Preparation of 1-methyl-4-phenyl-4-piperidyldiphenylcarbinol (VIII). An ethereal solution of 0.06 mole of phenyllithium and 1.1 g. (0.004 mole) of 1-methyl-4-phenyl-4-piperidyl phenyl ketone (VII) was heated under reflux for 12 hr. The mixture was poured into 20 ml. of concentrated hydrochloric acid and 50 g. of ice causing the precipitation of 1.3 g. (76.5%) of 1-methyl-4-phenyl-4-piperidyldiphenylcarbinol hydrobromide (VIIIa),[14] m.p. 220–225°.

Reduction of Ia with sodium borohydride. A solution of 10 g. of Ia in 50 ml. of methanol was treated with 4 g. of sodium borohydride in 30 ml. of methanol. A precipitate formed and was removed by filtration to give 1.5 g. of XVII. Removal of the solvent from the filtrate and addition of water to the residue gave an additional 4.42 g. of XVII for a total yield of 5.9 g. (76%) of XVII. The compound could not be purified by recrystallization; however, the material from the reaction mixture, m.p. 104–105°, gave the correct analytical values for carbon and hydrogen.

Anal. Calcd. for $C_{13}H_{15}BrNO$: C, 54.94; H, 6.38. Found: C, 55.16; H, 6.63.

An attempt to recrystallize a sample of XVII gave, on evaporation of the ethanol, a water soluble oil. Neutralization of the aqueous solution deposited an oil which formed an oily methiodide, a picrate (m.p. 199–201°), and an oxime (m.p. 188–190°). These melting points correspond to those of derivatives of 1-methyl-4-piperidyl phenyl ketone (III) as did the carbonyl stretching frequency (1675 cm.$^{-1}$) in the infrared absorption spectrum.[9]

Reduction of IIa with sodium borohydride. A solution of 1 g. of IIa in 7 ml. of methanol was treated with 0.3 g. of sodium borohydride. The solid which precipitated was removed by filtration to give 0.5 g. of XXI, m.p. 139–141°. Evaporation of the filtrate without heating and addition of water caused the precipitation of an additional 0.24 g. of XXI, m.p. 138–140°. The combined yield of XXI represented 85% of the starting IIa. The identity of the compound was confirmed as XXI by mixture melting point determination with an authentic sample,[9] m.p. 140.0–140.5°.

Reduction of Ia with lithium aluminum hydride. A suspension of 20.0 g. of Ia in ether was added to 4.0 g. of lithium aluminum hydride suspended in ether. After heating under reflux for 2 hr., water was added cautiously. The ether was separated from the inorganic precipitate, and the solid was washed with additional ether. Evaporation of the ether gave 11.2 g. of oily residue. Addition of petroleum ether to the oil caused the precipitation of 6.1 g. (55.5%) of 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenylcarbinol (XVI), m.p. 107–108°, which gave no depression of melting point when mixed with an authentic sample.[12]

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.78; H, 8.43. Found: C, 76.83; H, 8.51.

The petroleum ether solution remaining from the isolation of XVI was concentrated, and the residue was allowed to stand for 3 weeks to remove the remaining traces of XVI by decomposition. At the end of this time the 4.55 g. of oily residue was fractionally distilled under reduced pressure to give four fractions all boiling at about 115–126° at 7 mm. weighing a total of 3.5 g. This material was shown to be 1-methyl-4-benzylidene piperidine (XVII), $\lambda_{max}^{96\%\ EtOH} = 243\ m\mu$ ($\log \epsilon = 3.962$), contaminated with XVI and possibly XI.[15]

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.39; H, 9.16. Calcd. for $C_{13}H_{17}NO$: C, 76.78; H, 8.43. Found: C, 82.00; H, 8.70.

The reaction of 0.15 g. of impure XVI with methyliodide gave, after recrystallization from acetone, 0.06 g. of XVI methiodide, m.p. 213–215°.

Anal. Calcd. for $C_{14}H_{20}IN$: C, 51.06; H, 6.12; N, 4.26. Found: C, 51.83; H, 6.26; N, 3.71.

