gave the *cis,trans*-anhydride, mp 233–235°, identical with an authentic specimen.

***cis,trans*-α,α′-Dipiperonylidenesuccinic Acid Dimethyl Ester (IIb).**—A solution of diazomethane in ether was added to a suspension of *cis,trans*-α,α′-dipiperonylidenesuccinic acid (0.047 g) in ether (10.0 ml), the mixture was stored at 0° overnight, a few drops of acetic acid was added to destroy excess reagent, and the solvents were removed under reduced pressure. Crystallization of the pale yellow residue (0.046 g) from chloroform–methanol gave pale yellow needles of *cis,trans*-α,α′-dipiperonylidenesuccinic acid dimethyl ester: mp 205–207°; ν_{max} 1727 (C=O), 1230 (CO), 907 (OCH_2O), and 817 (Ph) cm^{-1}; $\lambda_{max}^{dioxane}$ 350 mμ (ε 29,200); δ 6.90 and 6.76 (aromatic CH, singlets) and 6.09 (methylenedioxy CH_2, singlet).

Anal. Calcd for $C_{22}H_{18}O_8$: C, 64.39; H, 4.42. Found: C, 64.53; H, 4.20.

***cis,trans*-α,α′-Dipiperonylidenesuccinic Acid Monoethyl Ester (IId).**—A suspension of *cis,trans*-α,α′-dipiperonylidenesuccinic anhydride (0.107 g) in ethanol (20.0 ml)–benzene (20.0 ml) containing 1 drop of concentrated sulfuric acid was refluxed for 4 days. The solution was decanted from some unchanged *cis,trans*-anhydride (0.022 g), and worked up as described for the *trans,trans*-monoethyl ester to afford crude, light yellow product (0.054 g), mp 220–225° (prior melting at 155°). Crystallization from benzene gave pale yellow needles of *cis,trans* half acid ethyl ester: mp 224–227°; neut equiv 422; ν_{max} 3500 (OH), 1710 (C=O), 1250 (CO), 913 (OCH_2O), and 801 (Ph) cm^{-1}; $\lambda_{max}^{ethanol}$ 346 mμ (ε 26,900).

Anal. Calcd for $C_{22}H_{18}O_8$: C, 64.39; H, 4.42. Found: C, 64.67; H, 4.57.

The *cis,trans* half acid ethyl ester was heated at 150° in an open tube for 30 min, during which the color changed from yellow to red. Crystallization of the product from benzene gave the *cis,trans*-anhydride, mp 231–232°, identical with an authentic specimen.

***cis,trans*-α,α′-Dipiperonylidenesuccinic Acid Monomethyl Ester (IIe).**—A few drops of concentrated sulfuric acid was added to a suspension of *cis,trans*-α,α′-dipiperonylidenesuccinic anhydride (0.100 g) in methanol (100 ml) and the mixture was refluxed for 24 hr. Concentration of the solution caused separation of a small quantity of unchanged *cis,trans*-anhydride (mp 229–230°), which was removed by filtration. The filtrate was diluted with water and extracted with ether, and the dried (sodium sulfate) extract was evaporated to give a semicrystalline, yellow solid (0.061 g), mp 216–221° (turns orange at 120°). Crystallization from chloroform–methanol gave yellow prisms of *cis,trans*-α,α′-dipiperonylidenesuccinic acid monomethyl ester: mp 218–223° (with prior color change); δ 6.85 (aromatic CH, multiplet), 6.62 and 6.50 (aromatic CH, singlets), 6.07 (methylenedioxy CH_2, singlet), 3.79 (ester CH_3, singlet), and 3.27 (solvate CH_3, singlet.

Anal. Calcd for $C_{21}H_{16}O_8 \cdot CH_3OH$: C, 61.68; H, 4.71. Found: C, 61.96; H, 4.47.

Treatment of the above *cis,trans*-monomethyl ester (0.034 g) with an ethereal solution of diazomethane gave the *cis,trans*-dimethyl ester, mp 202–204°, identical with an authentic specimen.

6,7-Methylenedioxy-1-(3′,4′-methylenedioxyphenyl)naphthalene-2,3-dicarboxylic Acid Anhydride (III). A. Bromine Cyclization of *cis,trans*-α,α′-Dipiperonylidenesuccinic Anhydride.—A solution of bromine (0.104 g) in dioxane (2.0 ml) was added to a solution of *cis,trans*-α,α′-dipiperonylidenesuccinic anhydride (0.053 g) in dioxane (10.0 ml), the mixture was allowed to stand overnight at room temperature, water was added, and the product was extracted with ether. Removal of the ether from the washed and dried extract gave a semicrystalline solid, which on two recrystallizations from chloroform–methanol yielded yellow crystals of 6,7-methylenedioxy-1-(3′,4′-methylenedioxyphenyl)-naphthalene-2,3-dicarboxylic acid anhydride, mp 220–226°, identical with an authentic specimen (lit.[16,33] mp 226°, 246°).

