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

Preparation and Ring Opening of 2-Methoxy-6-methyl-2-phenyl-1-ox-6-azaspiro[2.5]octane, an Epoxyether[1]

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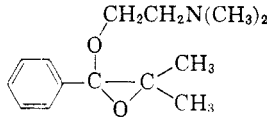
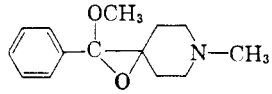
The title compound (II) was prepared by the reaction of 1-methyl-4-halo-4-piperidyl phenyl ketone hydrohalide with bases in absolute alcohol. Unlike the amino epoxyether (I) previously reported, II gave a facile reaction with acids. The reported methods of synthesis of 1-methyl-4-piperidyl phenyl ketone are evaluated, and an improved procedure is described.

The extensive research of Stevens[3a] on the chemistry of epoxyethers suggested the use of this type of compound as an intermediate in the synthesis of 4,4-disubstituted piperidines. Stevens, however, has shown that an epoxyether of an amino alcohol (I) was resistant to attack by acids due to the repulsion of the ammonium nitrogen for the attacking proton.[3b] The proposed piperidine epoxyether (II) would have the ammonium nitrogen separated from the oxirane ring by the same number of atoms as in I. Consequently, the effect of the positive charge on the ease of ring opening due to induction would be about the same in both compounds. This effect should be small, however, in comparison to the field effect which is possible with I but which should be of lesser importance with the rigid piperidine analog II. With this question of the reactivity in mind the synthesis of II was attempted.

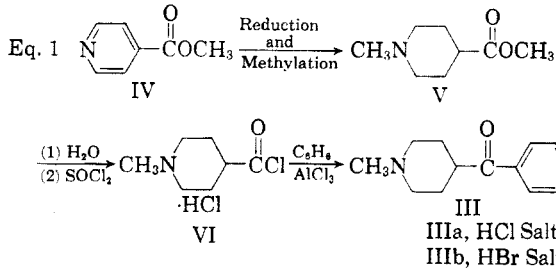


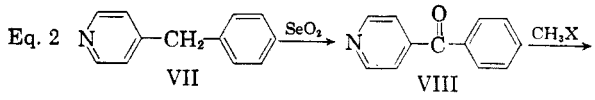
I

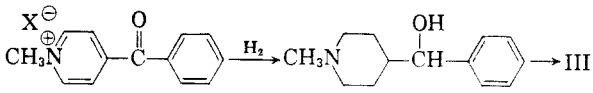


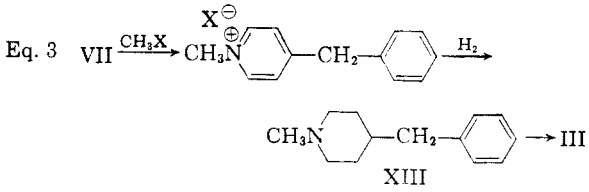
II

The successful use of II for the synthesis of piperidines required a convenient method of obtaining quantities of 1-methyl-4-piperidyl phenyl ketone (III). Three different synthetic routes were devised from reactions which had been reported, and each of these was investigated: (1) the Friedel-Crafts acylation of benzene with 1-methylisonipecotyl chloride hydrochloride (VI),[4] prepared from methyl isonicotinate (IV) (Equation 1), (2) the reduction of 1-methyl-4-benzoylpyridinium halide (IX) to 1-methyl-4-piperidylphenylcarbinol (X) and oxidation of X to III[5] (Equation 2), and (3) oxidation of 1-methyl-4-benzylpiperidine (XII),[4] prepared by the reduction of 1-methyl-4-benzylpyridinium halide (XI)[6] (Equation 3). Methyl 1-methylisonipecotate (V) used in the first method was prepared from methyl isonicotinate (IV) by the procedures of Lyle *et al.*[7] or Feldkamp *et al.*[8] Hydrolysis of the ester and conversion of the resulting acid to the acid chloride (VI) were achieved by standard methods, and the acylation followed the method of Villani *et al.*[4] The yields of III by this method were consistently good; how-









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

(2) Abstracted from the theses of S. A. L., H. J. T., and G. H. W. presented to the Graduate School of the University of New Hampshire in partial fulfillment of the requirements of the degree of Doctor of Philosophy.