Hydrogen bromide was added to a sample of 1.05 g. of impure XVI to give a hydrobromide, which was recrystallized twice from acetone yielding 0.3 g. of pure XVI hydrobromide, m.p. 199–201°, $\lambda_{max}^{95\%\ EtOH} = 241\ m\mu$ ($\log \epsilon = 4.163$).

Anal. Calcd. for $C_{13}H_{18}BrN$: C, 58.20; H, 6.75; N, 5.22. Found: C, 58.68, 58.52; H, 6.82, 6.58; N, 4.99.

Catalytic hydrogenation of XVI methiodide. A solution of 0.3 g. of XVI methiodide in 75 ml. of methanol was reduced over Raney nickel at 100 atm. of pressure of hydrogen. After 1 hr. the reduction was stopped, and the mixture was filtered to remove the catalyst. Evaporation of the solvent and trituration of the residue with acetone gave 0.2 g. of 1-methyl-4-benzylpiperidine methiodide, m.p. 208–210°. A mixture of this methiodide with an authentic sample melted at 208–209°.

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(15) From several reactions an impure solid, m.p. about 115–140°, was isolated. The material could not be purified by recrystallization, but since the melting point was higher than that of XVI, the solid was thought to be 1-methyl-4-piperidylphenylcarbinol (XI).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEW HAMPSHIRE]

A New Series of Potential Local Anesthetics

ROBERT E. LYLE, HENRY J. TROSCIANIEC,[1] AND GLENN H. WARNER[1]

Received July 9, 1958

A series of esters of 1-alkyl-4-aroyl-4-piperidinols has been prepared by the acidolysis of epoxy ethers. The esters have been screened for physiological activity and have been shown to produce local anesthesia. The irritability of the compounds precludes the usefulness of these compounds as local anesthetics.

Esters of 4-piperidinols have been shown to have pharmacological, as well as structural, similarities to the natural local anesthetic, cocaine,[2,3] and recently the esters of substituted 4-phenyl-4-piperidinols were demonstrated to be potent analgesics.[4] On the basis of Stevens' preparations

(1) Abstracted from the theses of HJT and GHW to be submitted to the Graduate School of the University of New Hampshire in partial fulfillment of the degree of Doctor of Philosophy.

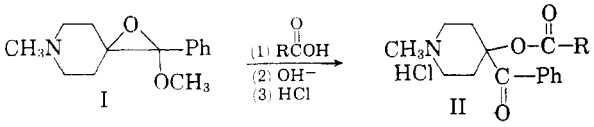
(2) S. M. McElvain, *J. Am. Chem. Soc.*, **46**, 1721 (1924).

(3) T. P. Carney, *Record Chem. Progr.*, **15**, 143 (1954).

(4) R. H. X. Foster and A. J. Carman, *J. Pharmacol. Exptl. Therap.*, **91**, 195 (1947). K. A. Jensen and F. Lundquist, *Dansk. Tids. Farm.*, **17**, 173 (1943); *Chem. Abstr.*, **39**, 2506 (1945). K. A. Jensen, U. S. Patent **2,589,943** (March 18, 1952); *Chem. Abstr.*, **46**, 11249 (1952). A. Ziering, L. Berger, S. D. Heineman, and J. Lee, *J. Org. Chem.*, **12**, 894 (1947).

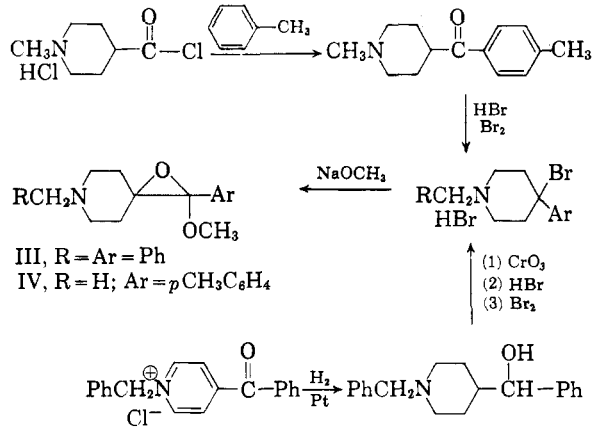
of esters of hydroxy ketones from epoxy ethers,[5] the synthesis of 2-methoxy-6-methyl-2-phenyl-1-ox-6-azaspiro[2.5]octane (I)[6] provided a method for preparing a series of esters (II) of 1-methyl-4-benzoyl-4-piperidinol, which are related structurally to the above esters.