B. Thermal Cyclization.—Solid *cis,trans*-α,α′-dipiperonylidenesuccinic anhydride (4.0 g) was heated at about 270° (refluxing ethyl cinnamate) for 1.5 hr, then triturated with ether to form a dark product (3.0 g), mp 210–215°. This material was dissolved in chloroform–benzene and chromatographed on silica gel (50.0 g). Elution with the same solvent mixture gave pale yellow crystals (1.0 g), mp 224–226°, which were recrystallized from chloroform to yield the naphthalenic anhydride, mp 230–231°.

C. Bromine Cyclization of *trans,trans*-α,α′-Dipiperonylidenesuccinic Anhydride.[35]—A solution of the yellow *trans,trans* anhydride (0.05 g) in dioxane (10.0 ml) was treated with bromine as in A above. Crystallization of the product from chloroform–methanol gave yellow crystals of the naphthalenic anhydride (0.019 g), mp 229–231°.

Acknowledgment.—The authors wish to thank the National Science Foundation (G-14528) and the National Institutes of Health (GM-12120-02) for financial support.

(35) We are indebted to Miss Carol Deutsch for this experiment.

Nuclear Magnetic Resonance Studies of Spiro[tetralin-1,4′-piperidine] Compounds

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Received October 21, 1965

The nmr spectra of unreported 7-methoxy-1′-methyl-2-oxospiro[tetralin-1,4′-piperidine] (I), its salts, and the corresponding alcohol (III) have been measured in a variety of solvents, and the results have been analyzed using a provisional first-order approach. Model compounds have been used to assist in the analysis, as well as temperature, decoupling, and deuteration experiments. Unusual chemical shift data have been used to study conformational equilibria in this series of molecules. The nmr spectrum of compound I hydrochloride, measured in deuteriochloroform, showed an aromatic proton selectively deshielded 24 cps compared with the aromatic protons of the free base I. In compound I hydrochloride measured in aprotic solvents the 3′,5′-equatorial protons of the piperidine ring appeared at higher field than the corresponding axial ones.

The unreported 1′-alkyl-2-oxospiro[tetralin-1,4′-piperidine] ring system (*e.g.*, compound I) was synthesized,[2] and several salts and derivatives were prepared for a nuclear magnetic resonance (nmr) study that is the subject of this paper.

Compound I was prepared in a straightforward though rather specific fashion from 7-methoxy-2-tetralone, bis(2-chloroethyl)methylamine, and potassium tertiary butoxide in dimethyl sulfoxide under nitrogen (eq 1). 2-Tetralone behaved similarly forming 1′-methyl-2-oxospiro[tetralin-1,4′-piperidine] (II). Ketone I was reduced with sodium borohydride to the corresponding alcohol (III) which was converted to its acetyl derivative (IV). Hydrolysis of compound I

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(2) Some of the spiro compounds of this series were synthesized for their evaluation as analgesics. Compound V was found to be inactive at 100 mg/kg in the preliminary tail burn analgesic test when administered by intraperitoneal injection to rats. This inactivity compared with the open-chain piperidine analog 4-(3-hydroxyphenyl)-1-methyl-4-propionylpiperidine (see C. M. Suter in "Medicinal Chemistry," Vol. II, F. F. Blicke and C. M. Suter, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 227) is ascribed to the rigidity of the spiro structure in compound V.

