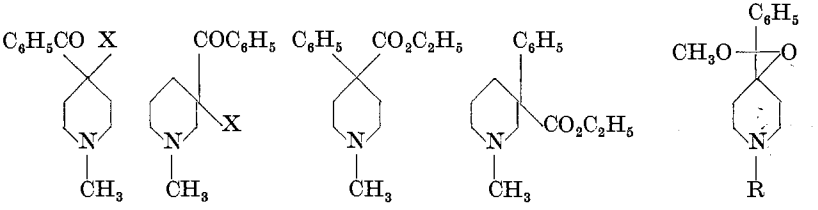
Journal of Medicinal and Pharmaceutical Chemistry

VOL. 3, No. 3 (1961)

The Syntheses of Potential Medicinal Agents from 1-Methyl-3-bromo-3-piperidyl Phenyl Ketone*

ROBERT E. LYLE and GLENN H. WARNER,† *Department of Chemistry, University of New Hampshire, Durham, New Hampshire*

The potential of α-haloketones in the piperidine series as synthetic intermediates for the preparation of known or likely medicinal agents was reported simultaneously by Smissman and Hite[1, 2, 3] and from this Laboratory.[4] The former research was concerned primarily with the Favorski rearrangement of 1-methyl-4-(and 3-) halogeno-4-(and 3-) piperidyl phenyl ketones (I and II, respectively) to meperidine (III) and β-pethidine (IV), while our interest in I was diverted from this purpose due to the facile conversion of I to the epoxy ether (Va).



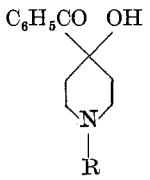
(Ia); X = Br (IIa); X = Br (III) (IV) (Va); R = CH_3
(Ib); X = Cl (IIb); X = Cl (Vb); R = $CH_2C_6H_5$
(Vc); R = COC_6H_5

The epoxy ethers (V) were very reactive and were transformed to the α-hydroxy ketones (VI) or the corresponding esters (VII) on treatment with mineral acids or organic acids respectively. Both VI and VII were shown to have local anaesthetic action when applied topically or subcutaneously; although, these materials

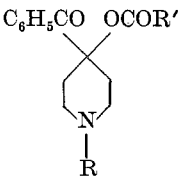
* This paper was presented before the Division of Medicinal Chemistry of the American Chemical Society at the 138th Meeting in New York, September 11–16, 1960.

† This material was abstracted in part from the Thesis of Glen H. Warner, presented to the Graduate School of the University of New Hampshire in partial fulfilment of the requirements for the Ph.D. degree. Present address: Carbide and Carbon Chemicals Company, Charleston, West Virginia.

produced irritation at the site of application.[4] It was therefore of interest to investigate the related compounds of the 3-piperidyl series in an effort to increase the activity markedly or reduce the irritancy significantly.



(VIa); R = CH_3
(VIb); R = $C_6H_5CH_2$
(VIc); R = C_6H_5CO



(VII)

1-Methyl-3-bromo-3-piperidyl phenyl ketone (II) was prepared by the catalytic hydrogenation of 1-methyl-3-benzoylpyridinium bromide (VIII) and bromination of the resulting 1-methyl-3-piperidyl phenyl ketone (IX). That the ketone IX and not the corresponding alcohol X was the major product of the reduction was unexpected in view of previous reports of similar hydrogenations[5, 6] and is the subject of a discussion to appear elsewhere.[7]

The 1-methyl-3-bromo-3-piperidyl phenyl ketone (II) was readily converted to the epoxy ether, 2-methoxy-5-methyl-2-phenyl-1-ox-5-azaspiro[2,5]octane (XI), by treatment with sodium methoxide in methanol. As anticipated, XI gave 1-methyl-3-hydroxy-3-piperidyl phenyl ketone (XII) with mineral acids, and organic acids caused the conversion of XI to the organic acid esters XIII of XII. The relative activities of the esters VII in the 4-series suggested that the benzoate ester XIIIa would have the greatest promise of activity in the 3-series. Thus the benzoate (XIIIa), *m*-hydroxybenzoate (XIIIb), furoate (XIIIc), and *o*-hydroxybenzoate (XIIId) esters were prepared following this lead, and the acetate (XIIId) was made for comparison with the 4-series. The results of the preliminary pharmocological screening of these compounds are indicated below (see Table I).

