in methanol). The mixture was heated for 6 hr. and allowed to stand overnight. The solvent was removed by distillation under reduced pressure, and the residue was washed with 150 ml. of ether. The ether solution was distilled under reduced pressure to give 1.9 g. (83%) of 2-methoxy-6-methyl-2-phenyl-1-ox-6-azaspiro[2.5]octane (II), $n_D^{26.5}$ 1.5170.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21. Found: C, 71.59, 71.91; H, 8.10, 8.27.

(b) A similar reaction of XIII with 5.0 g. of sodium hydroxide in methanol gave an 87% yield of the epoxyether (II), b.p. 145–146° at 8 mm., $n_D^{27.5}$ 1.5165.

(c) 1-Methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIV) (2.8 g.) was added to a solution of 4 g. of sodium in 100 ml. of methanol, and the reaction mixture was treated as in (a). 2-Methoxy-6-methyl-2-phenyl-1-ox-6-azaspiro[2,5]octane (II) (2.0 g., 84%) was obtained as the fraction, b.p. 170–175° at 25 mm., n_D^{30} 1.5158.

Reaction of 2-methoxy-6-methyl-2-phenyl-1-ox-6-azaspiro[2,5]octane (II) with hydrochloric acid. A mixture of 2.9 g. of the epoxyether (II), 5 ml. of concentrated hydrochloric acid, and 30 ml. of water on neutralization with sodium carbonate gave 2.7 g. (100%) of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XV), m.p. 130–131°.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.22; H, 7.82. Found: C, 71.46, 71.55; H, 7.99, 7.90.

The *hydrochloride*, m.p. 170–172°, was prepared by the usual method.

Anal. Calcd. for $C_{13}H_{18}ClNO_2$: Cl, 13.74. Found, Cl, 13.62, 13.65.

Preparation of the *oxime* of XV by the usual procedure gave the derivative, m.p. 204–205°.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74. Found, C, 66.78; H, 7.68.

Reactions of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIII) in ether. (a) The base from 1.35 g. of XIII was obtained by saturating a solution of the salt in water with sodium bicarbonate. The slightly basic mixture was extracted with two 30 ml. portions of ether. The ether extracts were dried over Drierite for 20 min. and added, after filtration, to a suspension of 1.0 g. of sodium methoxide or sodium ethoxide in 50 ml. of ether. The mixture was heated under reflux for 3 hr. and allowed to stand at room temperature for 8 hr. The insoluble salts were removed by filtration, and the solvent was distilled from the filtrate to yield 0.5–0.8 g. (62–95%) of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XV), m.p. 130–131°.

(b) The base was obtained from 3.6 g. of the bromoketone hydrobromide (XIII) by treatment with 0.8 g. of *n*-butylamine in 150 ml. of anhydrous ether. After being stirred for 5 hr., the solution was filtered to remove the butylamine hydrobromide, and the filtrate was added to 0.4 g. of sodium hydroxide. The mixture was heated under reflux for 11 hr. and, filtered, and the filtrate was concentrated to give 1.0 g. (45.5%) of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XV), m.p. 130–131°.

(c) To 3.6 g. of XIII in 150 ml. of anhydrous ether 1 g. of powdered sodium hydroxide was added, and the mixture was heated under reflux for 16 hr. The insoluble material was removed by filtration, and the filtrate was concentrated to give 0.25 g. (37%) of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XV), m.p. 130–131°.

DURHAM, N. H.

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

Some Reactions of 1-Methyl-4-halo-4-piperidyl Phenyl Ketones[1]

ROBERT E. LYLE AND HENRY J. TROSCIANIEC[2]

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Reactions of the title compounds with organometallics, hydrogen over catalysts, lithium aluminum hydride, and sodium borohydride are described. The results of these reactions show that any effect of the amine function is subtile and cannot be directly traced to the slight differences in the products from the piperidine derivatives as compared with the cyclohexane analogs.