The conversion of the epoxyether (I) to esters of simple organic acids was accomplished with ease by mixing a solution of I with the organic acid in ether and collecting the organic acid salt of the amino ester which precipitated. The amine was freed from this salt and converted to the desired mineral acid salt by conventional methods. Attempts to prepare the corresponding esters from amino acids by this method failed; such reactions gave the parent hydroxy ketone (XV). The esters of the amino acids did form, however, when pyridine was used as the solvent.



I II

The promising results of the early pharmacological screening led to the expansion of the series of esters to include a number of esters of 1-benzyl-4-benzoyl-4-piperidinol (V) and 1-methyl-4-*p*-toluyl-4-piperidinol (X). These compounds were prepared by the same general procedures as used in the synthesis of the esters of 1-methyl-4-benzoyl-4-piperidinol (II).[6]



III, R = Ar = Ph
IV, R = H; Ar = *p*-$CH_3C_6H_4$

The only step which was questionable in these syntheses was the Friedel-Crafts acylation of toluene with 1-methylisonipecotyl chloride hydrochloride. That *para* substitution occurred, as would be predicted, was confirmed by the infrared absorption spectra of the derived epoxyether (IV) and the esters produced from IV. The absorption due to out-of-plane bending of the aromatic C—H bonds was at 823 cm.$^{-1}$, which is characteristic of *para* disubstituted benzenes and not the *ortho* isomers.[7]

Preliminary results of pharmacological tests. The esters VI–XVII (see Table I) were screened for local anesthetic action by the corneal irrigation and the infiltration methods. On the basis of the activity in both tests the more potent esters were the benzoates, IX and XVII. The *p*-aminobenzoate analog (XII) of XVII was much less active than XVII, which is surprising in view of the local anesthetic action of other esters of this amino acid.[3]

The data in Table I do not indicate any overall structure-activity relationships; however, in general, replacement of the 4-benzoyl by 4-*p*-toluyl gave esters of higher potency (compare XIV and XI, XV and X, and XVII and IX). Except for the benzoate (VIII), the esters of 1-benzyl-4-benzoyl-4-piperidinol (V) were more active than the corresponding derivatives of the 1-methyl-4-piperidinols, XV and X. The esters of V, however, formed salts of low solubility in water and thus could not be evaluated completely as to activity. This decreased solubility perhaps accounts for the lack of anesthetic action of VIII in the corneal irrigation procedure, for this lack of activity was unexpected in view of the high potency of the benzoates, IX and XVII, relative to this series.

All of the esters produced signs of irritation and thus the local anesthetic action is of no practical use. The esters of 1-benzyl-4-benzoyl-4-piperidinol (V) were significantly more irritating than those of the other two piperidinols.

The possibility that these compounds might have pharmacological activity of some other type was also investigated. 1-Methyl-4-benzoyl-4-piperidinol methobromide and 1-methyl-4-benzoyl-4-piperidyl benzoate hydrochloride (XVII) were screened for analgesic effects, and 1-methyl-4-benzoyl-4-piperidinol hydrochloride (XV) was tested for antispasmodic action and hypothermia. All of the tests indicated no activity in these areas.

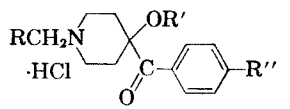
XV and XVII caused a rapid decrease in the blood pressure of test animals, and the animals recovered quickly from the effects of XV. XVII gave little change in heart rate. Neither of these compounds was successful in relieving hypertension.

The antispasmodic action of diphenylacetic

(5) C. L. Stevens and Bruce V. Ettling, *J. Am. Chem. Soc.*, **77**, 5412 (1955) and preceding papers.

(6) R. E. Lyle, S. A. Leone, H. J. Troscianiec, and G. H. Warner, *J. Org. Chem.*, **24**, 330 (1959).

(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, 1954.

TABLE I. 