Epoxy ethers not containing a basic nitrogen have been shown to undergo a molecular rearrangement on treatment with a Lewis acid.[8] Had such a rearrangement occurred with V or XI, an interesting series of 7-membered-ring ketones would have been

(VIII)
(IX)
(X)
(XI)
(XII)
(XIII)
(XIIIa); R = C_6H_5
(XIIIb); R = *m*-HOC_6H_5
(XIIIc); R =
(XIIId); R = *o*-HOC_6H_4
(XIIIe); R = CH_3

anticipated as products. The reactions of the epoxy ether, 6-benzyl-2-methoxy-2-phenyl-1-ox-6-azaspiro[2,5]octane Vb, with the Lewis acids, boron trifluoride or magnesium bromide, however, gave 1-benzyl-4-hydroxy-4-piperidyl phenyl ketone (VIb) hydrochloride as the only product on work-up of the reactions. The epoxy ether (Vb) appeared to form an insoluble salt immediately on addition of the Lewis acid, thus preventing further reaction. To diminish the basicity of the nitrogen in the epoxy ether, the reaction was also attempted with 6-benzoyl-2-methoxy-2-phenyl-1-ox-6-azaspiro[2,5]octane (Vc); however, again only the corresponding α-hydroxyketone (VIc) could be isolated.

The suggestion by Smissman and Hite[1, 3] that the basic nitrogen of the bromoketones I and II was the cause of the poor yields of the products of the Favorski rearrangement prompted the investigation of the reactions of 1,3- (and 1,4-) dibenzoyl-3- (and 4-) bromopiperidines (XIV and XV) with electrophilic catalysts. In these compounds, the basicity of the nitrogen has been diminished by conversion to an amide function. A second attempt to block any participation of the nitrogen in the reaction was made by preparing the quaternary salts of I and II by an indirect procedure, for the reaction of I and II with methyl iodide led to the methiodides of the corresponding α-hydroxyketones.

The reaction of the quaternary salts of I and II with electrophilic catalysts, such as silver ion, or with bases in non-polar solvents gave no characterizable products. 1,4-Dibenzoyl-4-bromopiperidine (XV) with silver or mercuric ions gave 1-benzoyl-4-phenyl-4-piperidinecarboxylic acid (XVI) in yields of 13–23 per cent. The 3-substituted analogue XIV was only dehydrohalogenated under these conditions, forming 1,3-dibenzoyl-1,4,5,6-tetrahydropyridine (XVII). The formation of meperidine (III) derivatives by this method thus appears impractical.

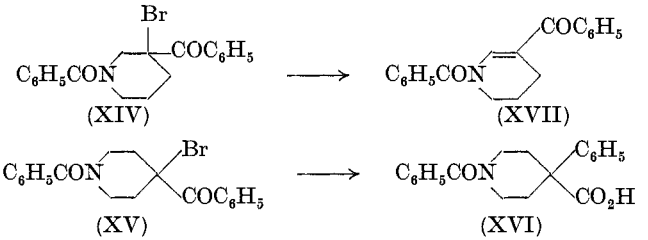
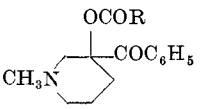