The displacement of the halogen of an α-haloketone by nucleophiles has been shown to lead to a wide variety of products, as reviewed recently by Tchoubar.[3] The results which have been reported arise largely from a study of alicyclic or acylic α-haloketones, and there has been no investigation of the reactions of analogous heterocyclic compounds. The investigation of the reactions of 1-methyl-4-halo-4-piperidyl phenyl ketone hydrohalides (Ia and IIa), reported in the preceding paper,[4] with nucleophilic reagents was of interest, for these heterocycles contain a nucleophile as a portion of the molecule. This amino function could participate in the reaction of the α-haloketones[5]

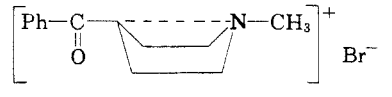
(1) This research was supported in part by a grant, H-1713, from the National Heart Institute of the National Institutes of Health, Public Health Service.

(2) Abstracted in part from the thesis of HJT submitted to the Graduate School of the University of New Hampshire in partial fulfillment of the degree of Doctor of Philosophy.

(3) B. Tchoubar, *Bull. Soc. Chim.*, 1362 (1955).

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

(5) The amino group could participate as (a) a proton acceptor as in the footnote 8 in S. M. McElvain and R. E. Lyle, *J. Am. Chem. Soc.*, **72**, 384 (1950), or (b) as a nucleophile in an intramolecular nucleophilic displacement such as that described by S. Archer and co-workers, *J. Am. Chem. Soc.*, **79**, 3603 (1957) and A. Bettini, C. A. Grob, and E. Schumacher, *Chem. & Ind.*, 757 (1958), to give an intermediate such as:



or have no effect on the reactivity of Ia or IIa resulting in the formation of products analogous to those from 1-halocyclohexyl phenyl ketone.[3] The following report describes the initial investigation of this question.

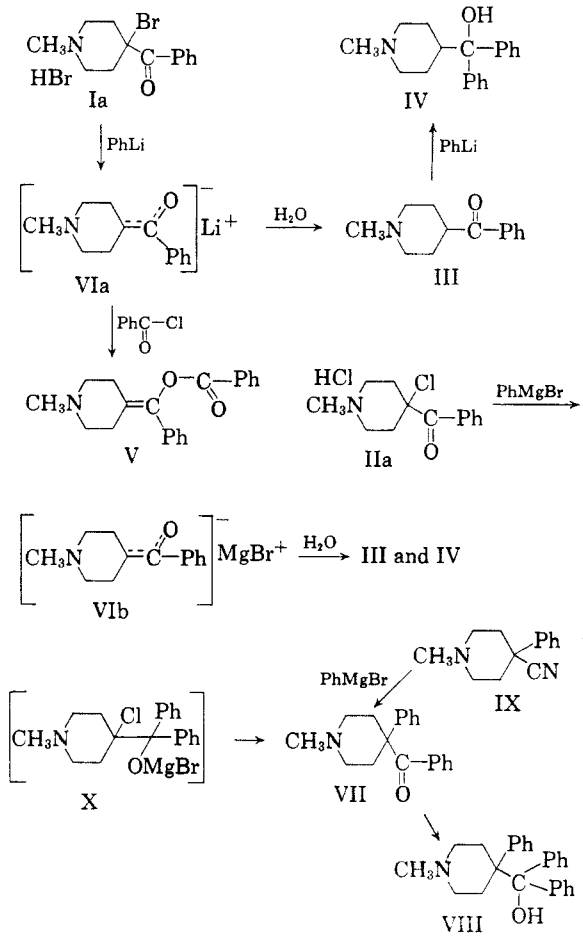
The major difference in the reactivity of the piperidine derivatives as compared with the cyclohexane analog was the failure of the former to undergo the Favorski rearrangement. Thus reactions of I or II with alkoxide, hydroxide, amines, or silver ion lead to the formation of the corresponding epoxyether, hydroxy ketone, or unsaturated ketone.[4]