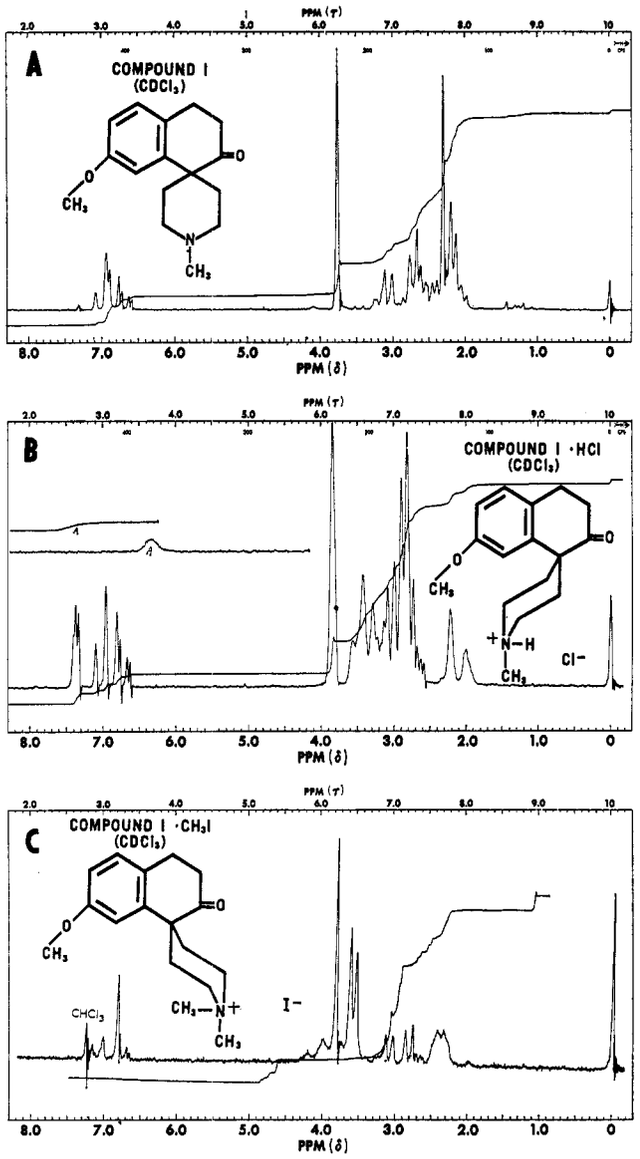
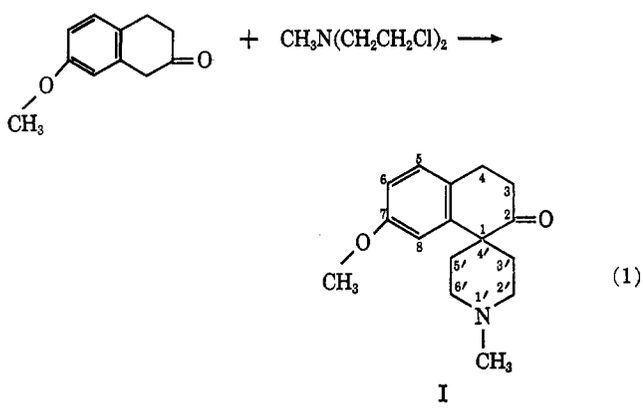


Figure 1.—Nmr spectra of spiro[tetralin-1,4′-piperidine] compounds.

with hydroiodic acid gave 7-hydroxy-1′-methyl-2-oxospiro[tetralin-1,4′-piperidine] hydroiodide (V).



(1)

I

Structural assignments of the spiro compounds are in agreement with the physical measurements. The infrared spectrum of compound I, although more complex, shows most of the major bands of the starting tetralone, and the titration data and nmr spectrum (Figure 1A) substantiated the structure.

The hydrochloride salt of compound I measured in deuteriochloroform (Figure 1B) displayed two unusual features. The aromatic proton at the 8 position[3] compared with the free base was shifted downfield 28 cps whereas the 5 and 6 protons were shifted downfield only about 4 cps. In addition, a pair of equatorial protons appeared alone upfield.

The equatorial pattern resulting from adjacent methylenes in substituted cyclohexanes has been discussed by others[4] and is in agreement with the coupling predicted from the Karplus equation.[5]

The equivalent equatorial protons at positions 3′,5′ give rise to a doublet as a result of a geminal coupling of approximately 12–15 cps, together with fine structure arising from a coupling of 2–4 cps with each of the vicinal protons at the 2′,6′ positions. In most examples[4,6] the geminal axial proton absorbs at higher field than the equatorial counterpart with the result that the upfield portion of the doublet is the more intense. When the axial proton is downfield from the geminal equatorial proton, then the shape of the doublet is reversed as in our example and that of De Jongh and Wynberg.[7]

In contrast with the spectrum of compound I hydrochloride measured in deuteriochloroform, the spectrum obtained in the protic solvents, deuterium oxide or methanol-d_4, was quite similar to that of the free base I.

The selective paramagnetic shift[8a] of the 8 proton of compound I hydrochloride measured in deuteriochloroform is clearly not due to inductive factors through bonds but must be due to a spatial magnetic anisotropy or an electric field effect.[9] Likewise, the high-field equatorial proton pattern, which is contrary to the general finding that axial protons appear at higher field than do equatorial ones in cyclohexanes[8b] and piperidines[6] must be due to spatial proximity magnetic factors.

In an attempt to explain these observations, the nmr spectra of compounds I–V and their salts were studied.

The shift values for 7-methoxy-2-tetralone were used as a model for the assignment of protons at positions 3 (τ 7.46 m) and 4 (τ 6.97 m) and the spectrum of the alcohol (III) was correlated with that of the reference alcohol 7-methoxy-1,2,3,4-tetrahydro-2-naphthol. The alcohol III hydrochloride was quite insoluble in chloroform but was soluble in dimethyl-d_6 sulfoxide; so, for comparison purposes, other salts were measured

(3) The aromatic protons of compound I are readily identified because the *ortho* and *meta* couplings in such a system give very characteristic patterns.