R	R′	R″	Yield, %	M.P., °C.	Formula	Analyses: Calcd. Element, %	Analyses: Found Element, %	Corneal Irrigation (Rabbit): Conc., %	Corneal Irrigation (Rabbit): Anesthesia, min.	Infiltration (Guinea Pig): Conc., %	Infiltration (Guinea Pig): Anesthesia, min.
VI Ph	CH_3CH_2CO	H	20[a]	246–249	$C_{22}H_{26}ClNO_3$	Cl, 9.22	Cl, 9.71	1	26[c]	0.05	29[d]
VII Ph	CH_3CO	H	39[a]	265–267	$C_{21}H_{24}ClNO_3$	Cl, 9.49	Cl, 9.53	1	17[c]	0.05	30[d]
VIII Ph	PhCO	H	41[a]	220–222	$C_{26}H_{26}ClNO_3$	Cl, 7.95	Cl, 8.13	2	0[c]	0.05 (0.1)	9 (87)[d]
IX H	PhCO	CH_3	69[a]	255–256	$C_{21}H_{24}ClNO_3$	Cl, 9.48	Cl, 9.47	0.4	25[c]	0.05	20[e]
X H	H	CH_3	See Experimental					1	23[f]	0.5 (0.25)	26 (9)[d]
XI H	CH_3CH_2CO	CH_3	68[a]	231–233	$C_{17}H_{24}ClNO_3$	Cl, 10.86	Cl, 10.73	1	8[c]	0.25	21[d]
XII H	p-$NH_2C_6H_4CO$	H	86[b]	179–180	$C_{22}H_{22}N_2O_3$[g]	C, 70.98; H, 6.71	C, 70.67; H, 6.61	1	15[c]	0.5 (0.25)	16 (12)[d]
XIII H	4-C_5H_4N-CO	H	85[b]	126–128	$C_{19}H_{20}N_2O_3$[g]	C, 70.38; H, 6.22	C, 70.21; H, 6.07	2	0[c]	0.25	37[d]
XIV H	CH_3CH_2CO	H	85[a]	254–255 dec.	$C_{16}H_{22}ClNO_3$	C, 61.64; H, 7.11; Cl, 11.37	C, 61.44; H, 7.34; Cl, 11.45	1	2[g]	1	14
XV H	H	H	Ref. 6					1	0[g]	0.25	25[h]
XVI H	$PhCONHCH_2CO$	H	39[a]	170 dec.	$C_{22}H_{25}ClN_2O_4$	Cl, 8.51	Cl, 8.41	1	60[g]	0.25 (0.1)	56 (12)[h]
XVII H	PhCO	H	85[a]	256–258 dec.	$C_{20}H_{22}ClNO_3$	Cl, 9.86	Cl, 10.00	1	33[g]	0.1 (0.05)	72 (14)[i]

[a] These compounds were prepared by Procedure *A*. [b] These compounds were prepared by Procedure *B*. [c] Mild irritation was noted at these concentrations. [d] No irritation was noted at these concentrations. [e] As in [b], however, greater concentration produced necrosis at the site of injection. [f] No irritation was observed at this concentration, but greater concentration produced mild irritation. [g] These corneal irrigation tests were determined using guinea pig's eye. [h] Irritation was slight when determined using rabbit skin. [i] Irritation was negligible when determined using rabbit skin.

acid esters of amino alcohols[8] suggested the synthesis and screening of 1-methyl-4-benzoyl-4-piperidyl diphenylacetate methobromide (XVIII). This compound as well as the hydrochloride showed no spasmolytic action, however.

EXPERIMENTAL

1-Methyl-4-benzoyl-4-piperidyl benzoate. A solution of 0.3 g. of 2-methoxy-6-methyl-2-phenyl-1-ox-6-azaspiro[2.5]-octane (I) in 10 ml. of ether was added to 0.25 g. of benzoic acid in 10 ml. of ether. After standing 3 hr., the solution was concentrated, and the residue crystallized on standing. The solid was recrystallized from ether–petroleum ether to give 0.5 g. (88%) of the benzoic acid salt of 1-methyl-4-benzoyl-4-piperidyl benzoate, m.p. 128–130°.

Anal. Calcd. for $C_{27}H_{27}NO_5$: C, 72 79; H, 6 11. Found: C, 72.16, 72.07; H, 6.17, 6.16.

