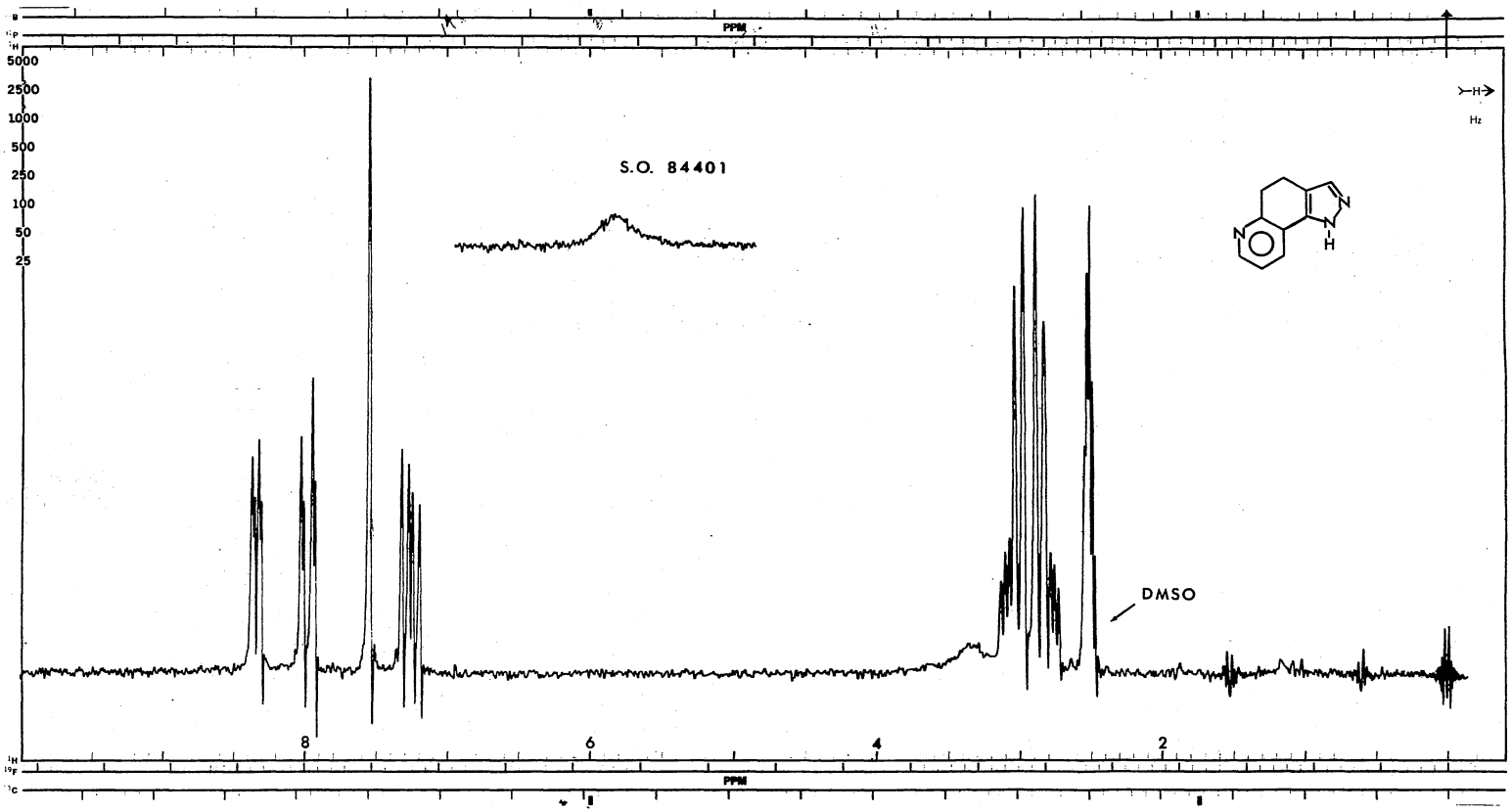
Solvent. . . . D_2O O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 70 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 82911 Hz S.A. . . . 2.0 Lock. .HOMO

PLATE V



4,5-Dihydro-1H-pyrazolo[3,4-f]quinoline (24), KBr Pellet

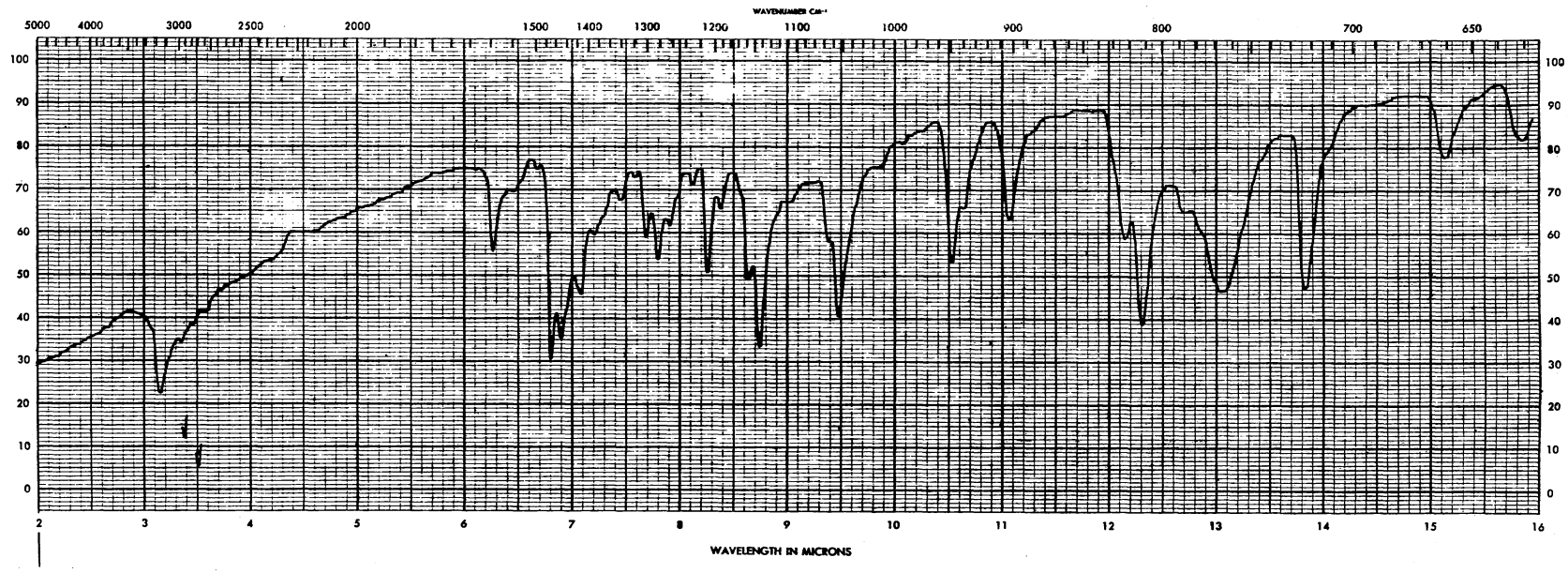
PLATE VI



4,5-Dihydro-1H-pyrazolo[3,4-f]quinoline (24)

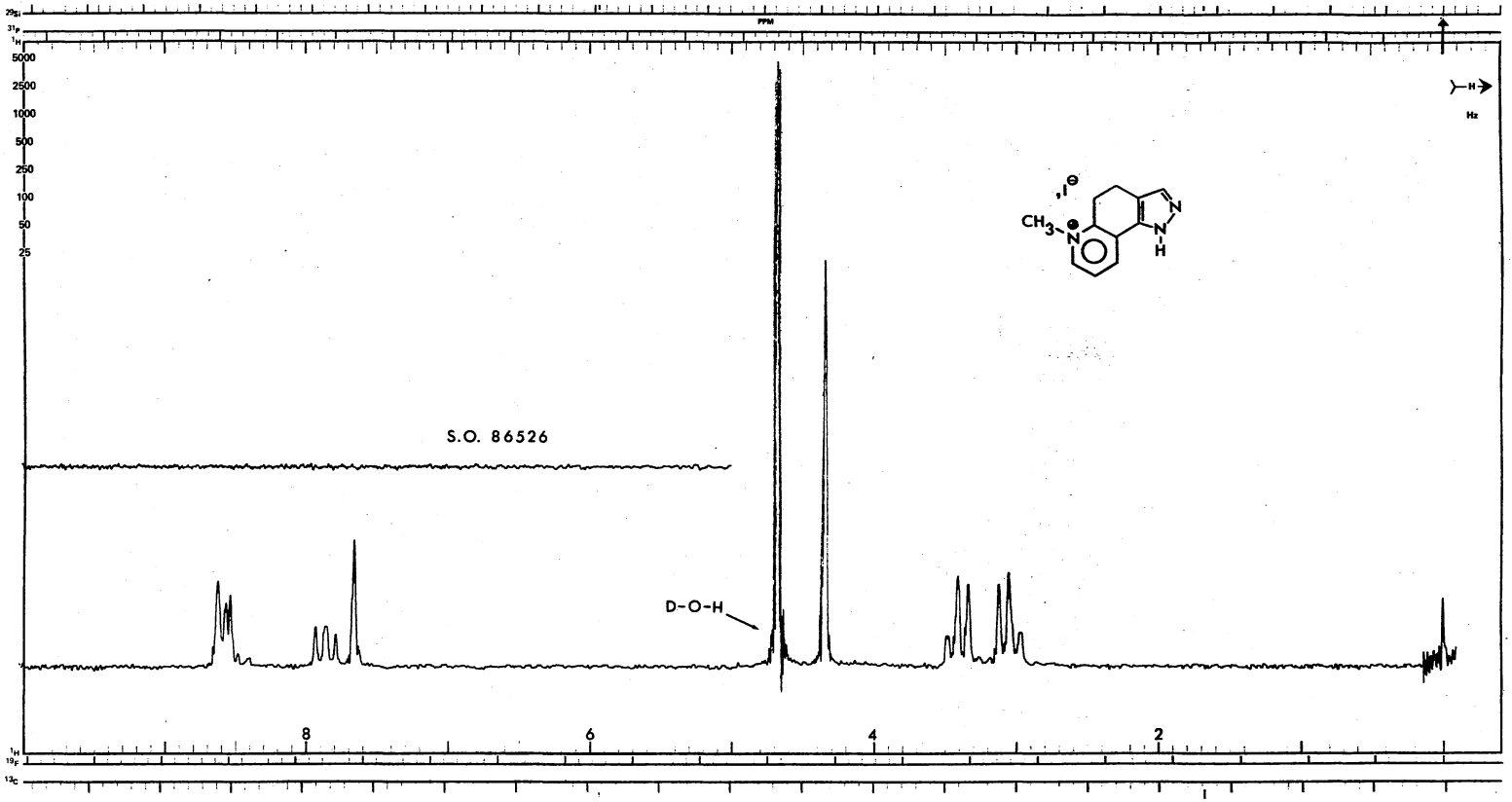
Solvent. . DMSO-d_6 O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 69 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . 8.0 Lock. .HOMO

PLATE VII



6-Methyl-4,5-dihydro-1H-pyrazolo[3,4-f]quinolinium Iodide (25), KBr Pellet

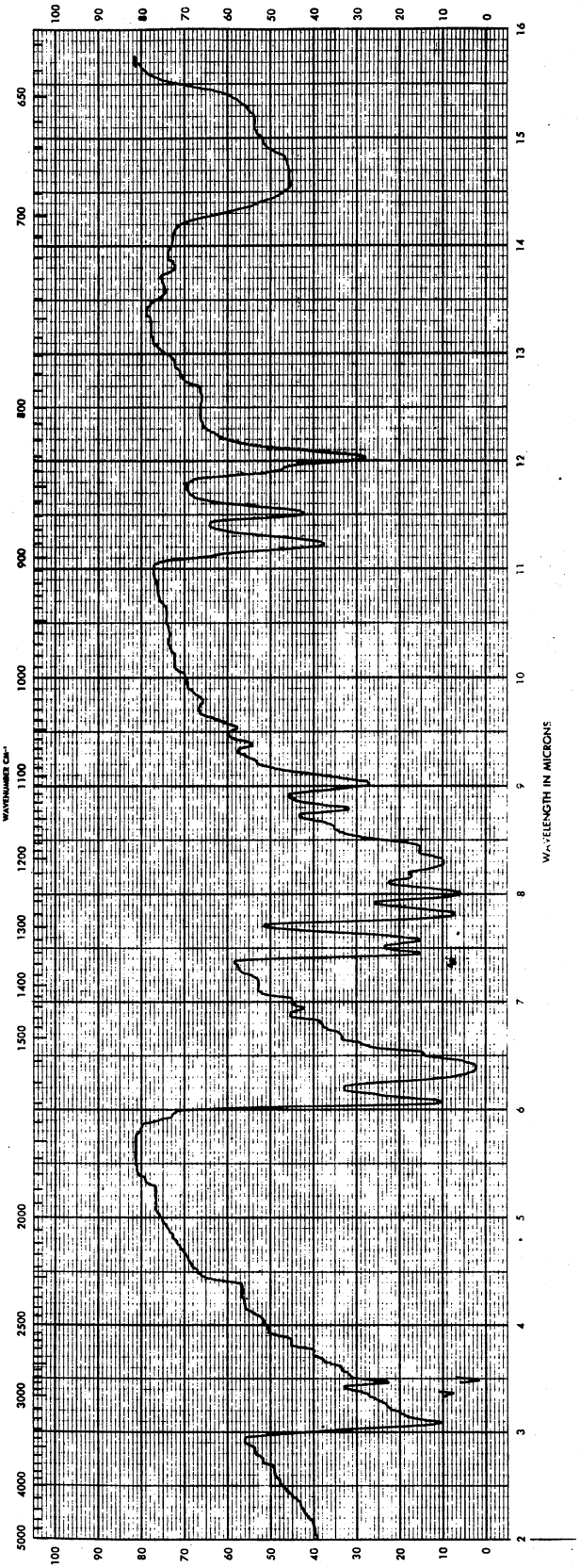
PLATE VIII



6-Methyl-4,5-dihydro-1H-pyrazolo[3,4-f]quinolinium Iodide (25)