Table I. Local anaesthetic action of



R	Conc., %	Duration of anaesthesia, min
	Irrigation	
m-Hydroxyphenyl	1·0	12
m-Hydroxyphenyl	1·0	26
2-Furyl	0·5	17
o-Hydroxyphenyl	0·5	10
Phenyl	0·4	24
Methyl	2·0	13
	Infiltration	
Phenyl	2·0 (0·05)	112 (26)
Methyl	2·0 (0·2)	81 (12)

Results of Preliminary Pharmacological Tests

The compounds were all tested for anaesthetic action by the corneal irrigation method using rabbit cornea, and the benzoate and acetate esters were evaluated for local anaesthetic action by injection in guinea pigs. It is evident from Table I that the aromatic esters were all more effective than the acetate in terms of duration of the effect; however, substituents on the aromatic ring did not enhance the activity of the benzoate. All of the compounds produced irritation with the acetate causing the mildest effect.

Representative members of this series were shown to have no analgesic activity, and slight antispasmodic activity against barium chloride and acetylcholine induced spasms in rabbit ileum. The methiodide of the hydroxyketone (XII) caused a rise in blood pressure, apparently due to ganglionic stimulation, while the acetate and benzoate esters, as hydrochlorides, caused a mild, transient drop in blood pressure.

Experimental

3-Benzoylpyridine. Thionyl chloride (500 ml) was added to nicotinic acid (123 g, 1 mole) in a three-necked apparatus over a period of 30 min. The mixture was heated under reflux for 2 h,

and excess thionyl chloride was removed by distillation. After most of the thionyl chloride had been removed, anhydrous benzene (200 ml) was added, the mixture was cooled in an ice-water bath, and aluminium chloride (330 g) was added with stirring over a period of 1 h. The reaction mixture was heated under reflux for 6 h and was poured into a 4-l. beaker filled with crushed ice and 200 ml of concentrated hydrochloric acid. The aqueous layer was separated and extracted with ether. The ether and benzene layers were discarded. The aqueous layer was made strongly basic with sodium hydroxide, and the oil which separated was collected by decantation. The crude oily layer was distilled under reduced pressure to give 141 g (77·2 per cent) of 3-benzoylpyridine, b.p. 132–145°/2 mm, lit.[9] b.p. 141–145°/2 mm.

1-Methyl-3-benzoylpyridinium bromide (VIII). A mixture of 3-benzoylpyridine (182·2 g) and methyl bromide (100 g) in isopropyl alcohol (350 ml) was allowed to stand at room temperature for 24 h in a tightly stoppered flask. The solid which precipitated was collected by filtration and washed with ether to give a quantitative yield of 1-methyl-3-benzoylpyridinium bromide (VIII), m.p. 146–148.°

Anal. Calcd. for $C_{13}H_{12}BrNO$: Br, 28·73. Found: Br, 28·69, 28·85.

1-Methyl-3-piperidyl phenyl ketone hydrobromide (IX). A solution of 1-methyl-3-benzoylpyridinium bromide (VIII) (75 g, 0·288 mole) in methanol (600 ml) was divided into three equal portions and each portion was hydrogenated with 0·3 g of platinum oxide with an initial pressure of hydrogen of 50 lb/in^2. The combined reaction mixtures were filtered to remove the catalyst, and the solvent was removed by distillation at reduced pressure. The residue was dissolved in hot isopropyl alcohol (300 ml); and on cooling 17·2 g of 1-methyl-3-benzoylpiperidine hydrobromide (IX) precipitated, m.p. 131–133°.

Anal. Calcd. for $C_{13}H_{18}BrNO \cdot H_2O$: Br, 26·50. Found: Br, 26·44, 26·17, 26·79.

The solvent was removed from the filtrate above, and the residue was dissolved in 300 ml of methanol. Hydrogenation was continued as previously and on treatment of the reduction mixture as above an additional 14·9 g of IX was obtained; total yield, 40·5 per cent.