(4) (a) J. I. Musher, *J. Chem. Phys.*, **34**, 594 (1961); (b) E. W. Garbisch, Jr., and D. B. Patterson, *J. Am. Chem. Soc.*, **85**, 3228 (1963).

(5) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *cf.* M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963).

(6) "High Resolution NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1963. Spectra No. 477–479 clearly show equatorial (essentially a doublet governed by J_{gem}) and axial (basically a triplet due to couplings $J_{gem} \simeq J_{aa}$) patterns for α protons of piperidines and also show that axial protons appear at higher field than do the geminal equatorial ones in this system. Although $\Delta\nu/J$ is considerably less than six, the shape of the axial and equatorial patterns are essentially unchanged from 60 to 100 Mc.

(7) H. A. P. De Jongh and H. Wynberg [*Tetrahedron*, **21**, 515 (1965)] reported the equatorial protons α to the carbonyl at higher field than the axial ones (see assignments their Figure 1) and cited references to this phenomenon for cyclohexanones.

(8) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959: (a) p 51, (b) p 116, (c) p 99.

(9) A. D. Buckingham, *Can. J. Chem.*, **38**, 300 (1960); J. I. Musher, *J. Chem. Phys.*, **37**, 34 (1961); S. Yamaguchi, S. Okuda, and N. Nakagawa, *Chem. Pharm. Bull.* (Tokyo), **11**, 1465 (1963).

TABLE I

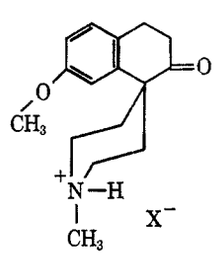
NMR ASSIGNMENTS OF SPIRO[TETRALIN-1,4′-PIPERIDINE] COMPOUNDS AT ROOM TEMPERATURE

Compound	Solvent	Proposed equilibrium condn[a]	Proton position (τ) 8	1′	2′	3′
7-Methoxy-2-tetralone[b]	$CDCl_3$	N	3.28 d			
I	$CDCl_3$	N	3.10 d	7.71 s	~7.5	~7.9 t
I·HCl	$CDCl_3$	F_1	2.62 d	7.15 d	6.5–6.7	7.8 d (eq) ~7.0 (ax)
I·HCl	D_2O	N	3.04 d	6.97 s	6.4 m	7.6 m
I·CH_3I	$CDCl_3$	G_1	3.16 d	6.35 and 6.43	5.9 (eq)	7.6 m
II	$CDCl_3$	N		7.67 s	~7.5	~7.8
II·HCl	$CDCl_3$	F_1	2.25 m	7.13 d	~6.5 m	8.0 (eq)
7-Methoxy-1,2,3,4-tetrahydro-2-naphthol[c]	$CDCl_3$		3.41 s			
III	$CDCl_3$	E	3.02 d	7.67 s		
III·HCl	DMSO-d_6	F_2	2.91 d	7.25 d	6.7 m	~7.7 (eq) ~8.2 (ax)

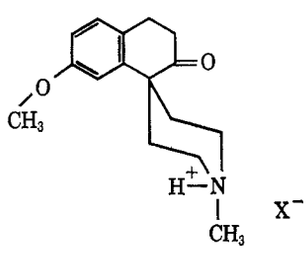
[a] N = ring equilibrating rapidly and equilibrium not in favor of one conformation. F_1 = ring B as in N and ring C equilibrium predominately in favor of the F conformation. G_1 = ring B as in N and ring C equilibrium predominately in favor of the G conformation. E = 2 function of ring B predominately axial. F_2 = ring B as in E and ring C as in F_1. [b] The signal for the protons at the 1 position is τ 6.42 s. [c] The signal for the protons at the 1 position is τ 7.17 m. The resonance for the proton at the 2 position (τ 5.9) was broad (18 cps at half-peak height) suggesting that the equilibrium favored the hydroxyl (τ 7.47 s) equatorial. The 3- and 4-proton shifts were at τ 8.12 m and 7.17 m, respectively.

in that solvent. It was hoped that the spectrum of the alcohol III hydrochloride would clearly show that the ketone of compound I hydrochloride was responsible for the deshielding of the 3′,5′-axial protons in nonprotic solvents. Shift assignments for the alcohol (III) and its acetyl derivative, however, were less distinctive than for the ketone (I), and, as a result, deuteration experiments were done to assist in the analysis.

The rings of the spiro system (I) are designated A, B, and C, representing the aromatic, the fused ketone, and the piperidine rings, respectively. By virtue of the symmetry of the spiro molecules the 3′ and 5′ protons are magnetically equivalent in *cis* pairs as are the 2′ and 6′ protons. Considering only the chair form for ring C, the two conformations of compound I·HX are represented by structures F and G, such designation being arbitrarily assigned. In structure F the 1,2 bond is equatorial at the 4′ position of the piperidine ring. Stuart–Briegleb and Dreiding models show conformer G to be less sterically hindered than conformer F.