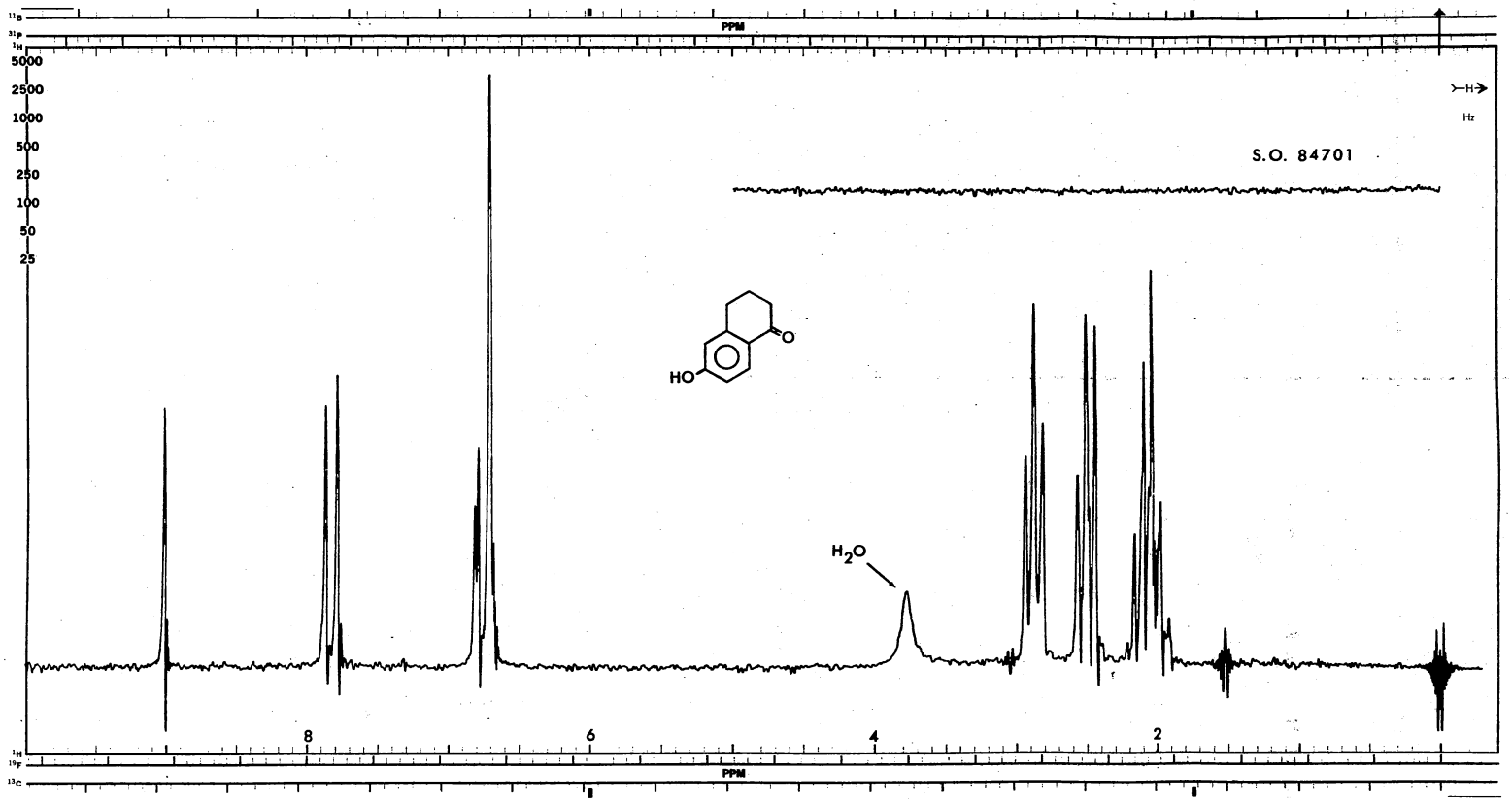
Solvent. . . . D_2O	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 71 dB
S.W. . . . 1000 Hz	S.T. . . . . 250 sec	S.O. . . 83701 Hz	S.A. . . . 4.0 Lock. .HOMO

PLATE IX



6-Hydroxy-1-tetralone (33), KBr Pellet

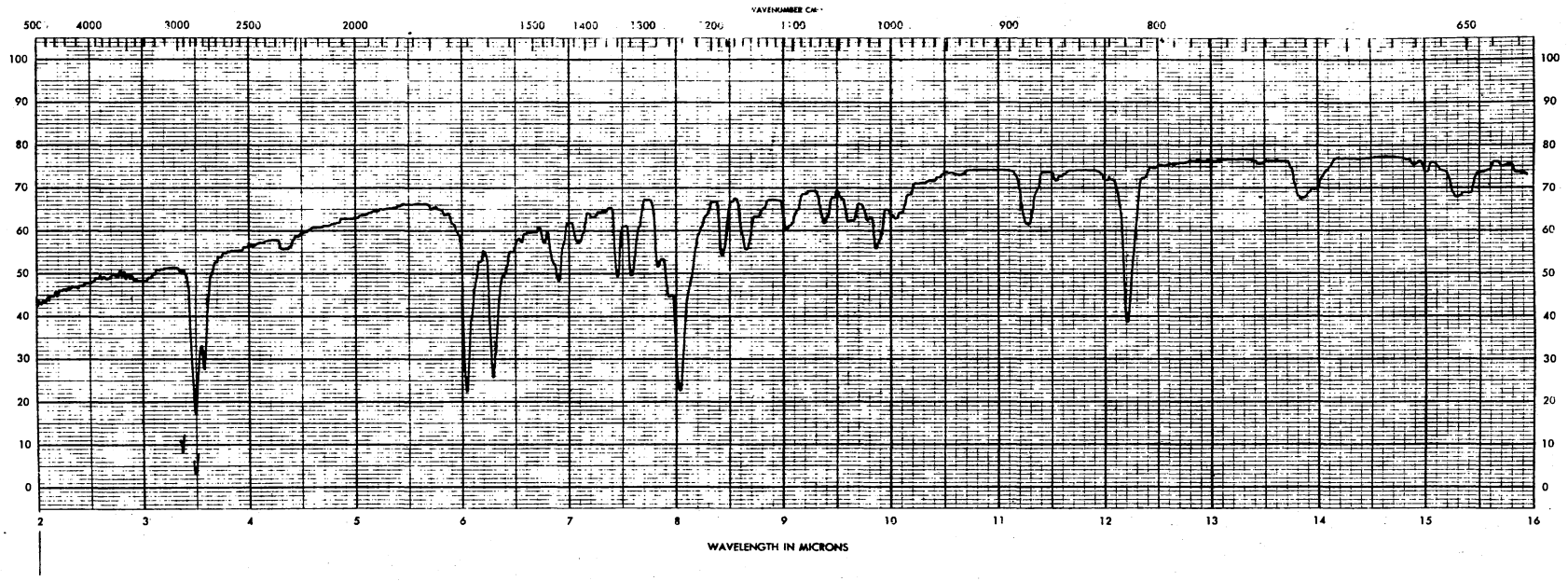
PLATE X



6-Hydroxy-1-tetralone (33)

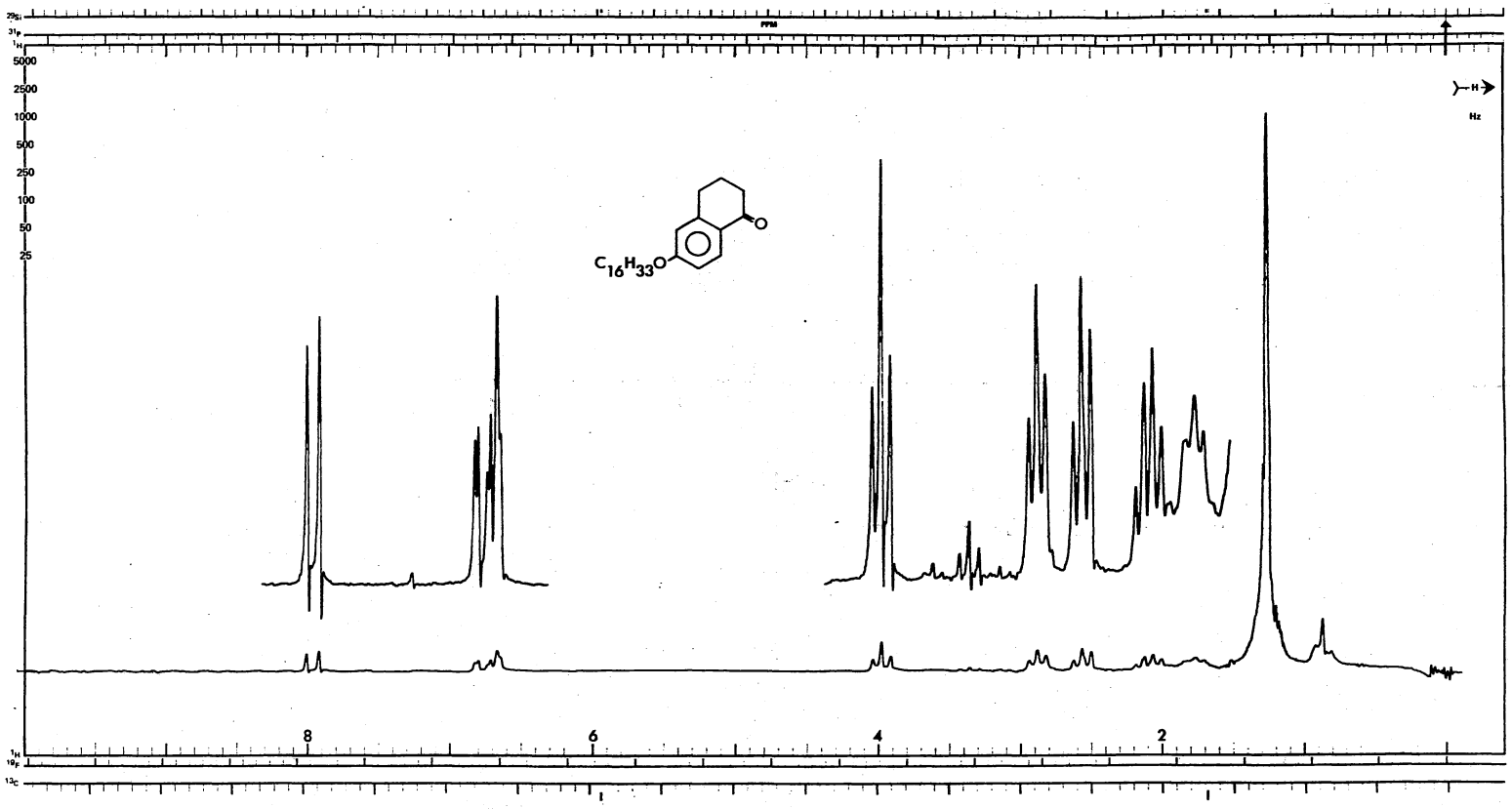
Solvent. .Acetone-d_6 O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 40 dB
S.W. . . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . 6.3 Lock. .HOMO

PLATE XI



6-(Hexadecyloxy)-3,4-dihydro-1(2H)-naphthalenone (26), KBr Pellet

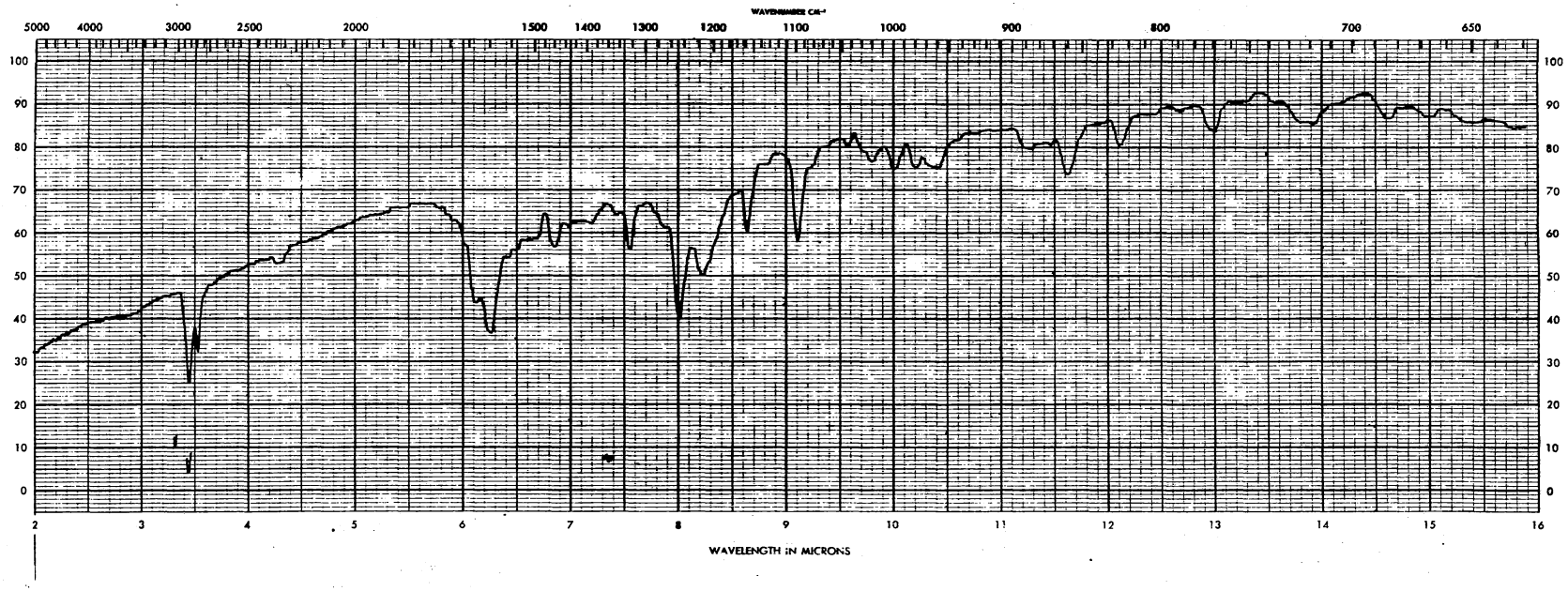
PLATE XII



6-(Hexadecyloxy)-3,4-dihydro-1(2H)-naphthalenone (26)