Some difference in the course of the reactions of I or II with organometallics as compared with the cyclohexane analog[3,6] was also observed, for extensive metal halogen interchange occurred with the piperidine derivatives. The reaction of phenyllithium with Ia gave 1-methyl-4-piperidyl phenyl ketone (III), 30%, and 1-methyl-4-piperidyldiphenylcarbinol (IV), maximum yield 32%. That metal halogen exchange rather than addition occurred was confirmed by adding benzoyl chloride to the reaction mixture before hydrolysis to give 1-methyl-4-(α-benzoyloxybenzylidene)piperidine (V). Although V could not be purified as the hydrobromide to give an analytical sample, the picrate of V was obtained pure. The structure of V was proved by the ultraviolet and infrared absorption spectra and by hydrolysis of V to III and benzoic acid.

The method of formation of IV in this reaction was not obvious, for the reaction of phenyllithium with the enolate (VIa) was highly unlikely. Hydrolysis of the reaction mixture by slow addition to aqueous acid, rather than the reverse, gave a 65% yield of III and only 3% of the alcohol (IV). Thus, hydrolysis by addition of aqueous acid to the reaction mixture was causing the conversion of the enolate (VIa) to the ketone (III) before the excess phenyllithium was decomposed. The ketone (III) then gave IV with phenyllithium.

With the more electronegative chlorine in IIa and the less nucleophilic organometallic, the Grignard reagent, slightly different results were obtained. The reaction of II with phenylmagnesium bromide gave a complex mixture of products. From one reaction the ketonic products were isolated by distillation of the product mixture to give 36% of 1-methyl-4-piperidyl phenyl ketone (III) and 34% of 1-methyl-4-phenyl-4-piperidyl phenyl ketone (VII). The slight solubility of 1-methyl-4-phenyl-4-piperidyldiphenylcarbinol (VIII) hydrobromide in water led to its isolation in about 18% yield from several reactions. 1-Methyl-4-piperidyldiphenylcarbinol (IV) was found also in several reactions, but the amount of this compound present was dependent on the method of hydrolysis used. Thus, the yield varied considerably from reaction to reaction. The yield of VIII did not appear to be dependent on the hydrolytic procedure.

The identity of the products was established by comparison with authentic samples. The reaction of phenyllithium with VII, prepared from 1-methyl-4-phenylisonipectonitrile (IX) and phenylmagnesium bromide,[7] gave VIII.[8] The reaction of Demerol, ethyl 1-methyl-4-phenylisonipectotate, with phenylmagnesium bromide failed to give VIII.



The formation of III and IV occurred by the same course, through the intermediate VIb, as that discussed under the phenyllithium reaction. VII probably resulted from the rearrangement of the 1,2-addition product (X) of II and phenylmagnesium bromide.[3,6] The formation of VIII clearly indicated that VII was formed during the reaction proper, for the yield of VIII was unaffected by the method of hydrolysis.

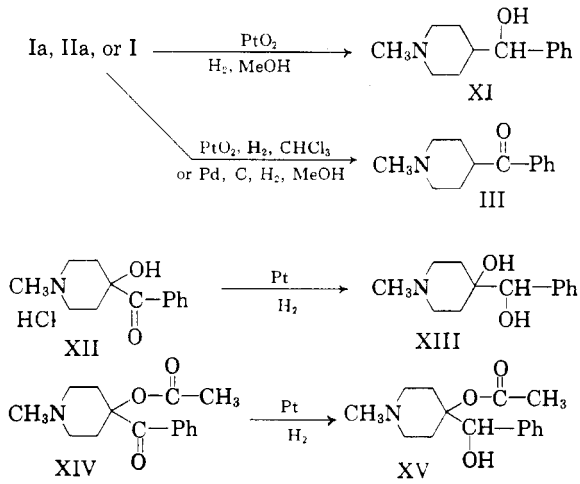
In an effort to prepare another series of piperidine derivatives for comparison with the cyclo-

(6) R. L. Huang, *J. Chem. Soc.*, 4089 (1957); G. Cauquil and J. Rouzaud, *Bull. Soc. Chim.*, 285 (1954).