F



G

Structure F has the charged nitrogen center relatively near to the 8 proton. Models also show the 3′,5′-axial protons are more in the deshielding region of the carbonyl[10] as well as being closer to the charged nitrogen center than are the 3′,5′-equatorial ones. At the position where the plane of the aromatic ring perpendicularly bisects the piperidinium ring, the two equivalent 3′- and 5′-equatorial protons fall near the neutral magnetic region of the aromatic ring.[11]

(10) See ref 8, p 124. Since ring B is equilibrating, the structure midway between the equilibrating forms was used for this consideration.

Structure F could well have two distinctive features: (a) the 8 proton could be deshielded through space by the charged nitrogen center, and (b) the 3′,5′-axial protons could be deshielded preferentially by the carbonyl to an extent that they resonate below the 3′,5′-equatorial ones, *and thus offer an explanation for the original observations made on compound I hydrochloride.*

Structure G, analyzed in a similar fashion, has the nitrogen atom considerably removed from the aromatic ring, and the 3′,5′-axial protons are outside the influence of the carbonyl function.

Throughout this paper A_2B_2 patterns for the proton pairs of ring B have been interpreted as arising from the ring being in rapid equilibration. When the 3′,5′ protons and the 2′,6′ protons of ring C appeared as unresolved envelopes, the equilibrium was presumed not to be in favor of one conformation. Such conditions have arbitrarily been assigned the symbol N. When the 3′,5′-equatorial pattern was upfield, then the equilibrium was interpreted as being in favor of conformation F and the conformational equilibrium has been designated F_1. When the 3′,5′-equatorial proton pattern was not upfield and 2′,6′-equatorial pattern was discernible, then the equilibrium was interpreted as being in favor of conformation G and the condition has been designated G_1. Other equilibrium conditions are defined in footnote *a* of Table I.

The nmr assignments of Table I were made using a provisional first-order approach.

Results and Discussion

Selected shift assignments and conformational equilibrium designations are given in Table I.

Ring A.—The aromatic protons 5 and 6 fell within narrow shift values and appeared as a doublet ($J_{6,5}$ = 7.8 cps) and a quartet ($J_{5,6}$ = 7.8 cps, $J_{8,6}$ = 2.5 cps), respectively. The protons of the methoxyl group at the 7 position fell within a narrow range, but the shift of the hydrochloride salt of compound I measured in chloroform was downfield 7 cps compared with the

(11) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

value for compound I. The 8 proton occurred as a doublet ($J_{6,8}$ = 2.5 cps). The spectrum of compound I hydroiodide measured in deuteriochloroform was almost identical with that of the corresponding hydrochloride. Studies were done to help evaluate the importance of anion concentration on the remarkable 8-proton shift in nonprotic solvent from free base I to the hydrochloride salt. In the first it was shown that the shift of all of the aromatic protons of a 20% solution of compound I hydrochloride in methanol-d_4 was unchanged when saturated with hydrogen chloride gas. In the second experiment it was found that the 8 proton was shifted upfield 5 cps when a 20% solution ($\cong$0.7 M) of compound I hydrochloride, measured in 95% dimethyl-d_6 sulfoxide–5% deuterium oxide mixture,[12] was diluted to 3% concentration (0.1 M). Simultaneously, the 5- and 6-proton resonances and the 7-methoxy proton resonances were essentially unchanged, but the N-methyl resonance was moved upfield 2 cps. In this dilution experiment the 8-proton resonance did not move upfield beyond that of the 5 proton. The 5-cps change was relatively small compared with 28 cps, and considering the results of the first experiment, it was concluded that the ion-pair concentration does not play the major role in the observed deshielding of the 8 proton.[13]

Ring C.—The nmr spectra for the free bases measured in deuteriochloroform and for certain salts measured in protic solvents (shift assignments Table I) displayed unresolved upfield multiplets that were assigned to the 2′,6′ and 3′,5′ protons of the piperidinium ring C.

Temperature studies on the free base of compound I measured in deuteriochloroform at 37 and 60° showed sharp peaks that indicated that both rings B and C were in rapid equilibration. At −37°, however, the upfield proton signals that arose from the piperidine ring began to coalesce and were seen as a rounded peak, while the protons associated with 3 and 4 positions of ring B were still sharp multiplets. Under these conditions ring B was still in rapid equilibration and ring C was equilibrating slowly.[8c]

The spectra of compound I hydrochloride, measured in deuteriochloroform at 60° or in dimethyl-d_6 sulfoxide at 120°, were essentially unchanged compared with those at normal probe temperature, but in deuteriochloroform at −36° the peaks attributed to ring C were somewhat rounded. This indicated that for compound I hydrochloride in nonprotic solvents, at room temperature, ring C was in rapid equilibration. Since the 3′,5′-equatorial protons were at highest field, the equilibrium was largely in favor of conformation F.