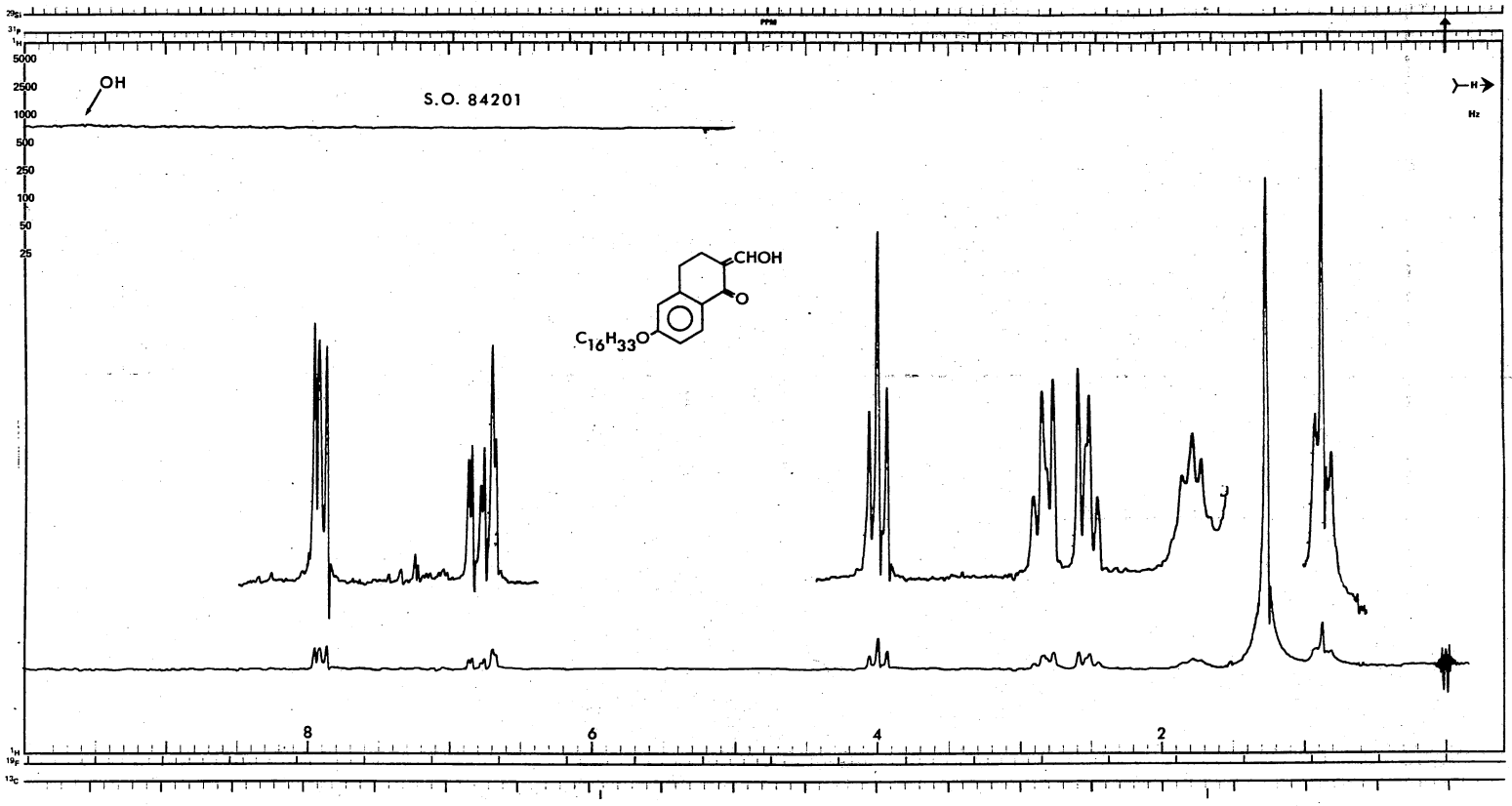
Solvent. . . $DCCl_3$	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 59 dB
S.W. . . . 1000 Hz	S.T. . . . . 250 sec	S.O. . . 83701 Hz	S.A. . . . 1.0 Lock. .HOMO

PLATE XIII



6-(Hexadecyloxy)-2-(hydroxymethylene)-3,4-dihydro-1-naphthalenone (36), KBr Pellet

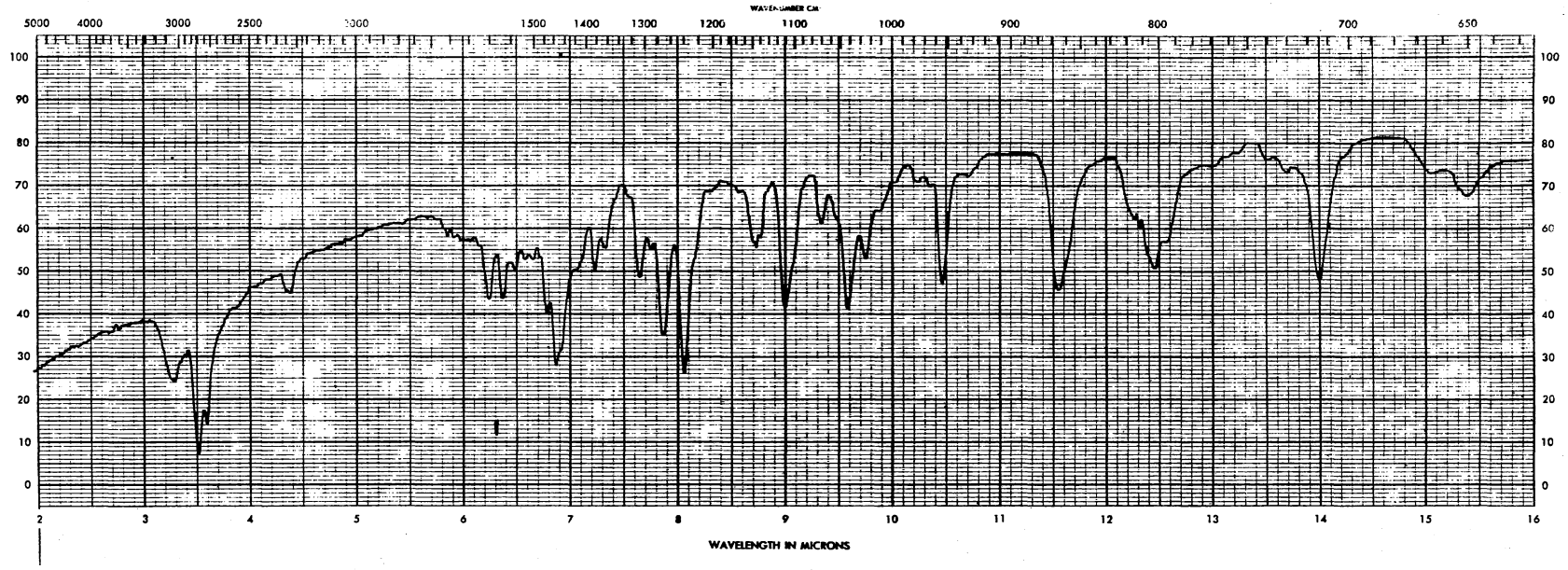
PLATE XIV



6-(Hexadecyloxy)-2-(hydroxymethylene)-3,4-dihydro-1-naphthalenone (36)

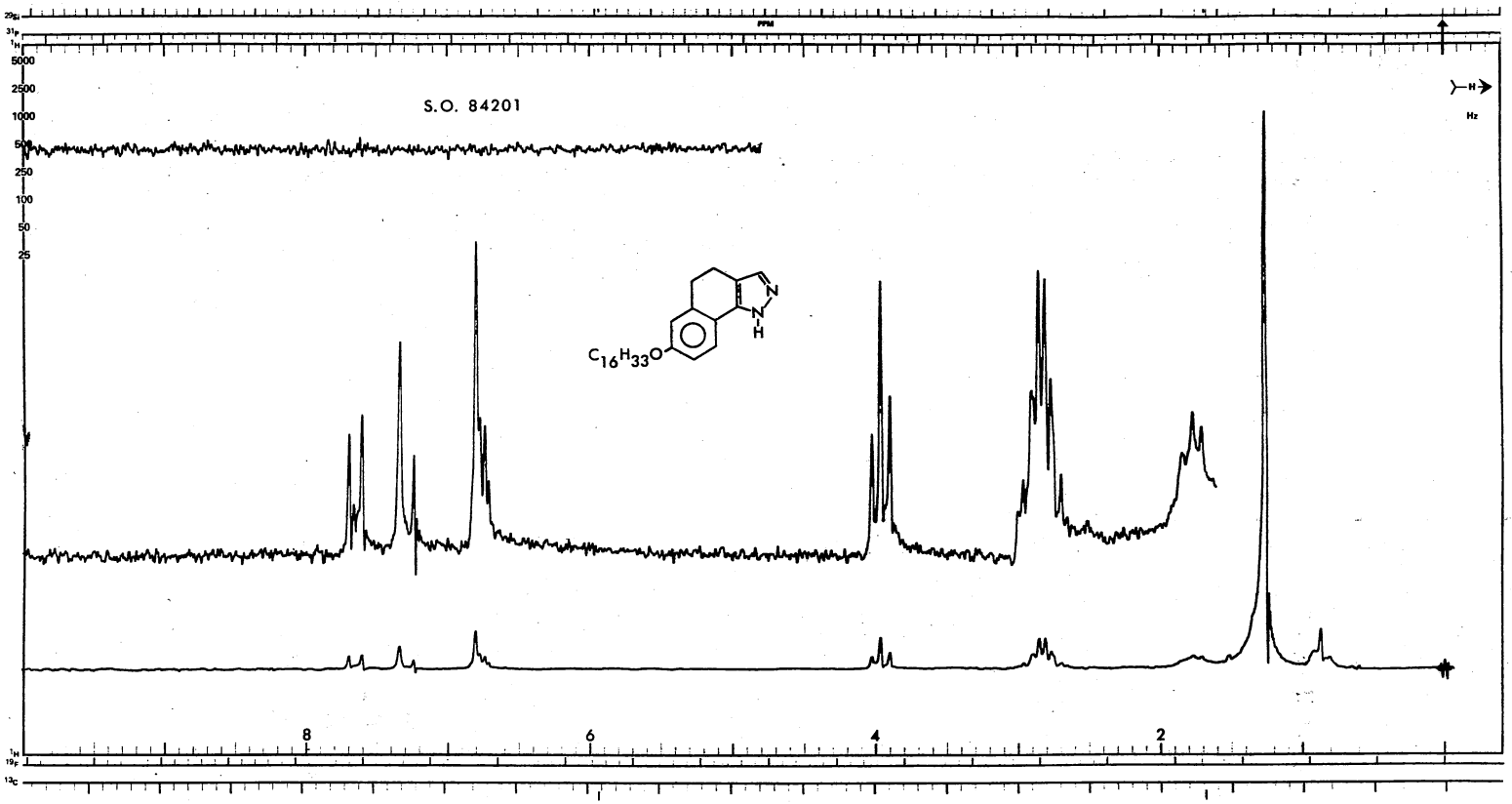
Solvent. . . $DCCl_3$	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 58 dB
S.W. . . . 1000 Hz	S.T. . . . . 250 sec	S.O. . . 83701 Hz	S.A. . . . 1.6 Lock. .HOMO

PLATE XV



7-(Hexadecyloxy)-4,5-dihydro-1H-benz[g]indazole (9c), KBr Pellet

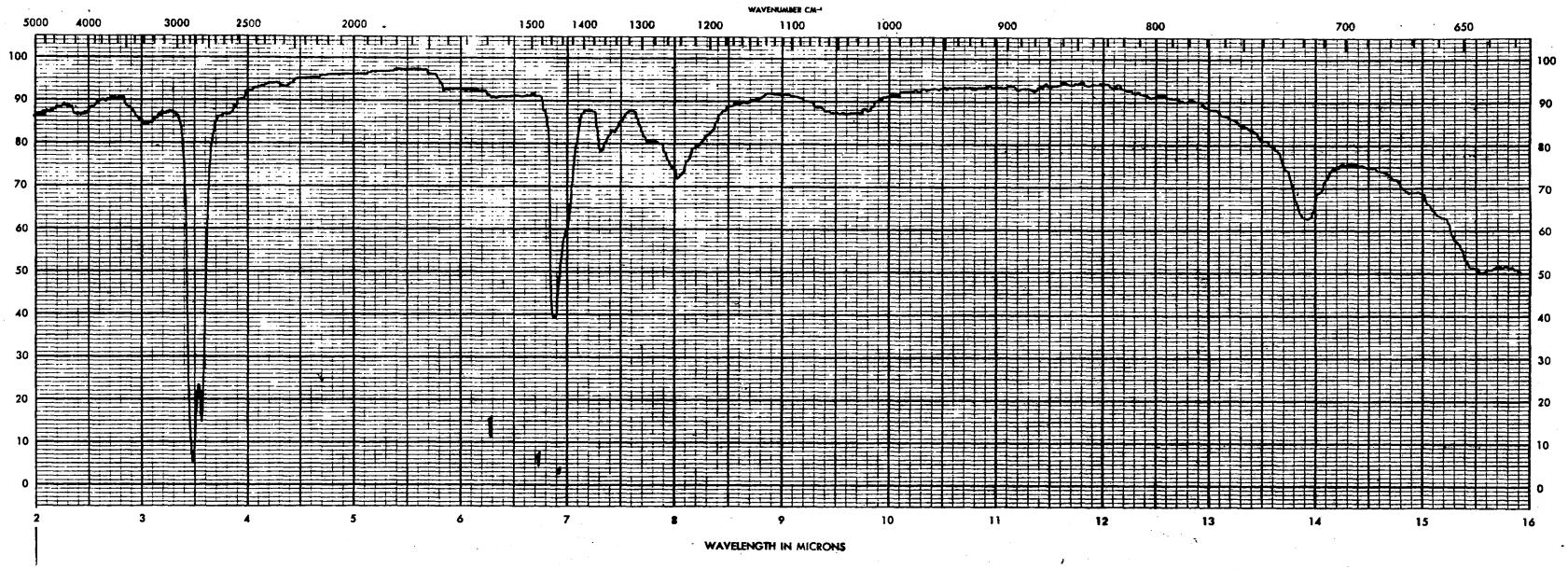
PLATE XVI



7-(Hexadecyloxy)-4,5-dihydro-1H-benz[g]indazole (9c)