(7) O. Eisleb, U. S. Patent 2,248,018, July 1, 1941.

(8) O. Schaumann, *Arch. exptl. Path. Pharmakol.*, 196, 109 (1940).

hexane analogs, the preparation of halohydrins by the reduction by several methods of the carbonyl function of the α-haloketones II, Ia, and IIa was investigated and led to interesting observations. II, Ia, and IIa on hydrogenation over platinum catalyst in methanol produced 1-methyl-4-piperidylphenylcarbinol (XI). If the catalyst were changed to palladium on charcoal or the solvent to chloroform, 1-methyl-4-piperidyl phenyl ketone (III) was formed. Since 1-methyl-4-piperidyl phenyl ketone hydrochloride (IIIa) was not affected by hydrogen over platinum catalyst under conditions effective for the reduction of the haloketones II, Ia, and IIa,[9] hydrogenolysis of the carbon-halogen bond followed by reduction of the carbonyl group did not offer an adequate explanation of these reactions. The ease of metal halogen exchange of the haloketones with organometallics suggested a similar mechanism for the catalytic hydrogenation, for a molecule of the haloketone oriented on the surface of the catalyst with the oxygen and halogen atoms adjacent to a hydrogen molecule could, by a concerted shift of electrons, form the enol (VI) and hydrogen bromide. Because of steric relationships the enol (VI) would be expected to be adsorbed on the catalyst with greater ease than the ketone (IIIa).[10] Thus, whether the carbinol (XI) or the ketone (III) is the product of the hydrogenation of the α-haloketone under a given set of conditions depends on the relative



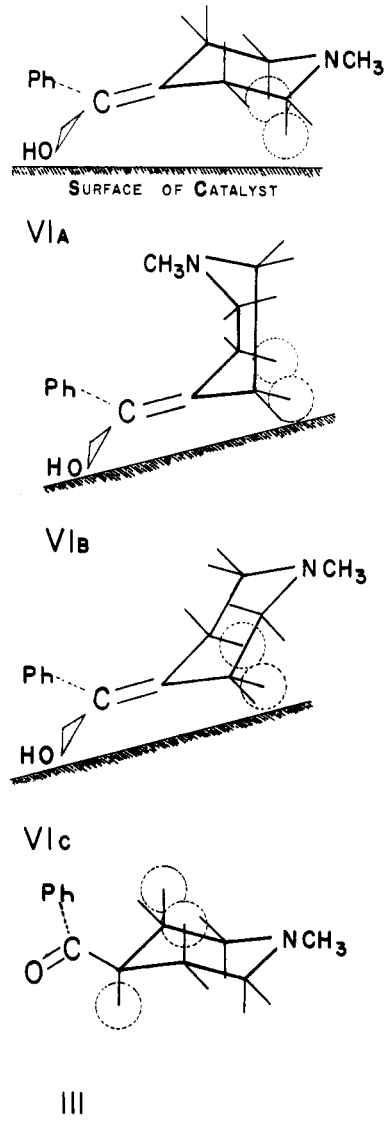
rates of ketonization or reduction of the enol VI. An analogous effect of conditions and mechanism was reported for the hydrogenation of the allylic halide, 14-bromocodeinone.[11]

Polar groups, other than halogen, on the 4-position of 1-methyl-4-piperidyl phenyl ketone were not hydrogenolyzed. Thus 1-methyl-4-hydroxy-4-piperidyl phenyl ketone hydrochloride (XII) gave 1-methyl-4-hydroxy-4-piperidylphenylcarbinol (XIII), and 1-methyl-4-acetoxy-4-piperidyl phenyl ketone (XIV) gave 1-methyl-4-acetoxy-4-piperidylphenylcarbinol (XV)[9] on hydrogenation over platinum in methanol.