The spectrum of compound I hydrochloride, measured in deuterium oxide at room temperature, showed the four 3′,5′ protons as a multiplet that became somewhat sharper triplets at 90° indicating that ring C was in rapid equilibration, and the position of the equilibrium at room temperature was condition N.

Spin–spin decoupling experiments on compound I hydrochloride dissolved in deuteriochloroform showed that the 3′,5′-axial protons were centered 57 cycles below the 3′,5′-equatorial ones. The protons at the 3 position overlap the 3′,5′-axial protons in the spectrum of compound I hydrochloride measured in deuteriochloroform (Figure 1B). The spectrum of 3,3-dideuterio compound I hydrochloride permitted assignment of the 3′,5′-axial protons that was in close agreement with the decoupling data. This spectrum also permitted an accurate assignment of the 4 protons that appeared as a sharp singlet τ 6.94. The 3′,5′-equatorial shift for compound I hydrochloride measured in deuteriochloroform was τ 7.8 (J_{gem} = 12 cps).

Compound I Methiodide.—The nmr spectrum of compound I methiodide, measured in deuteriochloroform (Figure 1C), was best explained as resulting from the equilibrium of ring C being predominately in favor of the G conformation. It exhibited an equatorial pattern at τ 5.9 attributable to the 2′,6′ protons, but the 3′,5′-axial protons were not preferentially deshielded. There was a pronounced downfield shift of protons on carbon atoms α to nitrogen, but the 8 proton was not deshielded. The two methyl groups on nitrogen appeared at different shifts.[14]

Compound II.—The spectrum of compound II hydrochloride measured in deuteriochloroform had the 3′,5′-equatorial pattern upfield (τ 8.05, J_{gem} = 12 cps) and showed one of the aromatic protons at 15 cps lower field than the others. Based on analogy with the 7-methoxy series, the low-field proton is assigned to the 8 position, although in this molecule the 5 and 8 protons cannot be differentiated by splitting pattern differences.

Compound III.—The alcohol (III) was obtained by reduction of the ketospiro compound (I) using sodium borohydride.[15] The spectrum of compound III, determined in deuteriochloroform, displayed a signal for the 2 proton at τ 5.61 t with a peak width at half height of 7 cps.[16] The 2-proton signal for compound III hydrochloride measured in dimethyl-d_6 sulfoxide–deuterium oxide was likewise a narrow triplet at τ 5.72. The spectrum of the 3,3-dideuterio alcohol III hydrochloride measured in dimethyl-d_6 sulfoxide showed 5-cps coupling between the proton and the hydroxyl at the 2 position,[17] and on addition of deuterium oxide the signal became a sharp singlet at τ 5.70. The two protons at the 4 position were not a sharp singlet as they were in the corresponding deuterated ketone. These facts support the idea that ring B of compound III hydrochloride at room temperature is equilibrating, and the equilibrium is predominately in the form with the hydroxyl quasi-axial. The spectrum of 3,3-dideuterio compound III hydrochloride did not clearly show the axial and equatorial patterns, but the integral indicated that the upper one was more spread out and therefore likely arose from the 3′,5′-axial protons.

Experimental Section[18]

7-Methoxy-1′-methyl-2-oxospiro[tetralin-1,4′-piperidine] (I).—In a three-neck flask equipped with a mechanical stirrer, addi-

(12) The anion concentration effect seemed most likely to be observed under these conditions, since at higher concentration of deuterium oxide in the mixture the 8 proton is shifted to higher field.

(13) R. L. Buckson and S. G. Smith [*J. Phys. Chem.*, **68**, 1875 (1964)] studied concentration effects on the nmr of quaternary ammonium salts.

(14) J. K. Becconsall, R. A. Y. Jones, and J. McKenna [*J. Chem. Soc.*, 1726 (1965)] concluded that of the two N-methyl signals in the spectrum of 1,2-dimethylpiperidine hydrochloride the one at lower field corresponded to the equatorial methyl.

(15) H. O. House, H. Babad, R. B. Toothill, and A. W. Noltes [*J. Org. Chem.*, **27**, 4141 (1962)] studied the stereochemical course of such reductions.

(16) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

(17) O. L. Chapman and R. W. King, *ibid.*, **86**, 1256 (1964).