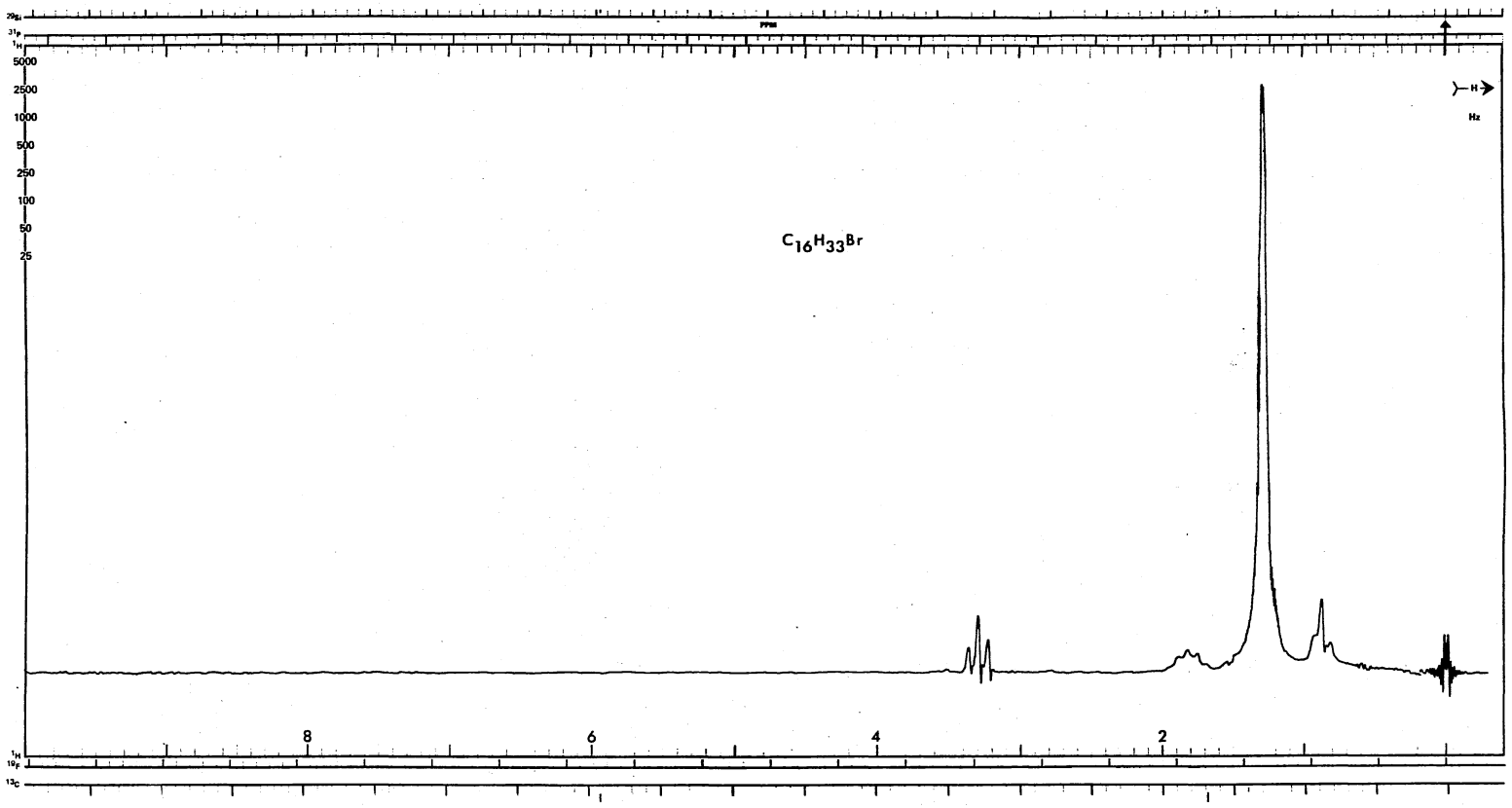
Solvent. . . $DCCl_3$ O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 70 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . 1.6 Lock. .HOMO

PLATE XVII



Cetyl Bromide (35), KBr Pellet

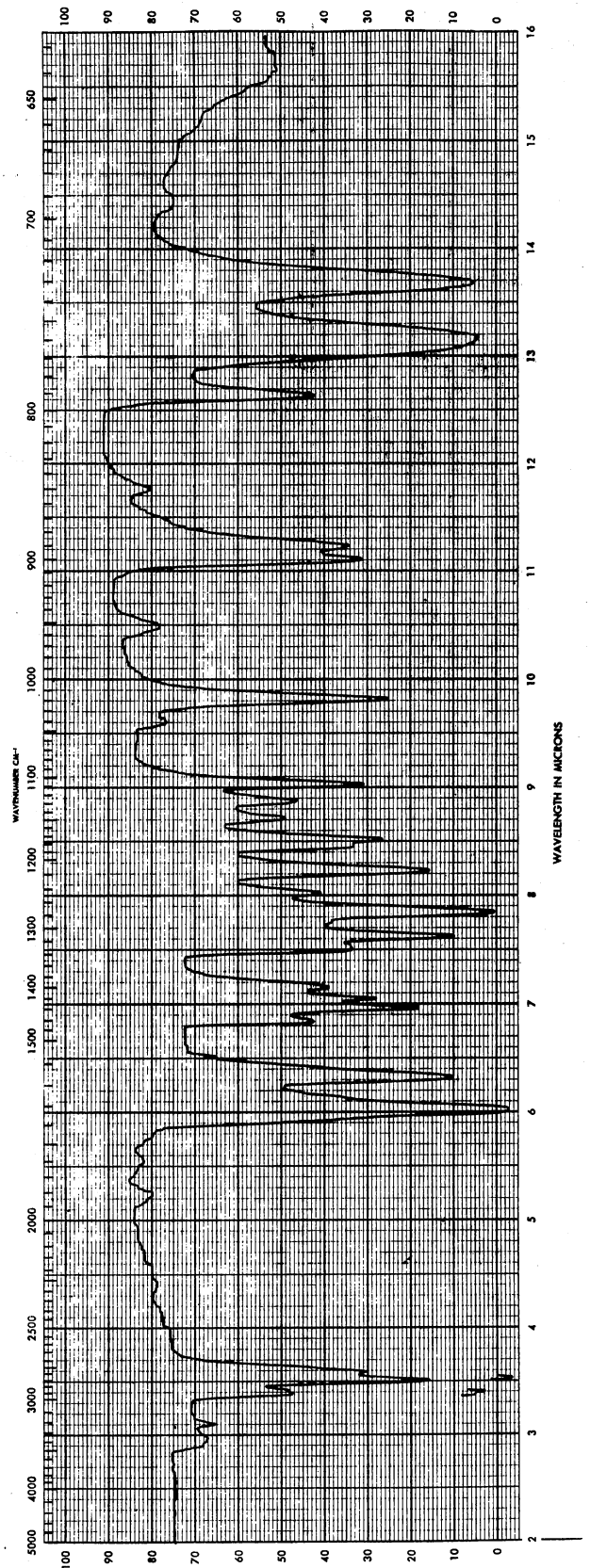
PLATE XVIII



Cetyl Bromide (35)

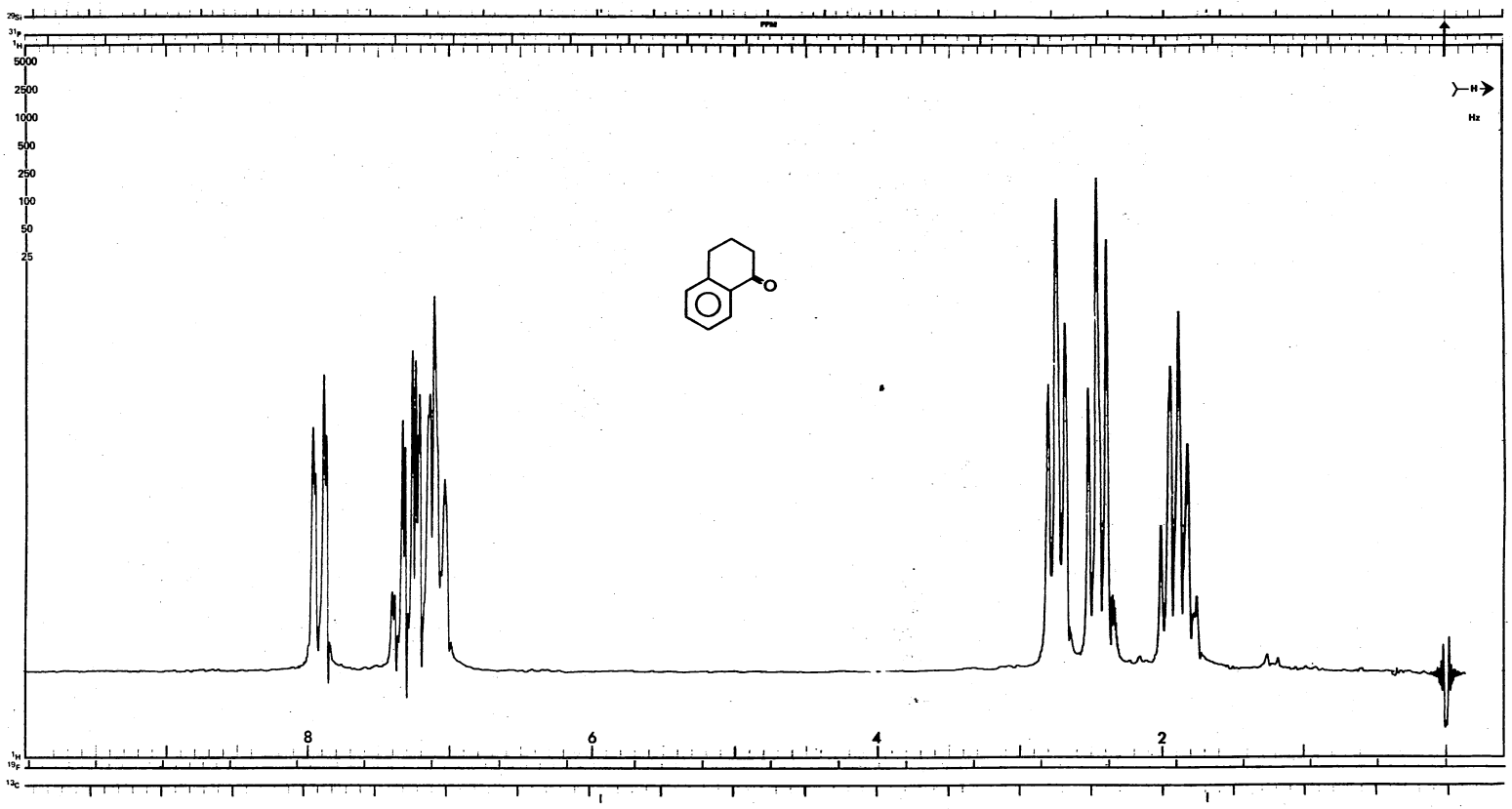
Solvent. . . Neat O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 60 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . 1.0 Lock. .HOMO

PLATE XIX



1-Tetralone (40), Film

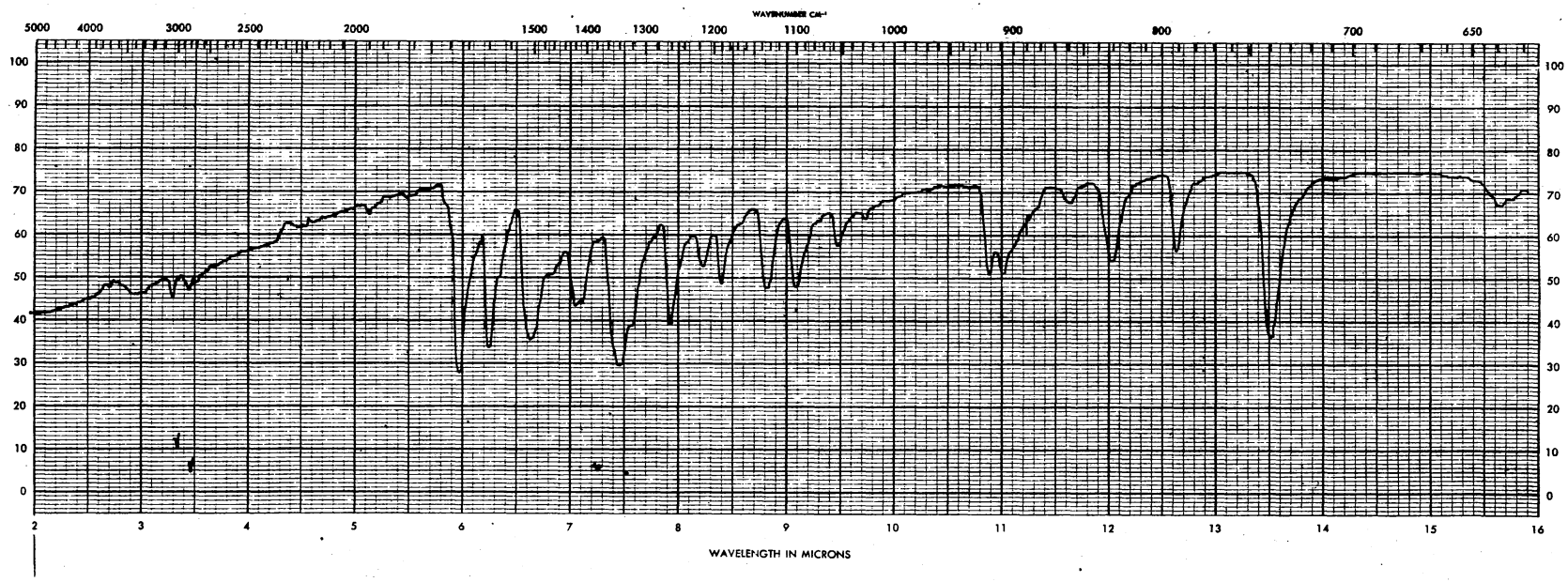
PLATE XX



1-Tetralone (40)