The alcoholic filtrate was evaporated to dryness and the residue dissolved in water. Neutralization of this solution caused the precipitation of a dark oil which was taken up in ether. The ether solution was dried over anhydrous potassium carbonate, and the ether removed from the solution by distillation. The residue crystallized on treatment with ligroin to give 6·1 g of one isomeric form of 1-methyl-3-piperidylphenylcarbinol (X), m.p. 122–125°; lit.[5] m.p. 122–125°.

Oxidation of 1-methyl-3-piperidylphenylcarbinol (X) (5·0 g) with chromic anhydride (1·7 g) in acetic acid (50 ml) was accomplished by heating for 1 h on a steam bath. The solvent was removed by distillation under reduced pressure, and the residue dissolved in a minimum of chloroform. The chloroform solution was saturated with anhydrous hydrogen bromide, and the solvent removed by distillation. The residue was recrystallized from isopropyl alcohol to give 3·8 g (54·1 per cent) of 1-methyl-3-piperidyl phenyl ketone hydrobromide (IX), m.p. 131–133°.

1-Methyl-3-bromo-3-piperidyl phenyl ketone hydrobromide (IIa). A solution of 1-methyl-3-piperidyl phenyl ketone hydrobromide (IX) (15·1 g) in chloroform (150 ml) was treated with bromine (8 ml) and allowed to stand overnight at room temperature. The solvent was removed by evaporation under reduced pressure, and the residue was dissolved in methanol and treated with phenol to decompose any perbromides. Addition of anhydrous ether to the methanol solution caused the precipitation of 15·3 g (56·2 per cent) of 1-methyl-3-bromo-3-piperidyl phenyl ketone hydrobromide (IIa), m.p. 142–144°.

Anal. Calcd. for $C_{13}H_{17}Br_2NO$: Br, 22·22 (ionic). Found: Br, 22·38, 22·18.

3-Piperidyl phenyl ketone hydrochloride. A solution of 3-pyridyl phenyl ketone hydrochloride (44 g) was hydrogenated in the same manner as 1-methyl-3-benzoylpyridinium bromide (VIII) to give 16·2 g of 3-piperidyl phenyl ketone hydrochloride, m.p. 187–189°.

Anal. Calcd. for $C_{12}H_{15}ClNO$: Cl, 15·71. Found: Cl, 15·81. 15·80.

1,3-Dibenzoylpiperidine. A solution of 3-piperidyl phenyl ketone hydrochloride (8 g) in water (40 ml) was neutralized with sodium hydroxide. While stirring the solution, benzoyl chloride

(5 g) was added, causing the precipitation of crude 1,3-dibenzoylpiperidine. Recrystallization of the crude solid from ligroin gave 7·1 g of 1,3-dibenzoylpiperidine, m.p. 92–94°.

Anal. Calcd. for $C_{19}H_{19}NO_2$: C, 77·84; H, 6·49. Found: C, 77·33; H, 6·78.

1,4-Dibenzoylpiperidine. The oxidation of 4-piperidylphenylcarbinol (4 g), prepared by the hydrogenation of 4-pyridyl phenyl ketone, was accomplished with chromic anhydride as described for the preparation of IX to give 3·2 g of 4-piperidyl phenyl ketone hydrochloride, m.p. 227–228°.

Anal. Calcd. for $C_{12}H_{14}ClNO$; Cl, 15·70. Found: Cl, 15·48, 15·67.

A solution of 4-piperidyl phenyl ketone hydrochloride (42 g) in water (200 ml) was treated with benzoyl chloride as in the preparation of 1,3-dibenzoylpiperidine above to give 38·2 g (64·5 per cent) of 1,4-dibenzoylpiperidine, m.p. 105–108°, after recrystallization from aqueous alcohol.

Anal. Calcd. for $C_{19}H_{19}NO_2$: C, 77·84; H, 6·49. Found: C, 76·95; H, 6·56.