(18) Melting points were taken with a Fisher-Johns apparatus.

tion funnel, and nitrogen inlet was placed 22 g (0.57 g-atom) of potassium and 500 ml of dry, distilled *t*-butyl alcohol. The mixture was heated to reflux and then stirred at room temperature overnight. Most of the butyl alcohol was removed by being heated on a steam bath under reduced press. About 1 l. of dry dimethyl sulfoxide was added, and dry N_2 was passed through the stirred system. A solution of 44 g (0.28 mole) of freshly distilled bis(2-chloroethyl)methylamine,[19] 50 g (0.28 mole) of freshly distilled 7-methoxy-2-tetralone,[20] and 100 ml of dry *t*-butyl alcohol was added at room temperature over a 1-hr period. Stirring at room temperature was continued overnight. A solution of 50 ml of concentrated HCl and 1 l. of H_2O, followed by 1 l. of ether, was added. The ether layer was removed, dried, and on evaporation yielded 11 g of starting tetralone. The aqueous layer was made strongly basic with Na_2CO_3 and was extracted with five 300-ml portions of ether. The ether solution was then extracted with six 100-ml portions of phosphate buffer, pH 7.0. The pH of the buffer was raised to 9.0, and it was extracted with four 200-ml portions of ether. This ether extract was dried over anhydrous $MgSO_4$ and then was concentrated by being heated on a steam bath. The residue was distilled, using a 24-in. spinning-band column with a column temperature of 160°. The yield of compound I, bp 135° (0.25 mm), was 11 g (15%). The physical data obtained for compound I included titration, $pK_a' = 8.10$ (66% dimethylformamide), and principal bands in the infrared at 3.40, 5.81, 6.18, 6.65, 8.00, and 9.56 μ ($CHCl_3$). *Anal.* Calcd for $C_{16}H_{21}O_2N$: C, 74.09; H, 8.16; N, 5.40. Found: C, 73.90; H, 8.31; N, 5.40.

Salts of Compound I. A. Hydrochloride.—The salt was recrystallized from an EtOH–ether mixture: mp 231–232°; $pK_a' = 8.00$ (66% dimethylformamide); infrared 3.36 s, 4.2 (broad), 5.81, 6.16, 6.79, 7.96, and 10.52 μ, all strong (Nujol mull). *Anal.* Calcd for $C_{16}H_{22}ClNO_2$ C, 64.96; H, 7.50; N, 4.70. Found: C, 64.71; H, 7.75; N, 4.80.

B. Hydroiodide.—The product was recrystallized from EtOH–ether, mp 257–259°. *Anal.* Calcd for $C_{16}H_{22}INO_2$: C, 49.62; H, 5.73; N, 3.62. Found: C, 49.74; H, 5.86; N, 3.47.

C. Methiodide.—The salt melted at 232–233°. *Anal.* Calcd for $C_{17}H_{24}INO_2$: C, 50.88; H, 6.03; N, 3.49. Found: C, 51.11; H, 6.01; N, 3.65.

1'-Methyl-2-oxospiro[tetralin-1,4'-piperidine] (II).—This compound was prepared in a manner analogous to that used for the preparation of compound I starting with β-tetralone.[21] The product was obtained in 10% yield and had the following physical characteristics: bp 114° (0.15 mm); $pK_a' = 8.10$ (66% dimethylformamide); infrared strong bands at 3.41, 5.81, 6.88, 7.22, 7.84, 8.80, 10.04, and 10.60 μ ($CHCl_3$). *Anal.* Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.33; H, 8.33; N, 6.14.

Compound II Hydrochloride.—The salt was recrystallized from an EtOH–ether mixture: mp 217–218°; $pK_a' = 8.05$ (66% dimethylformamide); infrared 3.38 s, 4.2 (broad), 5.82 s, 6.79 s, 8.81 m, 10.21 m, and 10.71 μ ($CHCl_3$). *Anal.* Calcd for $C_{15}H_{20}ClNO$: C, 67.78; H, 7.59; N, 5.27. Found: C, 67.97; H, 7.73; N, 5.14.

2-Hydroxy-7-methoxy-1'-methylspiro[tetralin-1,4'-piperidine] (III).—To a cooled solution of 1 g (4 mmole) of 7-methoxy-1'-methyl-2-oxospiro[tetralin-1,4'-piperidine] hydrochloride and 50 ml of EtOH was added 2 g (5 mmole) of sodium borohydride. The solution was stirred at room temperature overnight and then 5 ml of concentrated NH_4OH was added and stirring was continued an additional 2.5 hr. The solution was concentrated to near dryness and 10 ml of H_2O was added. The solid that formed was collected, and after being dried it was recrystallized from an ether–petroleum ether (bp 60–70°) mixture: mp 181–183°; principal infrared absorption bands, 2.78, 3.41, 3.58, 6.19, 6.66, 7.85, 8.08, 9.59, and 10.45 μ ($CHCl_3$). *Anal.* Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.39; H, 8.97; N, 5.21.

The HCl salt of compound III was recrystallized from an EtOH–ether mixture: mp 242–244°. *Anal.* Calcd for $C_{16}H_{24}ClNO_2$: C, 64.52; H, 8.12; N, 4.70. Found: C, 64.44; H, 8.20; N, 4.80.