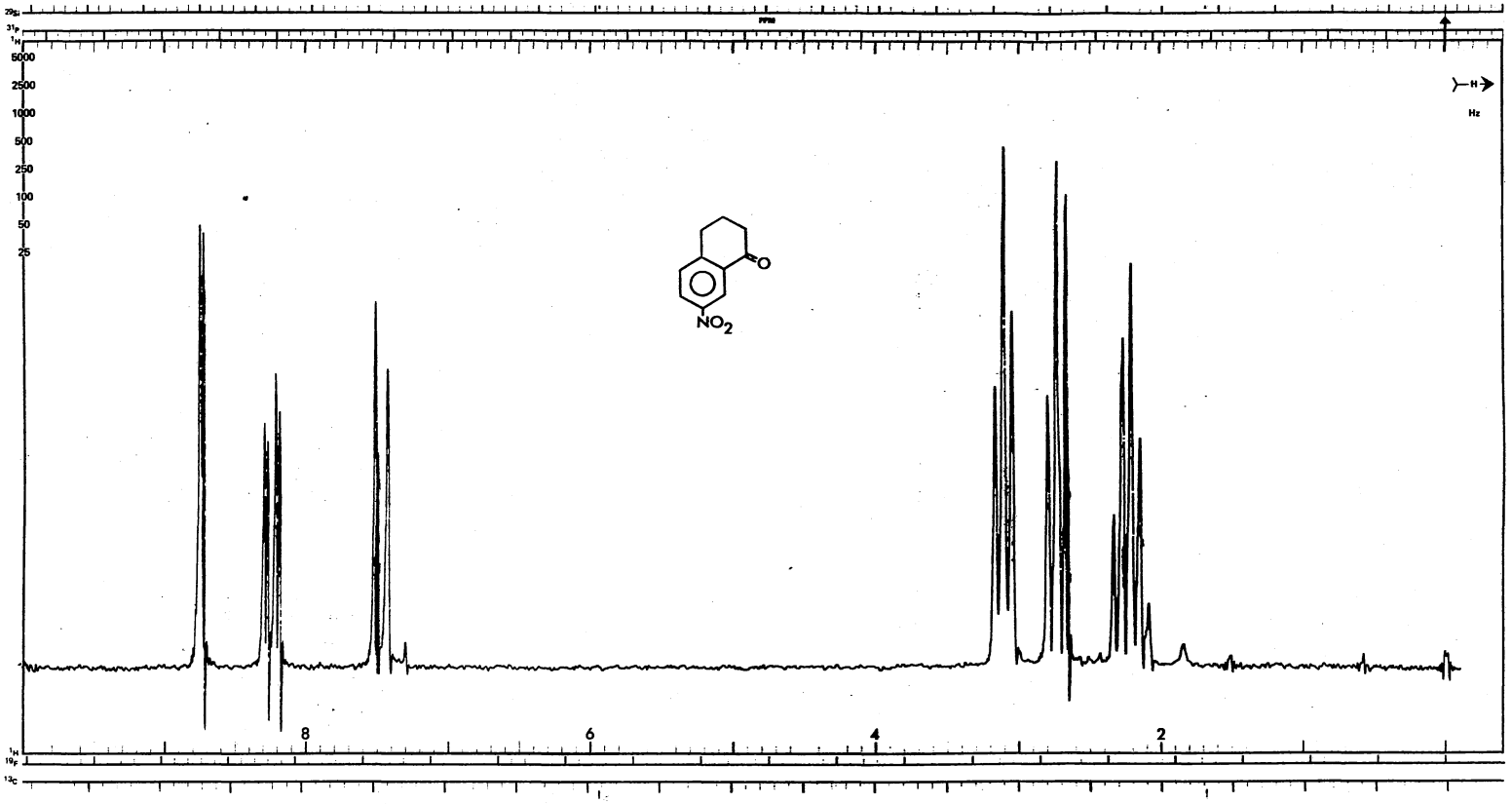
Solvent. . . Neat O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 60 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . 1.0 Lock. .HOMO

PLATE XXI



7-Nitro-1-tetralone (38), KBr Pellet

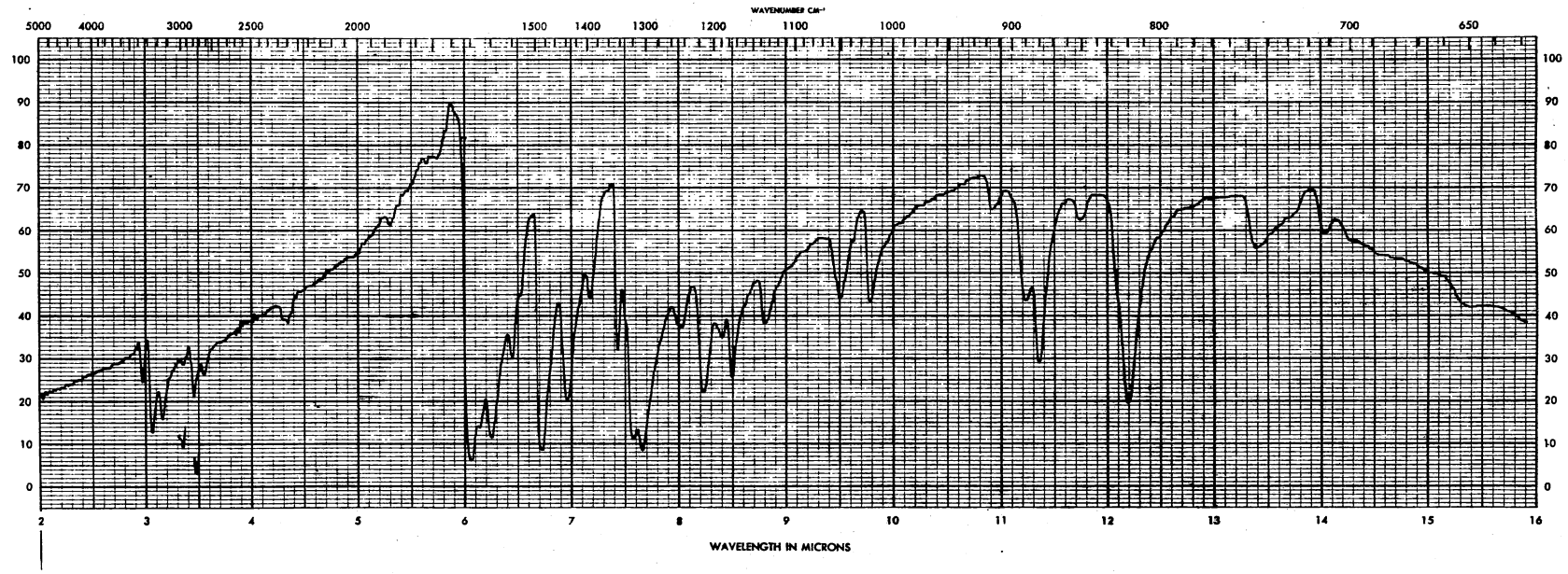
PLATE XXII



7-Nitro-1-tetralone (38)

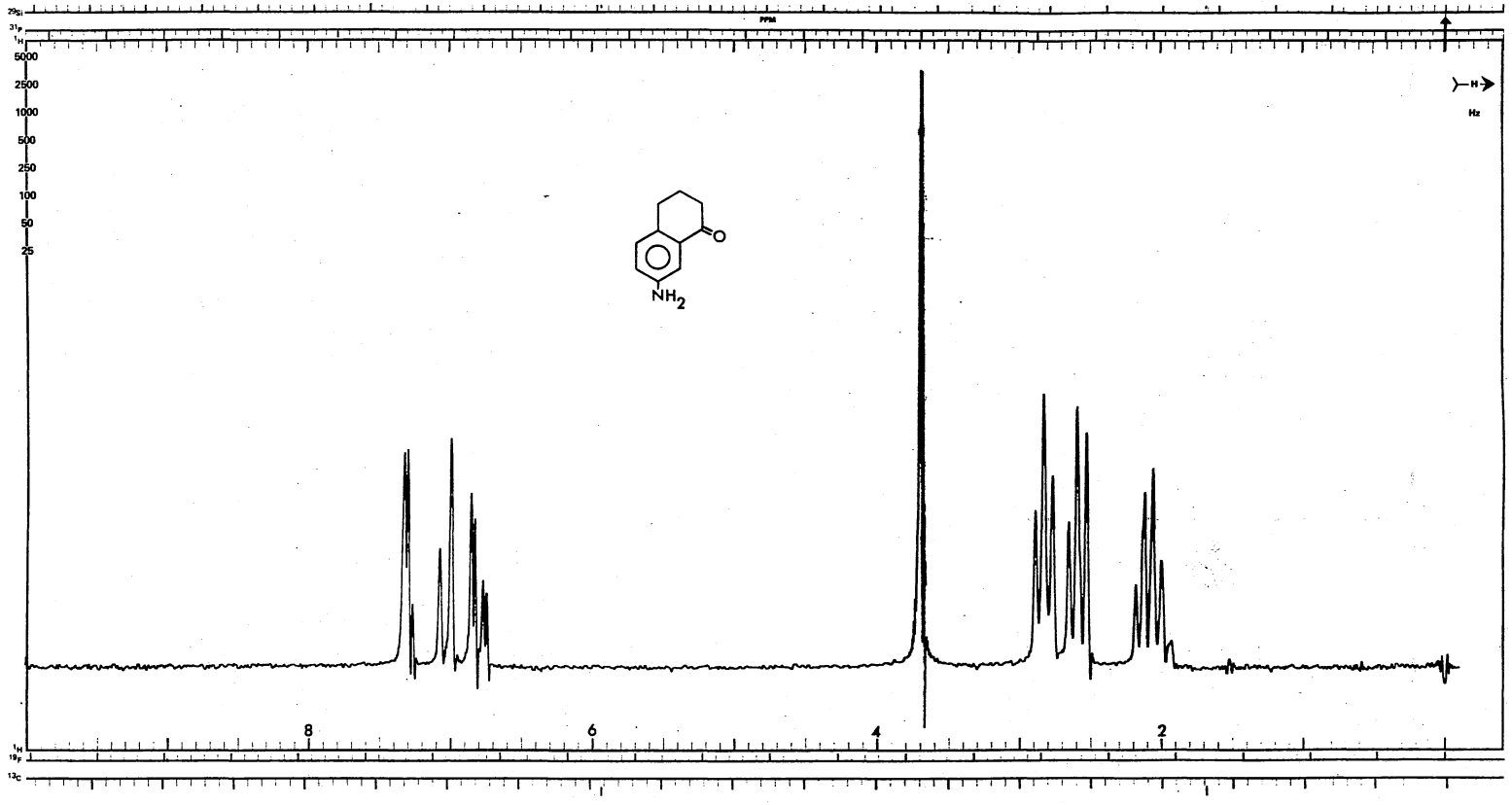
Solvent. . . $DCCl_3$ O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 69 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . 4.0 Lock. .HOMO

PLATE XXIII



7-Amino-1-tetralone (28), KBr Pellet

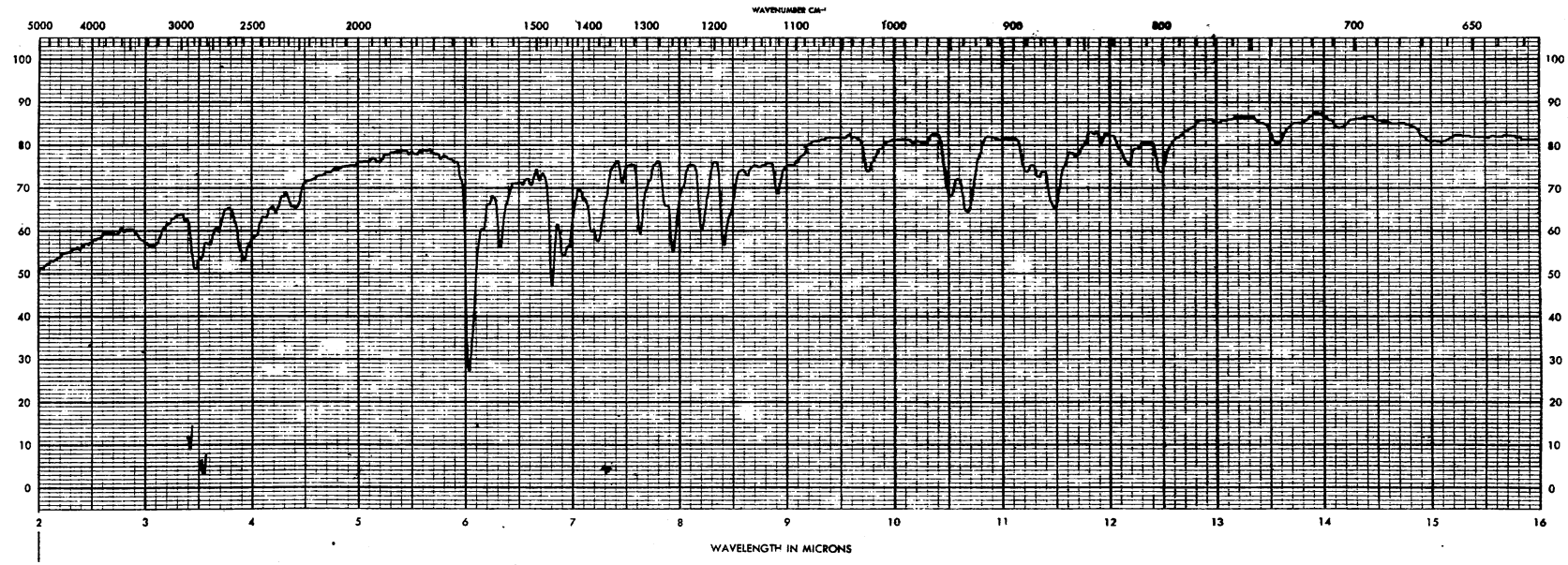
PLATE XXIV



7-Amino-1-tetralone (28)