The failure to produce halohydrins from I and II by catalytic reduction led to a study of the reactions of I with lithium aluminum hydride and sodium borohydride. The products isolated from

(9) S. A. Leone, Ph.D. thesis, University of New Hampshire (1958).

(10) The planar nature of the substituted benzylidene portion of the enol (VI) would allow adsorption on the surface of the catalyst, whereas the adsorption of the carbonyl group of the ketone (III) would be inhibited by interference of the *alpha* or *beta* axial hydrogens with the catalyst surface. The piperidine ring would be in an unfavorable

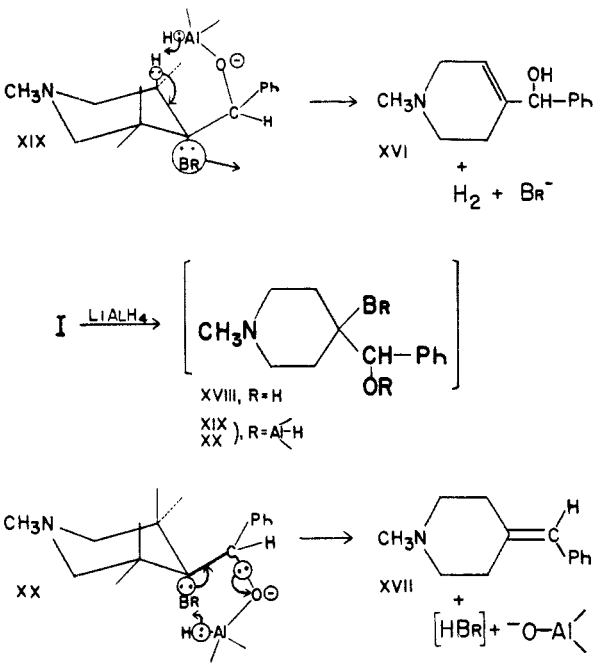


III

conformation for further reduction immediately after the hydrogenolysis (VIa), and rearrangement of the conformation to the boat form (VIb) [*Ann. Repts.*, **54**, 173 (1957)] or the inverted chair form (VIc) must occur before reduction to the carbinol (XI) can proceed. The necessity of these conformational changes allows time for rearrangement of the enol (VI) to the ketone (III) under some reaction conditions.

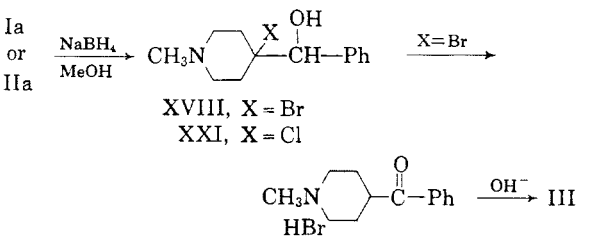
(11) H. Conroy, *J. Am. Chem. Soc.*, **77**, 5960 (1955).

the reaction of lithium aluminum hydride with I were found to be 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenylcarbinol (XVI),[12] 55%, and 1-methyl-4-benzylidenepiperidine (XVII), 34%. 1-Methyl-4-piperidylphenylcarbinol (XI) was isolated in trace amounts from some reactions. A plausible mechanism for the formation of these products would be the dehydrohalogenation of the bromohydrin (XVIII) to form XVI and dehydration of XI, the hydrogenolysis product of XVIII, to form XVII during the decomposition of the reaction mixture and the isolation of the products. The formation of XVI by this route cannot be disproved; however, a consideration of the properties of XVIII, as prepared below, makes this unlikely. Certainly, XVII cannot be formed in this manner, for dehydration of XI in acid led exclusively to 1-methyl-4-benzyl-1,2,3,6-tetrahydropyridine.[12] XI is not dehydrated under other conditions. It is further evident that these products do not arise by hydrogenolysis of the carbon-halogen bond prior to reduction of the carbonyl. These



products must be formed by the reaction of lithium aluminum hydride with the bromohydrin (XVIII). In this case the decomposition of the rotational conformations (XIX and XX) of the carbinol-to-piperidine ring bond, offer a possible explanation for the formation of XVI and XVII.