2-Acetoxy-7-methoxy-1'-methylspiro[tetralin-1,4'-piperidine] (IV).—A solution of 250 mg of 2-hydroxy-7-methoxy-1'-methylspiro[tetralin-1,4'-piperidine] and 5 ml of Ac_2O was heated on a steam bath for 2 hr. The mixture was concentrated by being heated on a steam bath under reduced pressure. About 10 ml of 10% Na_2CO_3 was added, and the mixture was extracted with three 30-ml portions of $CHCl_3$. The $CHCl_3$ solution was dried using anhydrous $MgSO_4$ and then the solvent was removed by evaporation. The oily residue was dissolved in petroleum ether (bp 60–70°) and gave 75 mg of product, mp 90°. *Anal.* Calcd for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31. Found: C, 70.94; H, 8.58.

The HCl salt of compound IV was formed in a chloroform hydrogen chloride–ether mixture, mp 284–285°.

7-Hydroxy-1'-methyl-2-oxospiro[tetralin-1,4'-piperidine] Hydroiodide (V).—A solution of 2 g of 7-methoxy-1'-methyl-2-oxospiro[tetralin-1,4'-piperidine] and 50 ml of 47% HI was heated under reflux for 4 hr. The solution was concentrated to dryness by being heated on a steam bath under reduced pressure. The residue was recrystallized from EtOH and gave 1 g of product: mp 221–223°; $pK_a' = 8.10$ and 12.50 (66% dimethylformamide); strong infrared absorption bands, 3.02, 3.57, 5.80, 6.16, 6.66, 7.80, 8.13, 9.19, 11.02, 11.50, 11.82, and 12.12 μ (Nujol mull). *Anal.* Calcd for $C_{15}H_{20}INO_2$: C, 48.27; H, 5.40; N, 3.75. Found: C, 48.28; H, 5.55; N, 3.65.

3,3-Dideuterio-7-methoxy-1'-methyl-2-oxospiro[tetralin,1,4'-piperidine] Hydrochloride.—A solution of $NaOCH_3$, formed from 10 mg of Na and 5 ml of methanol-d_1, and 600 mg of 7-methoxy-1'-methyl-2-oxospiro[tetralin-1,4'-piperidine] dissolved in 5 ml of methanol-d_1 was heated in a sealed vial at steam bath temperatures for 5 days. The MeOH was evaporated and fresh methanol-d_1 was added, and heating was continued for another 3 days. After removing the methanol by evaporation, the residue was extracted with 50 ml of dry ether and was filtered. Evaporation of the ether gave a residue that was recyclized according to the above procedure using fresh $NaOCH_3$. The new residue was treated with dry ether containing dissolved HCl. The salt that formed was collected and was recrystallized from EtOH–ether to give product, mp 227–228°.

3,3-Dideuterio-2-hydroxy-7-methoxy-1'-methylspiro[tetralin-1,4'-piperidine] Hydrochloride.—About 300 mg of the deuterated ketone described above was dissolved in 25 ml of EtOH and was reduced with 100 mg of sodium borohydride according to the procedure for the undeuterated material. The free base (150 mg) melted at 180–182°, and the HCl salt was recrystallized from a $CHCl_3$–ether mixture, mp 240°. The nmr spectrum showed a high deuterium incorporation.

7-Methoxy-1,2,3,4-tetrahydro-2-naphthol.—7-Methoxy-2-tetralone[20] was reduced with sodium borohydride in the usual manner and gave product, mp 67–69° (lit.[22] mp 71°).

Nmr Measurements.—The nmr spectra were measured with either a Varian A-60 or a Varian HA-60 spectrometer. Shifts are reported in τ units downfield from internal tetramethylsilane or Tier's salt. Solution concentration, unless otherwise noted, was approximately 7 to 10% weight per volume.

Acknowledgments.—This study would not have been possible without the cooperation of the individuals who determined the nmr spectra and did the temperature and decoupling investigations. It is a pleasure to acknowledge the help of J. L. Spahr, P. W. Landis, and L. Spangle. We also wish to acknowledge helpful discussion with R. A. Archer, L. G. Tensmeyer, J. C. Martin, and R. W. King. The microanalyses were done by W. L. Brown, H. L. Hunter, and C. Ashbrook. Analgesic screening was performed by J. A. Miller, Jr.

(19) Freshly generated from the hydrochloride salt prepared according to the method of K. A. Jansen and F. Lundquist, *Dansk Tidsakr. Farm.*, **15**, 201 (1941); *Chem. Abstr.*, **37**, 2337 (1943). Care should be taken when working with this compound as it is a vesicant.

(20) M. E. Keuhne, *J. Am. Chem. Soc.*, **83**, 1492 (1961).

(21) M. D. Soffer, M. P. Bellis, H. E. Gellerson, and R. A. Stewart, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons Inc., New York, N. Y., 1963, p 903.

(22) A. Windaus, *Ber.*, **57**, 1731 (1924).