A solution of 0.1 g. of the benzoic acid salt in water-methanol was neutralized with sodium carbonate, precipitating an oil which crystallized on standing. The solid on recrystallization from petroleum ether gave 0.06 g. (68%) of the base of XVII, m.p. 112–114°.

Anal. Calcd. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55. Found: C, 74.02, 74.23; H, 6.45, 6.49.

Preparation of 4-piperidinol esters. Procedure A. A solution of 1 mole of the epoxyether (I, III, or IV) and the organic acid, in excess of 2 moles (about 2.2 moles) in ether was allowed to stand for 12 hr. The solvent was removed by evaporation, and a solution of the residue in water was neutralized with base. The amine which precipitated was isolated by filtration, dried, and dissolved in anhydrous ether. Treatment of the ether solution with anhydrous hydrogen chloride caused the precipitation of the hydrochlorides listed in Table I.

Procedure B. A solution of 0.028 mole of the amino acid in 25 ml. of pyridine was added to 0.013 mole of the epoxy-ether (I) in 50 ml. of ether. After standing for 12 hr., the solution was concentrated, and the residue was dissolved in water. Addition of sodium carbonate to the water solution caused the precipitation of the amino acid esters listed in Table I.[9]

1-Methyl-4-benzoyl-4-piperidyl diphenylacetate. An ether solution of 4.0 g. of diphenylacetic acid and 2.2 g. of I was treated as in Procedure A to give 1.3 g. (34.9%) of the base of XVIII, m.p. 122–124°.

Anal. Calcd. for $C_{27}H_{27}NO_3$: C, 78.43; H, 6.58. Found: C, 78.54; H, 6.51.

The base of XVIII was converted to the hydrochloride in ether-acetone, and the salt was recrystallized from ethyl acetate–methanol giving *1-methyl-4-benzoyl-4-piperidyl diphenylacetate hydrochloride*, m.p. 246–248°.

Anal. Calcd. for $C_{27}H_{28}ClNO_3$: Cl, 7.88. Found: Cl, 8.02.

The base of XVIII was converted to the *methobromide* (XVIII) by methyl bromide in methanol. Recrystallization from ethyl acetate–methanol gave pure XVIII, m.p. 245–247°.

Anal. Calcd. for $C_{28}H_{30}BrNO_3$: Br, 15.72. Found: Br, 15.74.

1-Methyl-4-piperidyl p-tolyl ketone hydrobromide. The 1-methylisonipecotic acid hydrochloride (22.7 g., 0.14 mole) obtained from the hydrochloric acid hydrolysis of 20.0 g. of methyl 1-methylisonipecotate[6] was heated under reflux with 100 ml. of thionyl chloride for 2 hr., and the excess thionyl chloride was removed by distillation under reduced pressure. The residual solid was suspended in 150 ml. of anhydrous toluene, and 50 g. of anhydrous aluminum chloride was added in portions. The reaction mixture was heated for 10 hr., and, after cooling, was poured into 200 ml. of 10% hydrochloric acid and 100 g. of ice. The toluene was removed by steam distillation, and the remaining aqueous acidic solution was extracted with 300 ml. of ether which was discarded. The aqueous layer was made basic by the addition of solid sodium hydroxide, and the amine was removed by extraction with three portions of ether. The ether extracts were dried over anhydrous sodium carbonate, and gaseous hydrogen bromide was introduced. The solid which precipitated was collected by filtration and recrystallized from isopropyl alcohol giving an 82% yield of 1-methyl-4-piperidyl *p*-tolyl ketone hydrobromide, m.p. 217.5–219.5°.

Anal. Calcd. for $C_{14}H_{20}BrNO$: Br, 26.80. Found: Br, 26.86, 26.69.

1-Methyl-4-bromo-4-piperidyl p-tolyl ketone hydrobromide. A chloroform solution of 18.7 g. of 1-methyl-4-piperidyl *p*-tolyl ketone was treated with 9 ml. of bromine, and the mixture was allowed to stand overnight. The solvent and excess bromine were removed by distillation under reduced pressure. The residual solid was dissolved in methanol, and phenol was added to remove the perbromide-bromine.[6] On addition of ether 19.65 g. (96%) of 1-methyl-4-bromo-4-piperidyl *p*-tolyl ketone hydrobromide precipitated. The melting point was 157–158° after recrystallization from acetone.