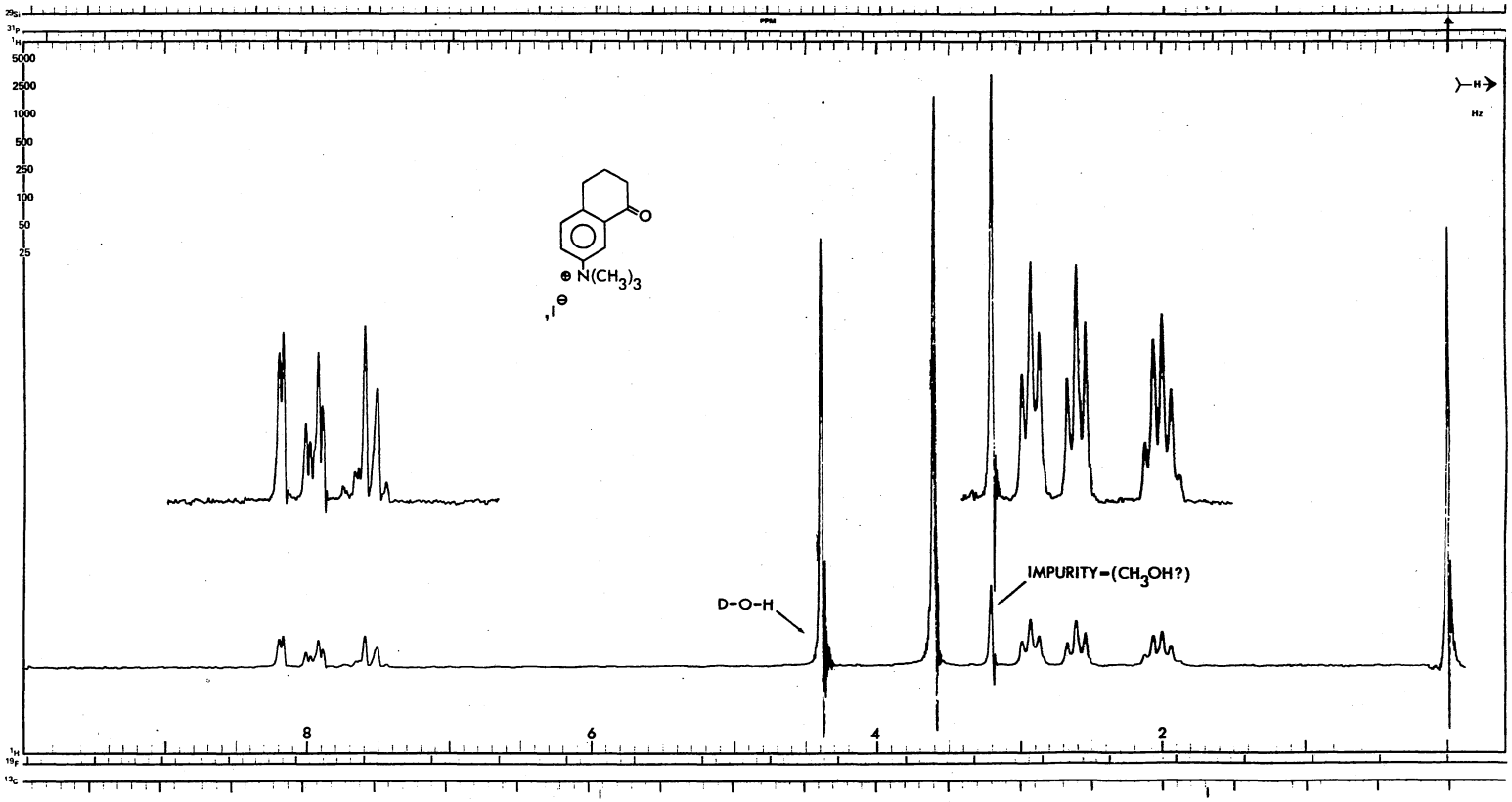
Solvent. . . $DCCl_3$ O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 65 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . 4.0 Lock. .HOMO

PLATE XXV



N,N,N-Trimethyl-5,6-dihydro-8(7H)-oxo-2-naphthylammonium Iodide (27), KBr Pellet

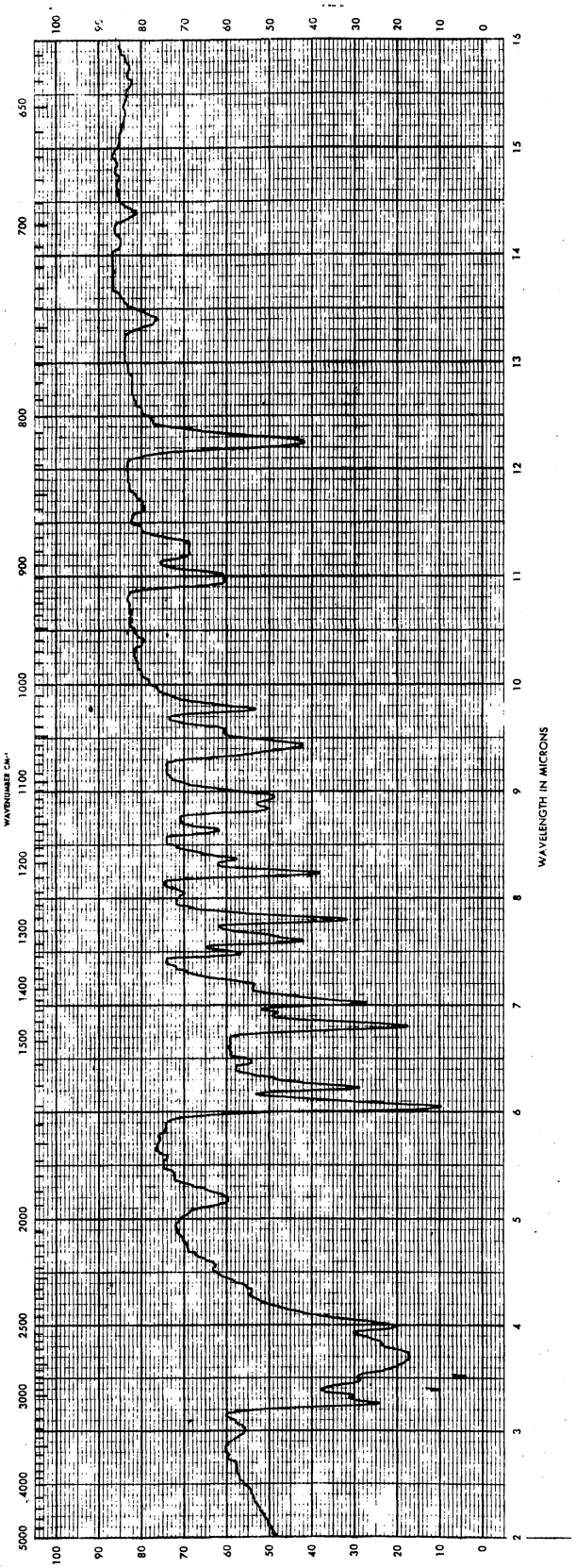
PLATE XXVI



N,N,N-Trimethyl-5,6-dihydro-8(7H)-oxo-2-naphthylammonium Iodide (27)

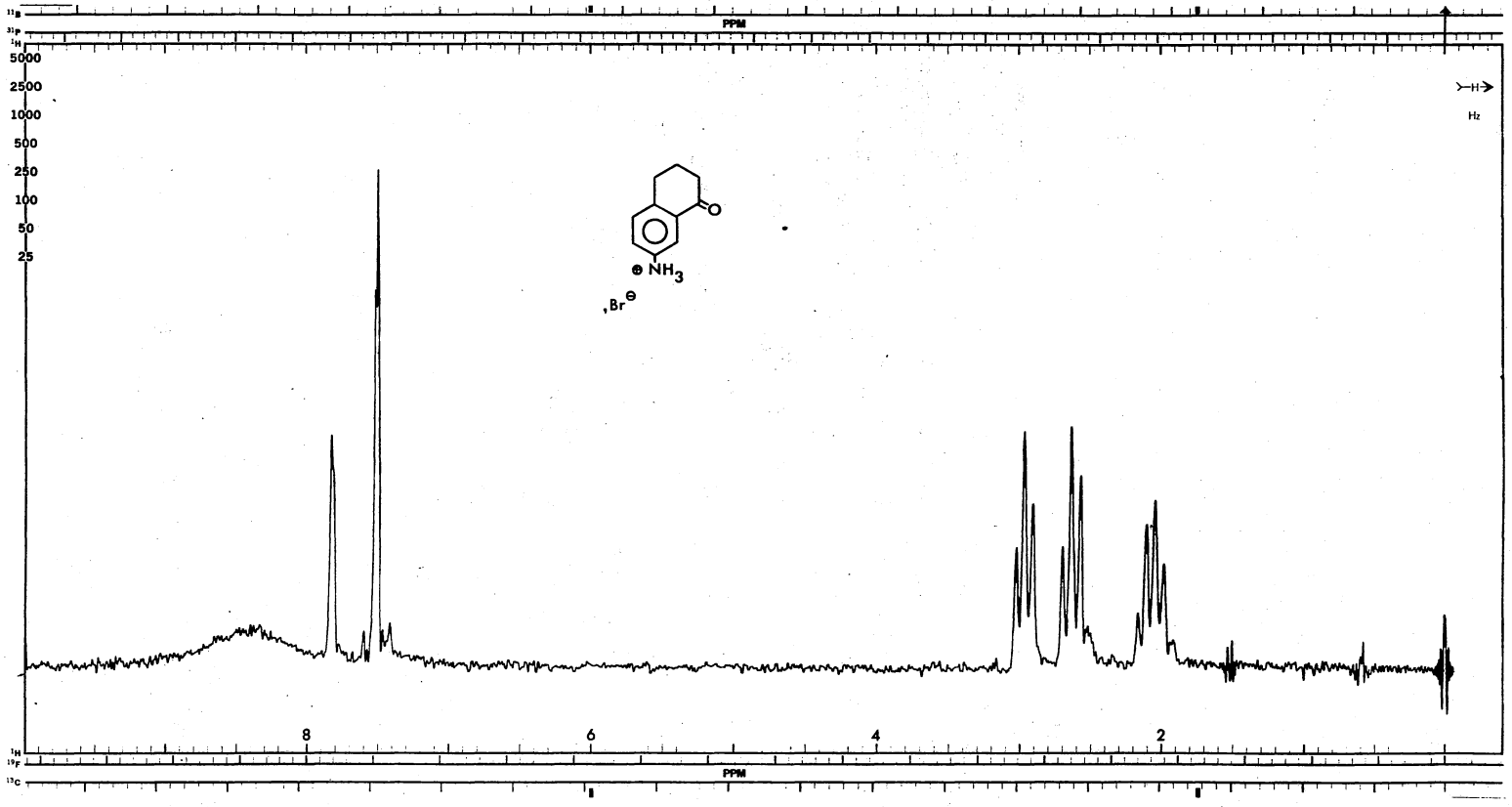
Solvent. . . . D_2O	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 70 dB
S.W. . . . 1000 Hz	S.T. . . . . 250 sec	S.O. . . 82911 Hz	S.A. . . . 1.0 Lock. .HOMO

PLATE XXVII



5,6-Dihydro-8(7H)-oxo-2-naphthylammonium Bromide (47), KBr Pellet

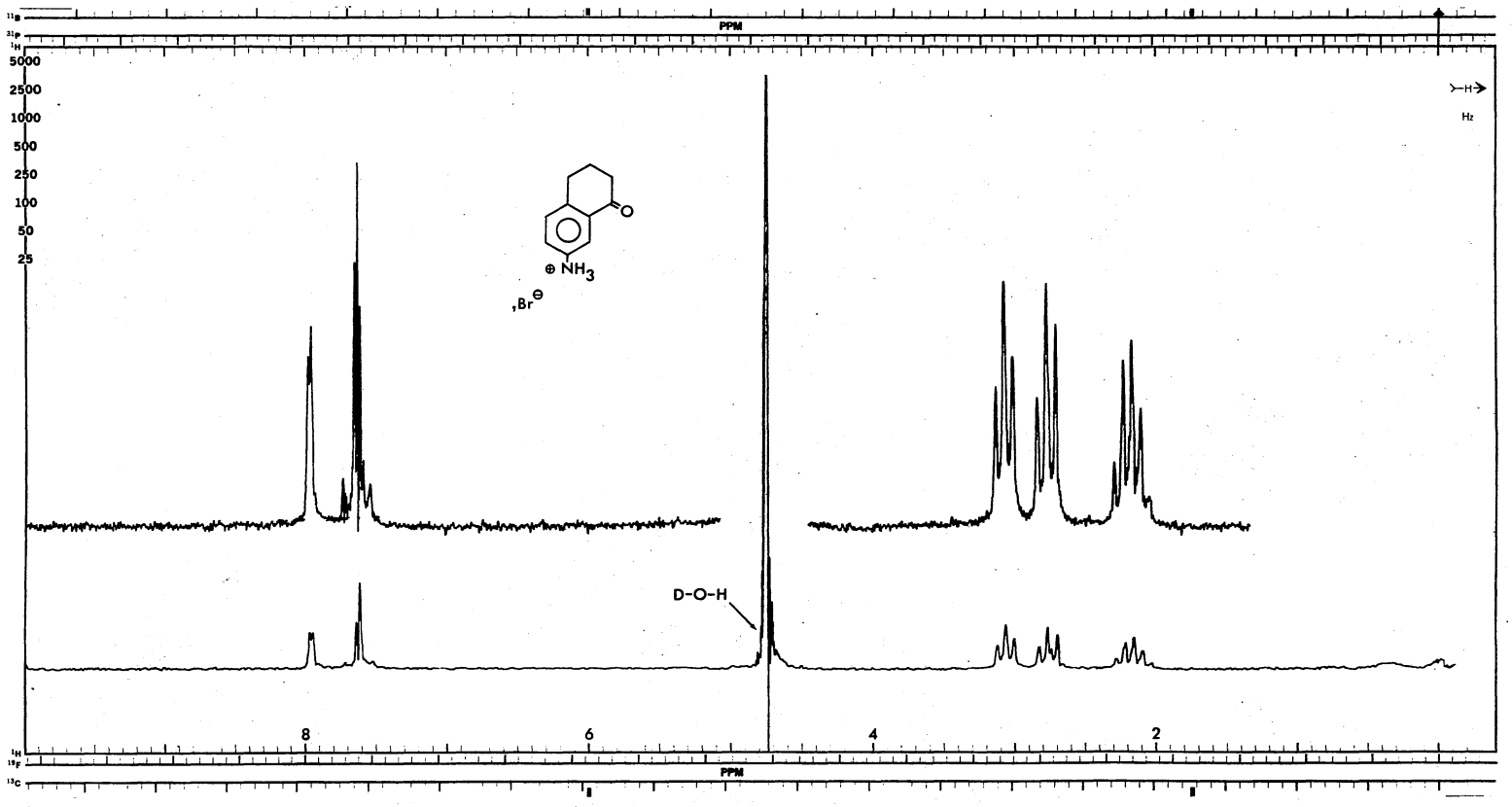
PLATE XXVIII



5,6-Dihydro-8(7H)-oxo-2-naphthylammonium Bromide (47)

Solvent. . . . DMSO-d_6	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . 72 dB	
S.W. . . . . 1000 Hz	S.T. . . . . 250 sec	S.O. . . 83701 Hz	S.A. . . .10.0	Lock. HOMO