1-Methyl-3-piperidyl phenyl ketone methobromide. The base from 10·2 g of 1-methyl-3-piperidyl phenyl ketone hydrobromide (IX) was treated with an ethereal solution of methyl bromide to give 10·8 g (94 per cent) of 1-methyl-3-piperidyl phenyl ketone methobromide monohydrate, m.p., 108–111° (the melt resolidifies and melts again at 201–203°).

Anal. Calcd. for $C_{14}H_{20}BrNO \cdot H_2O$: Br, 25·20. Found: Br, 25·70, 25·28.

In a similar manner, 1-methyl-4-piperidyl phenyl ketone hydrobromide (20 g) was converted to 1-methyl-4-piperidyl phenyl ketone methobromide (16·7 g, 79·5 per cent), m.p. 208–212°.

Anal. Calcd. for $C_{14}H_{20}BrNO$: Br, 26·91. Found: Br, 27·13, 27·70.

Bromination of 1-methyl-3-piperidyl phenyl ketone methobromide (9·86 g) as in the preparation of IIa with bromine (6 ml) gave 5·4 g (48 per cent) of 1-methyl-3-bromo-3-piperidyl phenyl ketone methobromide, m.p. 128–130°.

Anal. Calcd. for $C_{14}H_{19}Br_2NO$: Br, 21·2 (ionic). Found: Br, 21·2.

Bromination of 1-methyl-4-piperidyl phenyl ketone methobromide (15 g) as in the preparation of IIa with bromine (6 ml) gave 16·1 g (84 per cent) of 1-methyl-4-bromo-4-piperidyl phenyl ketone methobromide, m.p. 168–169°.

Anal. Calcd. for $C_{14}H_{19}Br_2NO$: Br, 21·2 (ionic). Found: Br, 21·27, 21·53.

1,3-Dibenzoyl-3-bromopiperidine (XIV). A solution of 1,3-dibenzoylpiperidine (7 g) in glacial acetic acid (100 ml) was treated with bromine (4 ml) heated on a steam bath for 4 h, and poured into water (200 ml). The aqueous solution was extracted with chloroform, and the chloroform extract washed with a solution of sodium thiosulphate and water. The solvent was removed from the solution by evaporation under reduced pressure to give, after recrystallization from ligroin, 3·8 g (47 per cent) of 1,3-dibenzoyl-3-bromopiperidine (XIV), m.p. 106–109°.

Anal. Calcd. for $C_{19}H_{18}BrNO_2$: Br, 21·00. Found: Br, 21·46, 21·18.

1,4-Dibenzoyl-4-bromopiperidine (XV). A suspension of 1,4-dibenzoylpiperidine (42 g) was brominated in chloroform with 15 ml of bromine. The residue, after removal of the solvent by distillation, was dissolved in ether, and the ether solution washed with sodium thiosulphate solution. The ether solution was dried over calcium sulphate, the solvent removed by evaporation, and the residue was recrystallized from isopropyl alcohol to give 27 g (52 per cent) of 1,4-dibenzoyl-4-bromopiperidine (XV), m.p. 108–109°.

Anal. Calcd. for $C_{19}H_{18}BrNO_2$: Br, 21·00. Found: Br, 21·50, 21·39.

2-Methoxy-5-methyl-2-phenyl-1-ox-5-azaspiro[2,5]octane (XI). A solution of 1-methyl-3-bromo-3-piperidyl phenyl ketone hydrobromide (IIa) (20·5 g) in methanol was added to a hot solution of sodium methoxide (13·5 g) in methanol (150 ml). The mixture was heated under reflux for 6 h and the solvent was partially removed by distillation. The residue was diluted with 200 ml of water and the mixture was extracted with three 100-ml portions of ether. After drying the ether solution (Ca_2SO_4 anhyd.), the solvent was removed by evaporation, and the residue was distilled under reduced pressure to give 4·2 g (33 per cent) of 2-methoxy-5-methyl-2-phenyl-1-ox-5-azaspiro[2,5]octane (XI), b.p. 117–119°/2 mm.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72·07; H, 8·21. Found: C, 72·14; H, 8·30.