The reduction of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (Ia) with sodium borohydride gave the bromohydrin (XVIII), and a similar reduction of IIa produced the chlorohydrin (XXI). Pure XVIII was stable in the solid state; however, attempted recrystallization of XVIII or the presence of impurities in solid XVIII caused the decomposition to a saltlike material. The product of the decomposition was soluble in water, and the water solution, on neutralization with base, deposited an oil. The infrared spectrum of the oil clearly showed it to be a mixture containing alcoholic and ketonic components. The oxime and picrate of the ketonic component were prepared from the mixture and were shown to be derivatives of 1-methyl-4-piperidyl phenyl ketone (III). The alcoholic component was not identified; however, the stability of the oil eliminates the possibility of the presence of 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenylcarbinol (XVI)[12] in the mixture. XXI was more stable than XVIII, for the chlorohydrin could be recrystallized from acetone.



The reactions of I and II indicate a positive nature associated with the 4-halo substituent which, in conjunction with the infrared absorption data, suggest that the most favorable conformation of I and II is that in which the halogen-carbon bond is approximately parallel with the *pi* orbital of the carbon of the carbonyl group. In this orientation the transition from the α-haloketone to the overlapping *pi* orbital system of the enol (VI) or enolate (VIa or VIb) can most easily occur.

EXPERIMENTAL

Catalytic hydrogenations of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (Ia) *and the chloro analog* (IIa). (*a*) *Platinum in methanol.* A solution of 3.6 g. of Ia in 75 ml. of methanol was treated with hydrogen (3 atm.) over 0.1 g. of platinum oxide as catalyst. When the pressure remained constant, the reaction mixture was filtered, and the solvent was removed by distillation leaving an oily residue. A portion (0.2 g.) of the oil was converted to the base to give 1-methyl-4-piperidylphenylcarbinol (XI), m.p. 152–155°, which did not depress the melting point, 154–157°, of an authentic sample on mixing. The remainder of the oily hydrobromide was crystallized from methanol-ether solution to give 1.35 g. (54.5% based on total oil) of 1-methyl-4-piperidylphenylcarbinol hydrobromide, m.p. 133–136°.

(*b*) *IIa over platinum in methanol.* A solution of 2.4 g. of IIa in 50 ml. of methanol was treated as in (a) to give an oily hydrochloride which on neutralization in aqueous solution gave 1.7 g. of XI. Recrystallization from benzene gave 1.1 g. (46%) of XI, m.p. 154–156°.

(*c*) *IIa—sodium carbonate over platinum in methanol.* A solution of 1.0 g. of 1-methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (IIa) in 50 ml. of methanol was treated with 0.5 g. of sodium carbonate to free the base. The solution of II was treated as in (a) to give 0.5 g. (66.7%) of 1-methyl-4-piperidylphenylcarbinol (XI), m.p. 142–150°.

(12) A. E. Kerlin, B.S. thesis, University of New Hampshire (1956).

Recrystallization of 0.4 g. from benzene gave 0.25 g. of XI, m.p. 153–155°.

(*d*) *Ia over platinum in chloroform.* A solution of 2.0 g. of Ia in 150 ml. of chloroform over 0.1 g. of platinum oxide was treated as in (a) to give, on evaporation of the solvent, an oily residue. Crystallization of the oil from methanol ether gave 0.7 g. (45%) of 1-methyl-4-piperidyl phenyl ketone hydrobromide (IIIb), m.p. 196–204°.[4]

(*e*) *Ia over palladium-on-charcoal in methanol.* A solution of 1.0 g. of Ia in 50 ml. of methanol over 0.2 g. of catalyst was treated as in (a). Ether was added to the concentrated reaction mixture to precipitate 0.35 g. (45%) of IIIb, m.p. 201–204°.