Anal. Calcd. for $C_{14}H_{19}Br_2NO$: 1-Br, 21.19. Found: Br, 21.25, 21.13.

1-Methyl-4-p-toluyl-4-piperidinol hydrochloride (X). A solution of 19.6 g. of 1-methyl-4-bromo-4-piperidyl-*p*-tolyl ketone hydrobromide in methanol was added to a solution of sodium methoxide prepared from 8.5 g. of sodium in 100 ml. of methanol. The mixture was heated under reflux for 1 hr., and most of the methanol was removed by distillation under reduced pressure. Water was added, and the remaining methanol was removed by warming the solution under reduced pressure. The aqueous layer was extracted with ether, and the extracts were dried over sodium carbonate. Removal of the ether by distillation gave 9.0 g. (87%) of 2-methoxy-6-methyl-2-*p*-tolyl-1-ox-6-azaspiro[2.5]octane (IV), b.p. 135–140° at 3 mm.

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.87; H, 8.56. Found: C, 73.07; H, 8.72.

The infrared absorption spectrum of IV had no bands between 3100 and 4000 cm.$^{-1}$ or between 1650 and 1800 cm.$^{-1}$ indicating the absence of an hydroxyl and a carbonyl group, respectively. Strong bands at 1280 and 1220 cm.$^{-1}$ due to the epoxide ring and at 1075 cm.$^{-1}$ indicative of an aliphatic ether confirmed the epoxyether function. The strong band at 823 cm.$^{-1}$ and lack of absorption at 750 cm.$^{-1}$ showed that the aromatic ring was *para*-disubstituted.[7]

The addition of 3.2 g. of IV to dilute hydrochloric acid gave the crude base of X on neutralization with sodium carbonate. 1-Methyl-4-*p*-toluyl-4-piperidinol, after recrystallization from ethyl acetate, was dissolved in ether, and dry hydrogen chloride was added. Recrystallization of the precipitated solid from acetone gave 2.5 g. of pure X, m.p. 223–225°.

Anal. Calcd. for $C_{14}H_{20}ClNO_2$: Cl, 13.14; N, 5.19. Found: Cl, 13.23, 13.28; N, 5.07, 5.12.

1-Benzyl-4-benzoylpyridinium chloride. A solution of 18.3 g. of 4-benzoylpyridine and 12.6 g. of benzyl chloride in 200 ml. of methanol was heated under reflux for 12 hr. Concentration of the solution gave 24.6 g. (82%) of the pyridinium salt, m.p. 186–188°.

Anal. Calcd. for $C_{19}H_{16}ClNO$: Cl, 11.45. Found: Cl, 11.37.

1-Benzyl-4-piperidylphenylcarbinol hydrochloride. A solution of 15 g. of 1-benzyl-4-benzoylpyridinium chloride in methanol was reduced by hydrogenation at 3 atm. over platinum catalyst to give, after removal of the solvent, 14.8 g. (90%) of 1-benzyl-4-piperidylphenylcarbinol hydrochloride, m.p. 184–185°.

(8) J. H. Biel, H. L. Friedman, H. A. Leiser, and E. P. Sprengler, *J. Am. Chem. Soc.*, **74**, 1485 (1952). R. R. Burtner and J. W. Cusic, *J. Am. Chem. Soc.*, 65, 262 (1943).

(9) The esters of amino acids were isolated and characterized as the base rather than the hydrochloride since the analyses of the salts indicated incomplete conversion to the dihydrochloride.

Anal. Calcd. for $C_{19}H_{24}ClNO$: Cl, 11.20. Found: Cl, 11.75, 11.77.

1-Benzyl-4-piperidyl phenyl ketone hydrobromide. A solution of 17 g. of 1-benzyl-4-piperidylphenylcarbinol hydrochloride and 4.1 g. of chromic acid in 200 ml. of acetic acid was heated on the steam bath for 1 hr. The solvent was removed by distillation under reduced pressure, and the residue was dissolved in chloroform. The solution was saturated with anhydrous hydrogen bromide, and the chloroform was removed by evaporation. The residue was recrystallized from isopropyl alcohol to give 12 g. (77%) of 1-benzyl-4-piperidyl phenyl ketone hydrobromide, m.p. 235–238°.