3-Hydroxy-1-methyl-3-piperidyl phenyl ketone (XII). A sample of 2-methoxy-5-methyl-2-phenyl-1-ox-5-azaspiro[2,5]octane (XI) (4·35 g) was added to dilute hydrochloric acid (100 ml). After standing at room temperature for 12 h, the solution was neutralized with sodium hydroxide and extracted with ether. The ether solution was dried (Ca_2SO_4 anhyd.), and the solvent removed by distillation. The residue was recrystallized from ligroin to give 2 g (48 per cent) of 3-hydroxy-1-methyl-3-piperidyl phenyl ketone (XII), m.p. 52–54°.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71·2; H, 7·76. Found: C, 71·65; H, 7·37.

The hydrochloride of XII was prepared in ether, m.p. 161–164°.

Anal. Calcd. for $C_{13}H_{16}ClNO_2$: Cl, 13·92. Found: Cl, 13·70.

3-Acetoxy-1-methyl-3-piperidyl phenyl ketone (XIIId). A solution of 2-methoxy-5-methyl-2-phenyl-1-ox-5-azaspiro[2,5]-octane (XI) (2·5 g) in anhydrous ether (50 ml) was added to ether (50 ml) containing glacial acetic acid (3 ml), and the resulting solution was allowed to stand at room temperature for 12 h. The ether was extracted with saturated sodium carbonate solutions, and the solvent removed by evaporation. The residue was recrystallized from petroleum ether to give 2·1 g (81 per cent) of 3-acetoxy-1-methyl-3-piperidyl phenyl ketone (XIIId), m.p. 88–89°.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 69·00; H, 7·28. Found: C, 68·80; H, 6·95.

The hydrochloride of XIIId was prepared in 70·5 per cent yield by a standard method; recrystallization from isopropyl alcohol gave an analytical sample, m.p. 248–250°.

Anal. Calcd. for $C_{15}H_{20}ClNO_3$: Cl, 11·95. Found: Cl, 11·68.

3-Benzoyloxy-1-methyl-3-piperidyl phenyl ketone (XIIIa). The reaction of XI (4·35 g) with benzoic acid (5 g) as above gave 4·1 g (66 per cent) of 3-benzoyloxy-1-methyl-3-piperidyl phenyl ketone (XIIIa), m.p. 114–115.

Anal. Calcd. for $C_{20}H_{21}NO_3$: C, 74·30; H, 6·50. Found: C, 74·32; H, 6·57.

The hydrochloride of XIIIa melted at 201–202°.

Anal. Calcd. for $C_{20}H_{22}ClNO_3$: Cl, 9·85. Found: Cl, 10·17.

*1-Methyl-3-*m*-hydroxybenzoyloxy-3-piperidyl phenyl ketone* (XIIIb). The reaction of XI (4·35 g) with *m*-hydroxybenzoic acid (5·5 g) as described above gave 3·3 g (40 per cent) of 1-methyl 3-*m*-hydroxybenzoyloxy-3-piperidyl phenyl ketone (XIIIb) maleate salt, m.p. 208–209°.

Anal. Calcd. for $C_{24}H_{25}NO_4$: C, 63·40; H, 5·50. Found: C, 63·39; H, 5·69.

*1-Methyl-3-*o*-hydroxybenzoyloxy-3-piperidyl phenyl ketone.* Treatment of XI (4·25 g) with *o*-hydroxybenzoic acid (5·5 g) as above gave 2·0 g (34 per cent) of 1-methyl-3-*o*-hydroxybenzoyloxy-3-piperidyl phenyl ketone (XIIId), m.p. 128–130°.

Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70·7; H, 6·21. Found: C, 70·5; H, 6·35.

The reaction of XIIId with hydrogen chloride gave the hydrochloride, m.p. 196–200°.