Catalytic hydrogenation of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone hydrochloride (XII). A solution of 1.0 g. of XII in 50 ml. of methanol with 0.1 g. of platinum oxide was treated as in (a). The residue was converted to the base in water, and an ether solution of the base deposited 0.8 g. of 1-methyl-4-hydroxy-4-piperidylphenylcarbinol (XIII), m.p. 142–144°.[9]

Reaction of Ia with phenyllithium. (a) A suspension of 3.6 g. (0.01 mole) of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (Ia) in 50 ml. of ether was added to a solution of 0.07 mole of phenyllithium [prepared from 1.4 g. (0.2 g. atom) of lithium and 10.05 g. (0.07 mole) of bromobenzene] in ether. The mixture was heated under reflux for 4 hr., and the reaction mixture was poured onto 75 g. of ice. The ether layer was separated, and the aqueous layer was extracted with ether. The combined ether solutions were dried over sodium carbonate, and the solvent was removed by distillation. Addition of 15 ml. of water and 3 ml. of 1:1 hydrochloric acid to the residual oil caused the precipitation of 1.0 g. (32%) of impure 1-methyl-4-piperidyldiphenylcarbinol hydrochloride (IVa), m.p. 283–287°. Recrystallization of a small sample gave pure IVa, m.p. 310–312° (dec.), lit.[13] m.p. 310–311° (dec.).

Anal. Calcd. for $C_{19}H_{23}ClNO$: Cl, 11.16. Found: Cl, 11.52.

The base was prepared from the hydrochloride above to give IV, m.p. 134–135°, which did not depress the melting point of an authentic sample on mixing.

The acidic solution which deposited IV was neutralized with sodium carbonate and extracted with ether. After drying, the ether solution was concentrated, and the residue was distilled under reduced pressure to give 0.6 g. (30%) of 1-methyl-4-piperidyl phenyl ketone (III), b.p. 154° at 4 mm. III was identified as the hydrochloride, m.p. 204–206°, and by conversion to IV, m.p. 132–134°, on reaction with phenyllithium.

Anal. Calcd. for $C_{13}H_{18}ClNO$: Cl, 14.79. Found: Cl, 14.68.

(b) The reaction above was repeated; however, the mixture was hydrolyzed by slow addition, 3 hr., to 150 ml. of 10% hydrochloric acid. The ether layer was separated and discarded. The acidic solution was neutralized with sodium carbonate and extracted with ether. The extracts were dried over sodium carbonate and concentrated to give 2.25 g. of oily residue. Addition of 20 ml. of water and 3 ml. of concentrated hydrochloric acid caused the precipitation of 0.1 g. (3%) of crude 1-methyl-4-piperidyldiphenylcarbinol hydrochloride (IVa), m.p. 295–298° (dec.).

The acidic solution was neutralized with sodium carbonate and extracted with ether. The ether was removed by distillation, and the residual oil was distilled under pressure to give 1.3 g. (65%) of 1-methyl-4-piperidyl phenyl ketone (III), b.p. 140° at 3 mm.

(c) Repetition of the above reaction and addition of 1.6 ml. of benzoyl chloride before hydrolysis gave a very exothermic reaction. The solvent was removed by distillation, and the residual oil was treated with methanol to give 1.95 g. (54%) of impure 1-methyl-4-(α-benzoyloxybenzylidene)-piperidine hydrobromide (Va), m.p. 247–253°. Recrystallization of Va from chloroform acetone raised the melting point to 255–257°. The infrared absorption spectrum of Va supported the assignment of structure and the ultraviolet absorption spectrum in 95% ethanol showed a maximum at 253 mμ, log ε = 4.424.

Anal. Calcd. for $C_{20}H_{22}BrNO_2$: C, 61.68; H, 5.71; Br, 20.58. Found: C, 60.49, 60.42; H, 5.69, 5.77; Br, 21.25.

The picrate of V was prepared in ethanol to give a derivative, m.p. 211–213°.

Anal. Calcd. for $C_{26}H_{24}N_4O_9$: C, 58.21; H, 4.51. Found: C, 58.01, 58.24; H, 4.39, 4.67.