Anal. Calcd. for $C_{19}H_{23}BrNO$: Br, 22.18. Found: Br, 22.05.

1-Benzyl-4-bromo-4-piperidyl phenyl ketone hydrobromide. A suspension of 12 g. of 1-benzyl-4-piperidyl phenyl ketone hydrobromide in chloroform was treated with 2.5 ml. of bromine, and the mixture was allowed to stand overnight. The solvent was removed by distillation, and the residue was dissolved in methanol. Phenol was added to remove the perbromide-bromine,[6] and 13 g. (88%) of 1-benzyl-4-bromo-4-piperidyl phenyl ketone hydrobromide, m.p. 162–164°, precipitated as a white solid on addition of ether.

Anal. Calcd. for $C_{19}H_{23}Br_2NO$: 1 Br, 18.20. Found: Br, 18.29.

6-Benzyl-2-methoxy-2-phenyl-1-ox-6-azaspiro[2.5]octane (III). To a solution of 13.5 g. of sodium methoxide in 150 ml. of methanol was added 11 g. of 1-benzyl-4-bromo-4-piperidyl phenyl ketone hydrobromide. The solution was heated under reflux for 4 hr., and the solvent was removed by distillation under reduced pressure. The residue was distilled under reduced pressure to give 6.5 g. of 6-benzyl-2-methoxy-2-phenyl-1-ox-6-azaspiro[2.5]octane (III), b.p. 170–175° at 2 mm., which on treatment with organic acids in ether gave the esters in Table I.

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.63; H, 7.49. Found: C, 77.60, 77.78; H, 7.39, 7.52.

Acknowledgment. The authors wish to express appreciation to the National Heart Institute of the National Institutes of Health for partial support of this research under grant Number H-1713. The authors further thank the pharmaceutical companies which assisted in the screening program and in particular the assistance of Dr. K. K. Chen of Eli Lilly and Co.

DURHAM, N. H.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEW HAMPSHIRE]

Hydrates of 1-Methyl-3- and -4-piperidone Hydrochlorides[1]

ROBERT E. LYLE, ROBERT E. ADEL,[2] AND GLORIA G. LYLE

Received July 9, 1958

The salts of 1-methyl-4-piperidone and 1-methyl-3-piperidone have been shown to crystallize with one molecule of water from solvents which contain water. The infrared absorption spectra of these hydrates clearly prove that the water is present as the hydrate of the carbonyl group. The preparation of 1-methyl-3-piperidone by a novel synthesis is reported.

The addition of water to the carbonyl group of aldehydes or ketones leads to stable hydrates in only a few cases. Those examples of stable hydrates that are known have in common one or more strongly electron-attracting groups attached to the carbonyl, and this structural feature is considered necessary for a stable hydrate. The formal positive charge of an amine salt, therefore, would be expected to stabilize the hydrate of a carbonyl located in the same molecule. Although stable hydrates of salts of amino-ketones have not been demonstrated, ketals have been reported to be formed by the reaction of 4-piperidone hydrochloride,[3b] 1-alkyl-4-piperidone quaternary salts,[4] and 1-alkyl-4-piperidone hydrochlorides[5] with alcohol. This reaction is promoted by the positive charge in the salt; however, the strain inherent in a tercovalent carbon within a six-membered ring[6] alone appears to provide the driving force for the formation of the ketal. Thus, unlike other ketones which undergo partial reaction with alcohols by addition,[7] cyclohexanone is converted to the ketal.[8] Since 1-methyl-4-piperidone hydrochloride

(1) This paper was presented in part before the Division of Organic Chemistry of the American Chemical Society, at the 130th meeting at Atlantic City, N. J., September 16–21, 1956. This research was supported in part by grant H-1713, National Heart Institute, National Institutes of Health, Bethesda 14, Md.

(2) Abstracted in part from the Thesis of REA submitted to the Graduate School of the University of New Hampshire in partial fulfillment of the requirements of the degree of Master of Science.

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