Anal. Calcd. for $C_{20}H_{22}ClNO_4$; Cl, 9·32. Found: Cl, 8·92.

3-(2-Furanoyloxy)-1-methyl-3-piperidyl phenyl ketone (XIIIe). The reaction of XI (4·25 g) with 2-furanoic acid (5 g) as described above gave 3 g (50·5 per cent) of 3-(2-furanoyloxy)-1-methyl-3-piperidyl phenyl ketone (XIIIe), m.p. 127–128°.

Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 69·00; H, 6·06. Found: C, 69·20; H, 6·08.

The hydrochloride of XIII melted at 210–212°.

Anal. Calcd. for $C_{16}H_{20}ClNO_4$: Cl, 10·60. Found: Cl, 10·31.

Reaction of 6-benzoyl-2-methoxy-2-phenyl-1-ox-6-azaspiro[2,5]-octane (Vc) with boron trifluoride. A solution of 1,4-dibenzoyl-4-bromopiperidine (XV) (25 g) in methanol (200 ml) was added to sodium methoxide (40 g) in methanol (350 ml). The reaction mixture was treated as in the preparation of XI; however, the product had too high a boiling-point to distil. Treatment with petroleum ether caused precipitation of 7·2 g (34·6 per cent) of 1,4-dibenzoyl-4-hydroxypiperidine (Vlc), m.p. 186–188°.

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73·80; H, 6·15. Found: C, 74·23; H, 6·20.

The filtrate from 1,4-dibenzoyl-4-hydroxypiperidine was contrated to give 14 g of crude Vc. A sample (8·4 g) of this crude material was dissolved in nitromethane (250 ml) and freshly distilled boron trifluoride etherate (10 ml) was added. After being heated under reflux for 12 h, the reaction mixture was

cooled and methanolic potassium hydroxide was added. The solids which precipitated were removed by filtration, and the solvents were removed from the filtrate by distillation under reduced pressure. The residue was recrystallized from isopropyl alcohol to give 4 g of 1,4-dibenzoyl-4-hydroxypiperidine (VIc), m.p. 186–188°.

Reaction of 6-benzyl-2-methoxy-2-phenyl-1-ox-6-azaspiro[2,5]-octane (Vb) with boron trifluoride etherate. The reaction of Vb (5·1 g) was run as above with Vc to give 4·2 g (73·4 per cent) of 1-benzyl-4-hydroxy-4-piperidyl phenyl ketone (VIb) isolated as the hydrochloride, m.p. 191–193°. The melting point was not depressed by mixing this product with an authentic sample of VIb, m.p. 190–192°, prepared as described below.

1-Benzyl-4-hydroxy-4-piperidyl phenyl ketone (VIb). A solution of 6-benzyl-2-methoxy-2-phenyl-1-ox-6-azaspiro[2,5]octane (Vb) (3 g) in dilute hydrochloric acid (100 ml) was cooled, causing the precipitation of 1-benzyl-4-hydroxy-4-piperidyl phenyl ketone hydrochloride. The solid was recrystallized from water to give 2·5 g of VIb hydrochloride, m.p. 190–192°.

Anal. Calcd. for $C_{19}H_{22}ClNO_2$: Cl, 10·68. Found: Cl, 10·10.

An aqueous solution of VIb hydrochloride was neutralized with sodium hydroxide to give a quantitative yield of 1-benzyl-4-hydroxy-4-piperidyl phenyl ketone (VIb), m.p. 68–70°.

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77·30; H, 7·14. Found: C, 77·33; H, 6·78.

Reaction of 1,3-dibenzoyl-3-bromopiperidine (XIV) with silver nitrate. A solution of XIV (3·8 g) in 80 per cent acetone (100 ml) was treated with a solution of silver nitrate (2 g) in water (10 ml). The mixture was heated under reflux for 12 h and the insoluble salts were removed by filtration. The filtrate was diluted with 250 ml of water, and the aqueous mixture was extracted with ether. The ethereal solution was dried and concentrated, and the residue was recrystallized from ligroin to give 1·3 g (45 per cent) of 1,3-dibenzoyl-1,4,5,6-tetrahydropyridine (XVII), m.p. 125–128°.

Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78·40; H, 5·85. Found: C, 77·85, 78·00; H, 5·86, 5·87.

Reaction of 1,4-dibenzoyl-4-bromopiperidine (XV) with silver nitrate. A solution of XV (3 g) and silver nitrate (2 g) in 50 per

cent acetone (100 ml) was heated under reflux for 12 h. The insoluble salts were removed by filtration and the filtrate was diluted with water. The aqueous mixture was extracted with ether and the ethereal extracts were extracted with saturated sodium carbonate solution. The basic extracts were neutralized with dilute hydrochloric acid and the solid which precipitated was collected by filtration. Recrystallization of the crude material from ligroin gave 0·4 g (15 per cent) of 1-benzoyl-4-phenylisonipecotic acid (XVI), m.p. 191–193°.

Anal. Calcd. for $C_{19}H_{19}NO_3$; C, 73·8; H, 6·15; neut. equiv., 309. Found: C, 74·21; H, 6·32: neut. equiv., 320.

A similar reaction of XV with silver ion in *t*-butyl alcohol gave a 23 per cent yield of XVI. The reaction of XV with mercuric acetate in acetic acid gave a 12 per cent yield of XVI.

Summary. 3-Bromo-1-methyl-3-piperidyl phenyl ketone (II) was converted to 2-methoxy-5-methyl-2-phenyl-1-ox-5-azaspiro[2,5]octane (XI) on reaction with sodium methoxide in methanol. The epoxy ether (XI) was cleaved to form 3-hydroxy-1-methyl-3-piperidyl phenyl ketone (XII) with mineral acids or 3-acyloxy-1-methyl-3-piperidyl phenyl ketones (XIII) with organic acids. These latter keto esters were screened for local anaesthetic activity, and the preliminary results of this investigation show that some members of this series are more potent but more irritating than lidocaine.

Attempts to cause the rearrangement of epoxy ethers (V) were unsuccessful. The attempts to form derivatives of meperidine by the Favorski rearrangement of 1-benzoyl-3- (or 4-) bromo-3- (or 4-) piperidyl phenyl ketone (XIV or XV) met with limited success.

Acknowledgements. This research was supported in part by research grant H-1713 and continuation grants from the National Heart Institute, the National Institutes of Health. The authors also wish to thank Dr. Ben Corson and the Koppers Chemical Corporation for a generous supply of the nicotinic acid used in this investigation.

(*Received 15 November, 1960*

References

[1] Smissman, E. E. and Hite, G. *J. Amer. chem. Soc.*, **81**, 1131 (1959)
[2] Hite, G., Smissman, E. E. and West, R. *J. Amer. chem. Soc.*, **82**, 1207 (1960)
[3] Smissman, E. E. and Hite, G. *J. Amer. chem. Soc.*, **82**, 3375 (1960)

[4] Lyle, R. E., Troscianiec, H. J. and Warner, G. H. *J. org. Chem.*, **24**, 330 (1959)
[5] Sugimoto N. and Kugita, H. *J. Pharm. Soc. Japan*, **73**, 66 (1955)
[6] Crook, K. E. and McElvain, S. M. *J. Amer. chem. Soc.*, **52**, 4006 (1930)
[7] Lyle, R. E. and Warner, G. H. Unpublished, to be submitted for publication in *J. org. Chem.*
[8] Stevens, C. L. and Ettling, B. V. *J. Amer. chem. Soc.*, **77**, 5412 (1955)
[9] Villiani, F. J., King, M. S. and Papa, D. *J. org. Chem.*, **17**, 249 (1952)