V (0.55 g.) on heating under reflux with 20 ml. of 20% hydrochloric acid gave 0.35 g. of 1-methyl-4-piperidyl phenyl ketone (III), characterized as the picrate, m.p. 200–201°, and 0.1 g. of benzoic acid, m.p. 121–122°.

Reaction of IIa with phenylmagnesium bromide. Because of the complex mixture of products from this reaction, several runs were necessary to isolate all of the products. Each reaction used 3.5 g. (0.013 mole) of IIa and 0.14 mole of phenylmagnesium bromide (prepared from 3.6 g. of magnesium and 22 g. of bromobenzene) in ether. The reaction mixture was heated under reflux for 1 hr. and then worked up as follows:

(a) The reaction mixture was poured onto 75 g. of ice, the ether layer was separated, and the aqueous layer was extracted with additional ether. The ether extract was extracted with dilute hydrochloric acid, and the acidic extract was neutralized. The basic solution was then extracted with ether. After drying over potassium carbonate the ether solution was concentrated, and the residual oil (4.9 g.) was distilled under reduced pressure to give 3.8 g. of distillate, b.p. 160–250° at 3 mm. Redistillation gave 1.45 g. (35.7%) of impure 1-methyl-4-piperidyl phenyl ketone (III), b.p. 110–112° at 1 mm., which was converted to 1.9 g. of the hydrobromide, m.p. 202–204°. A second fraction, b.p. 140–182°, was largely 1-methyl-4-phenyl-4-piperidyl phenyl ketone (VII) contaminated with a trace of 1-methyl-4-piperidyldiphenylcarbinol (IV). The composition was shown by treating 0.15 g. of this oil with dilute hydrochloric acid to precipitate 0.03 g. of 1-methyl-4-piperidyldiphenylcarbinol hydrochloride (IVa), m.p. 313–315°. A second sample, 0.5 g., was dissolved in 20 ml. of concentrated sulfuric acid to destroy the IV present. Dilution of the acid solution, neutralization, extraction with ether, and concentration of the ether solution gave 0.3 g. of impure 1-methyl-4-piperidyl phenyl ketone picrate, m.p. 195–211°, after addition of methanolic picric acid to the residue. One recrystallization of the solid from methanol gave 0.15 g. of VII picrate, m.p. 223–225°, which showed no depression of melting point on mixing with an authentic sample.

(b) A second reaction mixture was decomposed by dropwise addition to 30 ml. of water. The voluminous inorganic precipitate was dissolved by addition of 50 ml. of 1:1 hydrochloric acid solution. Extraction of the acidic solution with ether caused the precipitation of 3.0 g. of solid. Trituration of the solid with acetone gave 1.2 g. (18.2%) of 1-methyl-4-phenyl-4-piperidyldiphenylcarbinol hydrobromide (VIII),[14] m.p. 230–235°. The 1.8 g. of material which remained in acetone could not be crystallized; however, it was assumed to be largely salts of IV. Neutralization of a solution of 0.2 g. of VIIIa in water gave 0.15 g. of the crude base, which on recrystallization from ether-petroleum ether gave 0.1 g. of 1-methyl-4-phenyl-4-piperidyldiphenylcarbinol (VIII), m.p. 122–124°.[8]

Anal. Calcd. for $C_{25}H_{27}NO$: C, 83.99; H, 7.61. Found: C, 83.91; H, 7.73.

(13) F. J. Villani, M. S. King, and D. Papa, *J. Org. Chem.*, 17, 249 (1952).

(14) The amine hydrobromide precipitated from the solution containing both chloride and bromide ions because of the greater insolubility of the hydrobromide. Treatment of the base with hydrogen chloride gave VIII hydrochloride, m.p. 219–221° after recrystallization from acetone ether.

Anal. Calcd. for $C_{25}H_{28}ClNO$: Cl, 9.00. Found: Cl, 9.30.

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]

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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

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