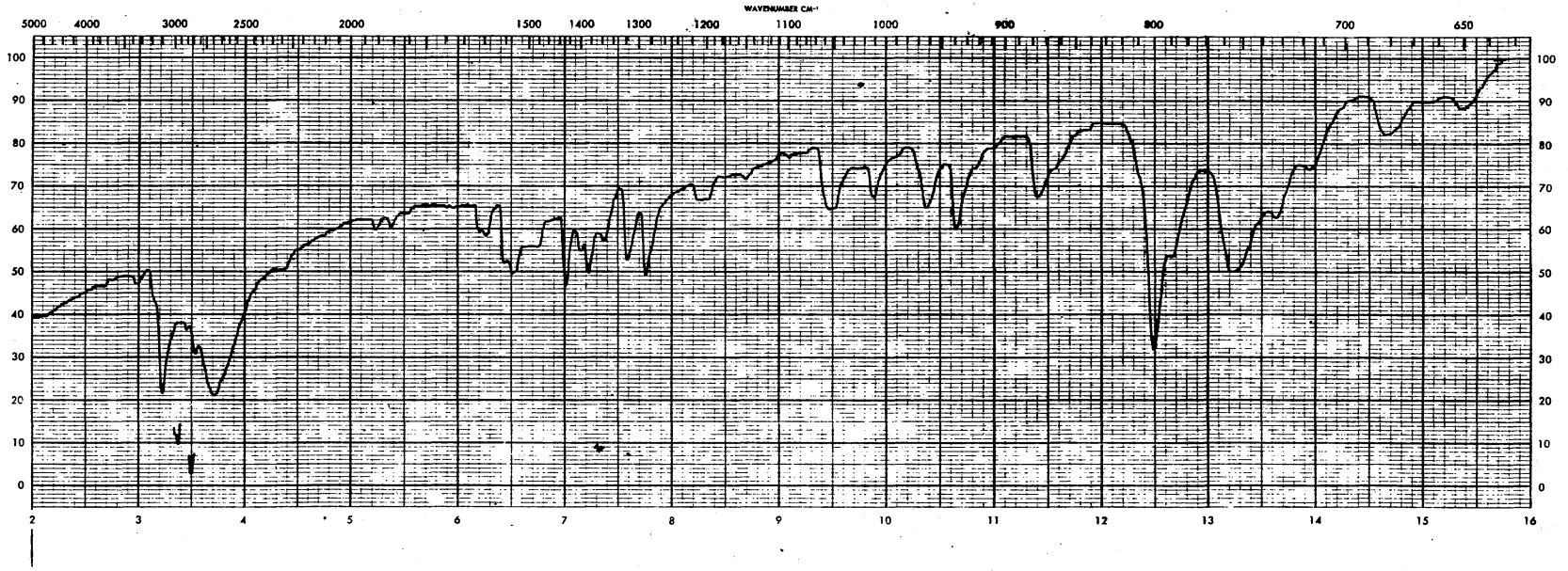
PLATE XXIX



5,6-Dihydro-8(7H)-oxo-2-naphthylammonium Bromide (47)

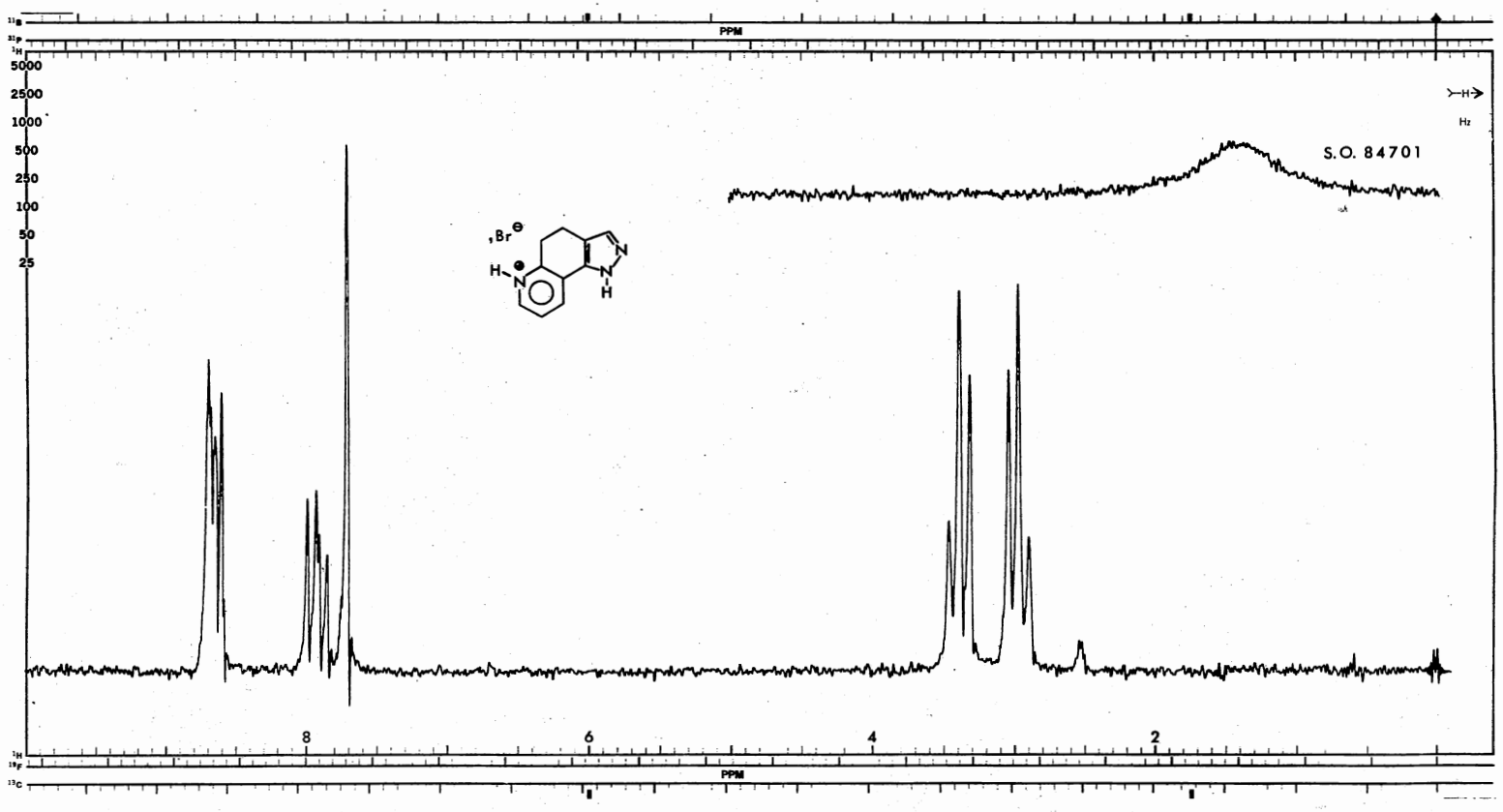
Solvent . . . . . D_2O O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 69 dB
S.W. . . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 86016 Hz S.A. . . . 2.0 Lock . . HOMO

PLATE XXX



4,5-Dihydro-1H-pyrazolo[3,4-f]quinolinium Bromide (49), KBr Pellet

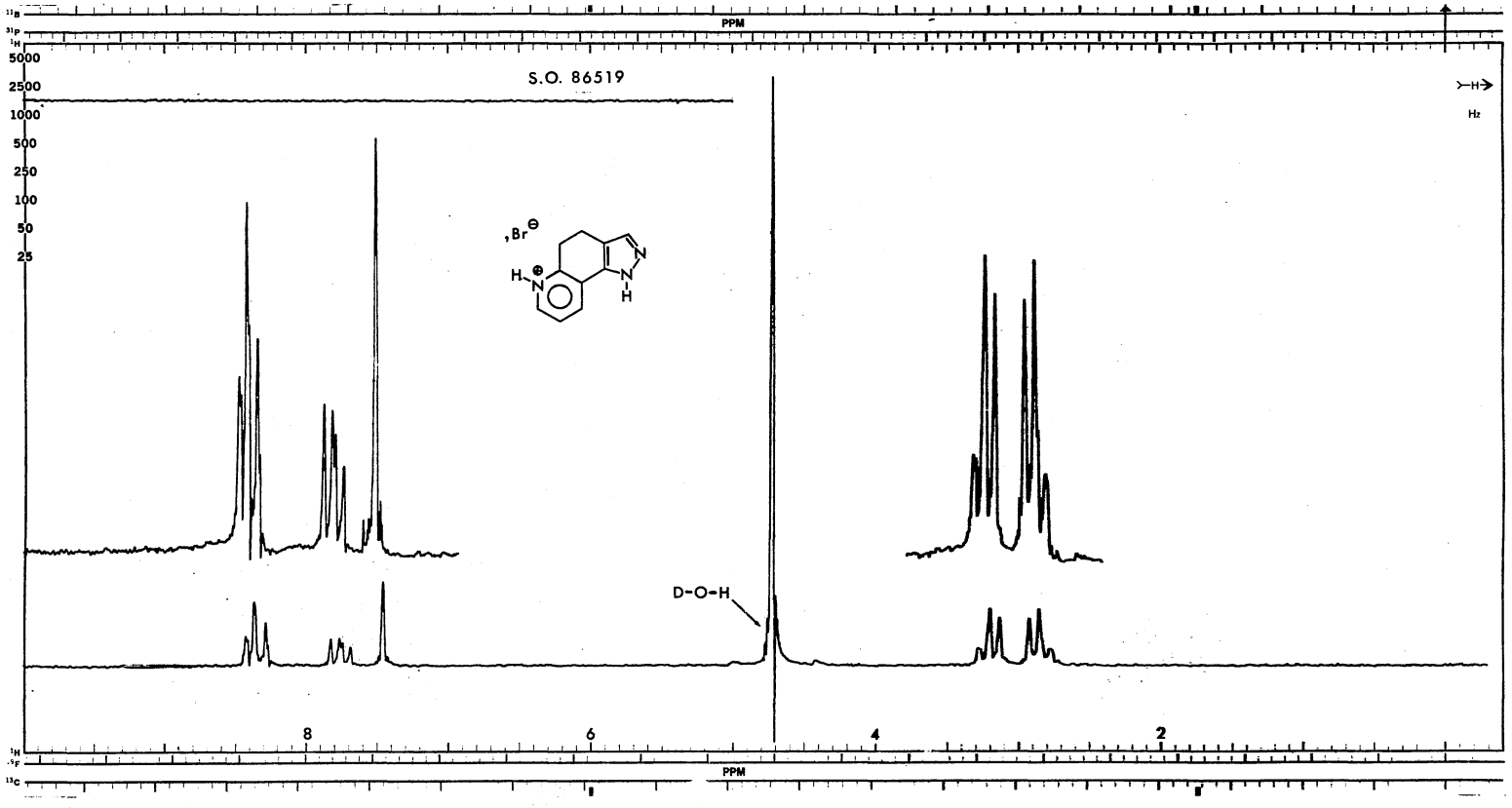
PLATE XXXI



4,5-Dihydro-1H-pyrazolo[3,4-f]quinolinium Bromide (49)

Solvent. . . DMSO-d_6 O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 73 dB
S.W. . . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . 10.0 Lock . . HOMO

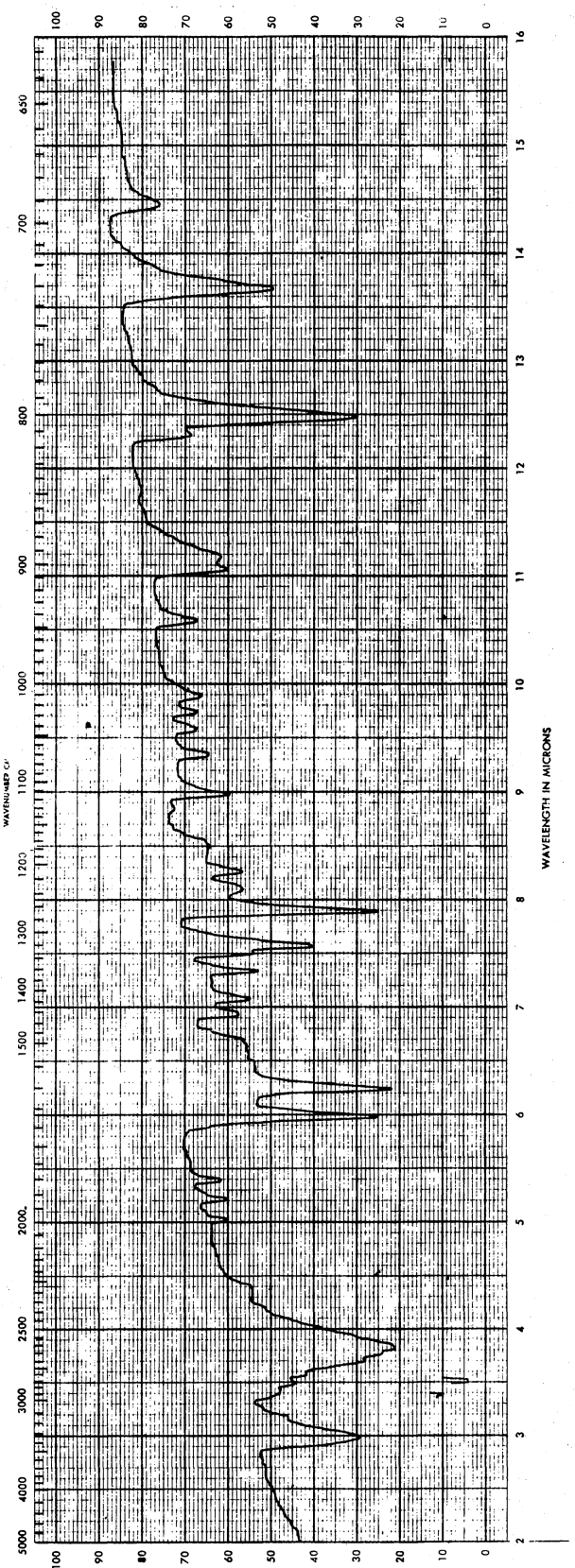
PLATE XXXII



4,5-Dihydro-1H-pyrazolo[3,4-f]quinolinium Bromide (49)

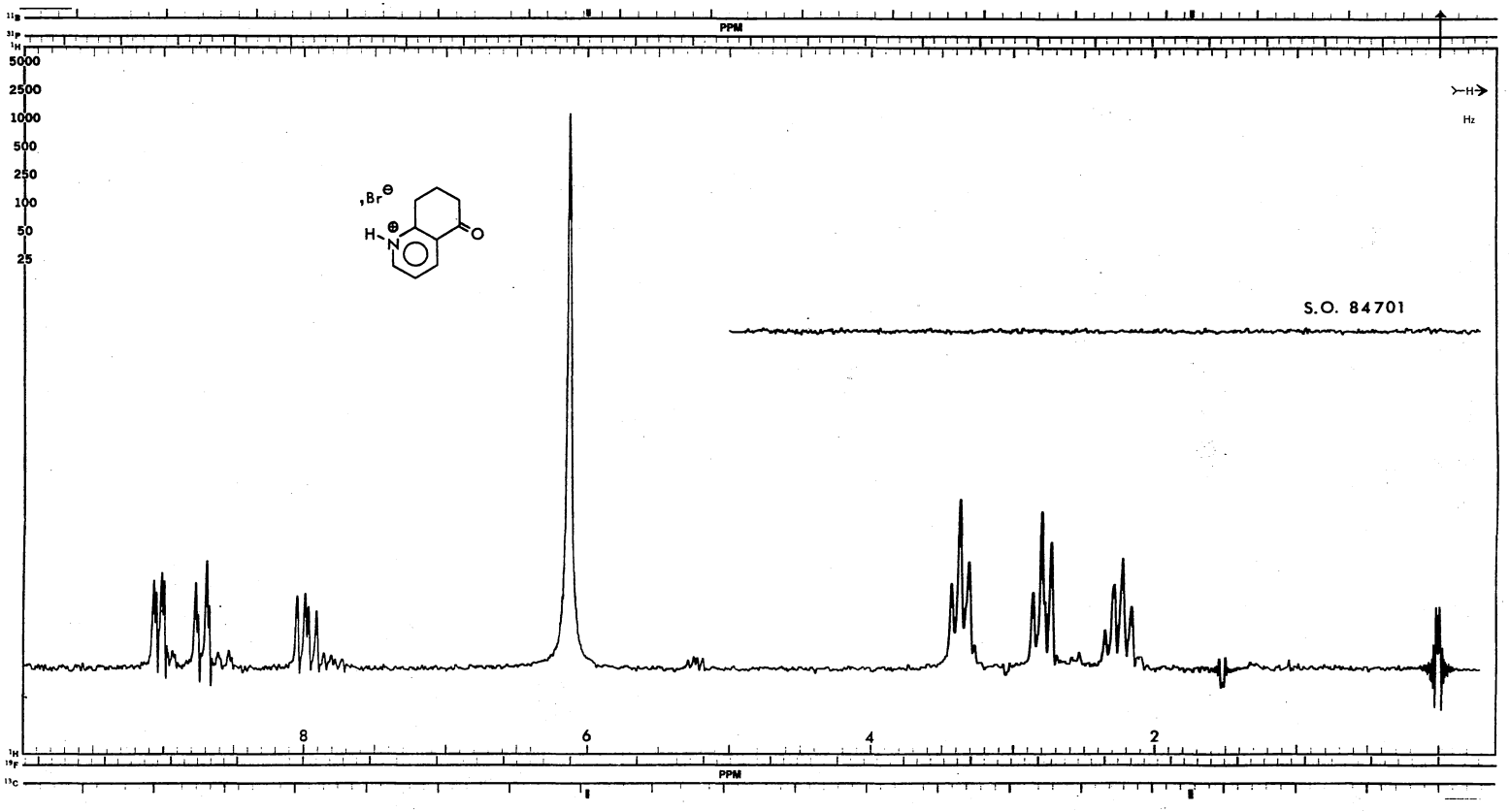
Solvent. . . . D_2O O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . .69 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 86019 Hz S.A. . . 1.25 Lock . . HOMO

PLATE XXXIII



7,8-Dihydro-5(6H)-oxoquinolinium Bromide (45), KBr Pellet

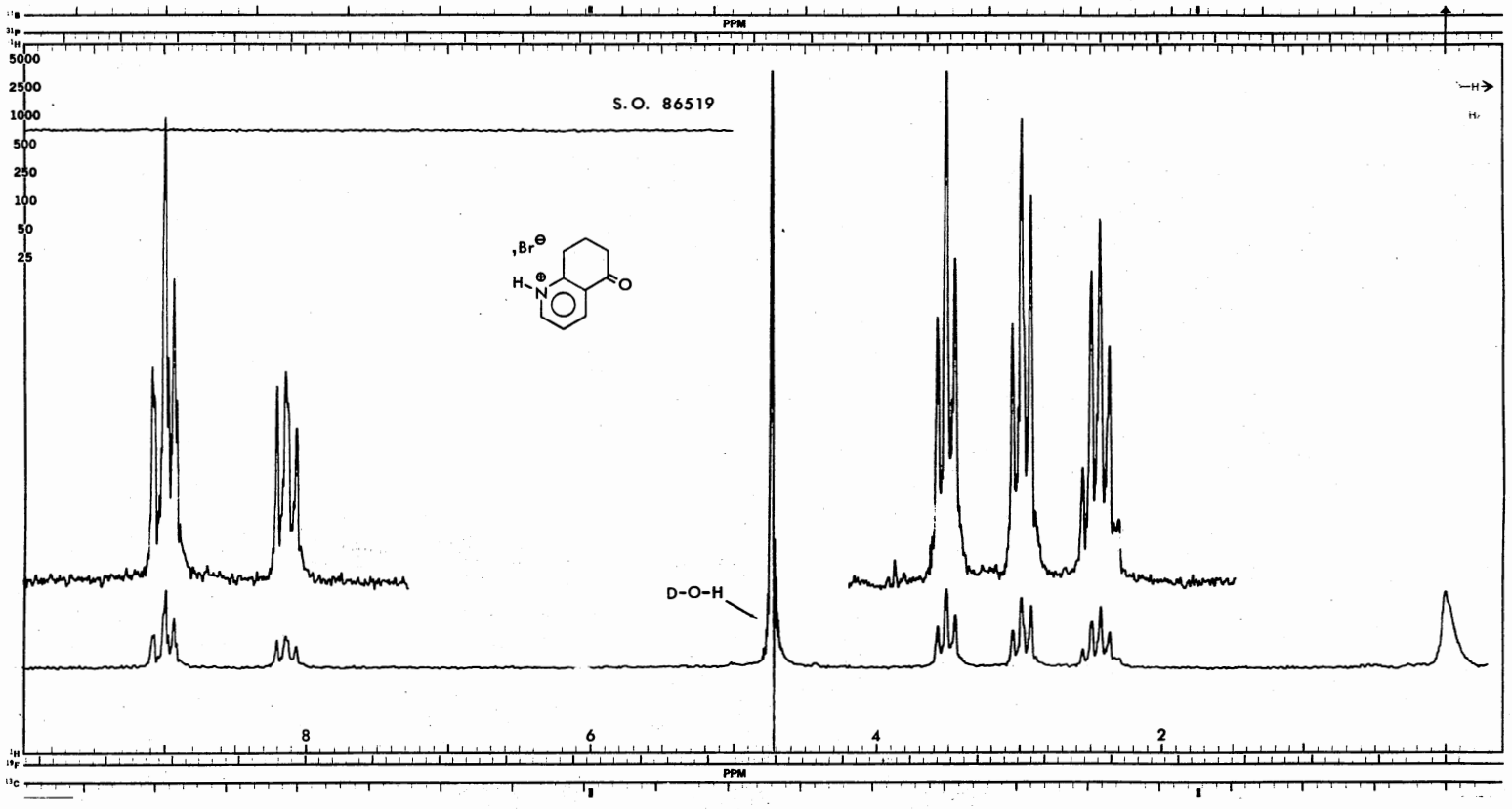
PLATE XXXIV



7,8-Dihydro-t(6H)-oxoquinolinium Bromide (45)

Solvent. . . DMSO-d_6 O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 64 dB
S.W. . . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83731 Hz S.A. . . . 5.0 Lock . . . HOMO

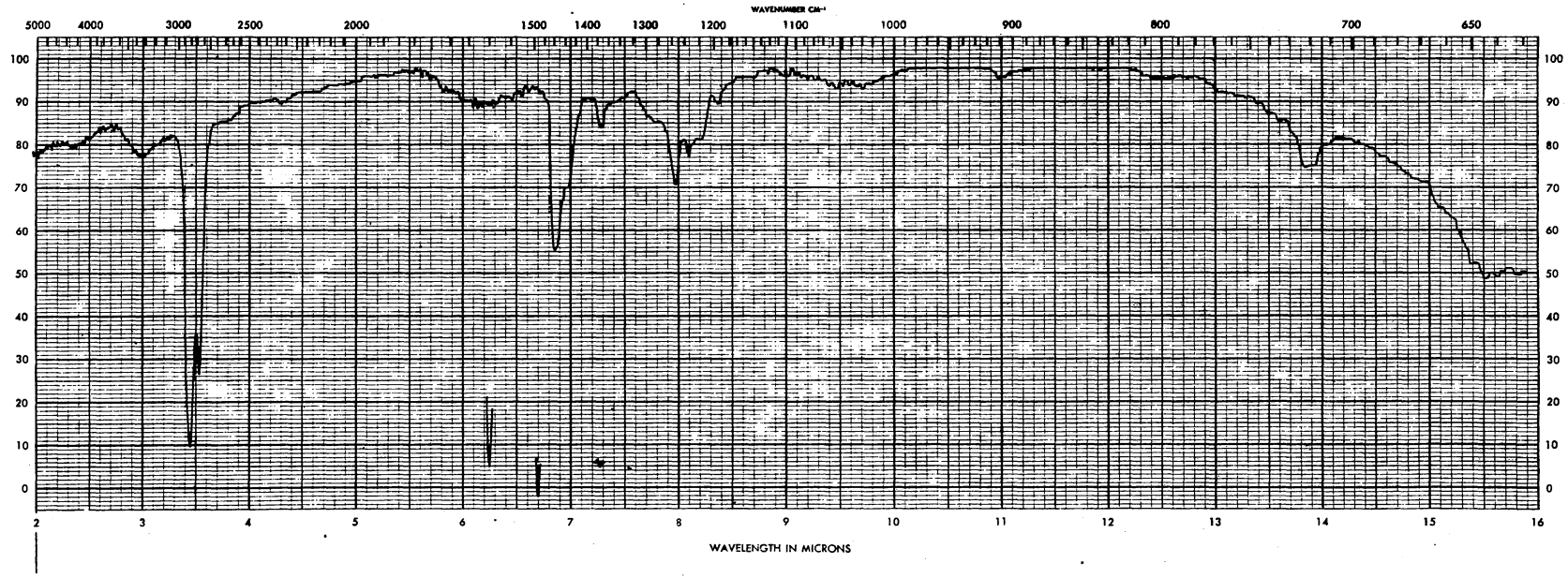
PLATE XXXV



7,8-Dihydro-5(6H)-oxo quinolinium Bromide (45)

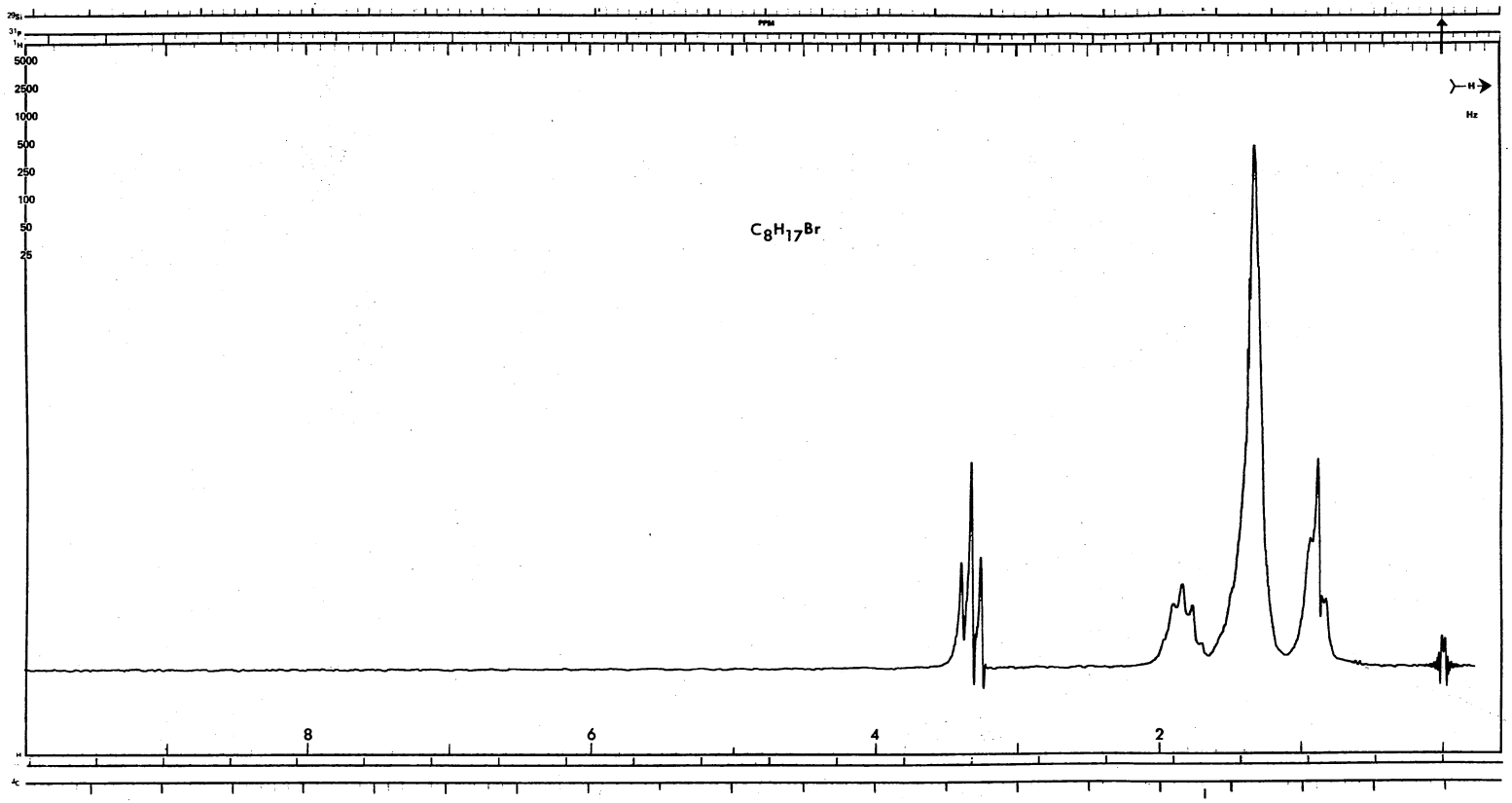
Solvent. . . . D_2O O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 69 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 86019 Hz S.A. . . . 2.0 Lock . . HOMO

PLATE XXXVI



Octyl Bromide ($\underset{\sim}{50}$), Film

PLATE XXXVII



Octyl Bromide (50)

Solvent. . . Neat O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 54 dB
S.W. . . .1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . 1.0 Lock . . HOMO

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