(3) (a) C. L. Stevens and B. T. Gillis, *J. Am. Chem. Soc.*, **79**, 3448 (1957) and preceding papers including: (b) C. L. Stevens and B. V. Ettling, *J. Am. Chem. Soc.*, **77**, 5412 (1955), and (c) C. L. Stevens and E. Farkas, *J. Am. Chem. Soc.*, **74**, 5352 (1952).

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

(5) N. Sugimoto, and H. Kugita, *J. Pharm. Soc. Japan*, **73**, 66 (1953); *Chem. Abstr.* **47**, 10523 (1953).

(6) A. P. Gray, W. L. Archer, E. E. Spinner, and C. J. Cavallito, *J. Am. Chem. Soc.*, **79**, 3805 (1957).

(7) R. E. Lyle, E. F. Perlowski, H. J. Troscianiec, and G. G. Lyle, *J. Org. Chem.*, **20**, 1761 (1955).

(8) R. F. Feldkamp, J. A. Faust, and A. J. Cushman, *J. Am. Chem. Soc.*, **74**, 3831 (1952).

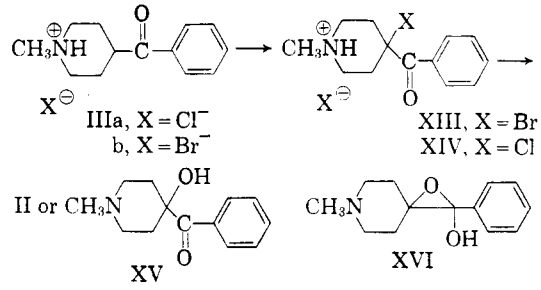
ever, the mechanical difficulty of separating the product from the aluminum salts in the last step was a disadvantage.

At the time this research was initiated 4-benzoylpyridine (VIII) was not available, and a study of method 2 required the synthesis of VIII from 4-benzylpyridine (VII). Although other oxidizing agents caused this conversion,[9,10] the most convenient procedure used selenium dioxide. Unfortunately the hydrogenation of VIII or its quaternary salts (IX) led to reduction of the carbonyl group as well as of the pyridine ring. Indeed it was found that unlike other ketonic pyridine derivatives,[11,12] the carbonyl group of VIII or IX underwent reduction before the pyridine ring. Detection of reduction reactions which had not gone to completion was easily accomplished, for the addition of base to the partially reduced reaction mixture produced a blue dye which faded on standing or on addition of more base. Although no hydrogenation procedure could be found which gave III directly from IX, a procedure for the oxidation of X was devised which led to the isolation of IIIb, thus avoiding the extraction of the base, III, from an aqueous mixture containing chromium hydroxide. This modification (Equation 2) was accepted as the best method of synthesis of III.

The successful oxidation of 4-benzylpyridine (VII) by selenium dioxide suggested the similar oxidation of 1-methyl-4-benzylpiperidine (XII) to III as a method of improving the synthesis of III (Equation 3). Villani *et al.*[4] had reported a poor yield of III from the oxidation of XII with chromic acid; however, it was found that XII was not oxidized by selenium dioxide.

The isolation of III (Equation 2) as the hydrobromide (IIIb) permitted its direct bromination to XIII. The product of the bromination was colored and did not give consistent analyses for halogen. This material apparently was the hydrobromide-perbromide, for addition of phenol to a methanolic solution of the red material caused decolorization and led to the isolation of colorless XIII.

The reactions of XIII with hydroxide or alkoxide in nonaqueous solvents led to one of two products, II or 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XV), depending on the solvent. In alcoholic medium II was consistently obtained in excellent yield, while in anhydrous ether XV resulted from the reaction of XIII with hydroxide. A consideration of the conditions of the reaction in ether precludes the formation of XV through II, and a nucleophilic attack of the hydroxide ion on the *tertiary* bromine in the 4-position seems unlikely. The epoxy-alcohol (XVI), analogous to that postulated by Stevens,[3c] appears to offer the most logical explanation for the formation of this product of heterogeneous catalysis. In the homogeneous medium, absolute alcohol, no hydroxy-ketone (XV) was obtained. This, of course, occurs since sodium hydroxide dissolved in absolute methanol is largely in the form of sodium methoxide. For this investigation II was prepared by the reaction of XIII with commercial sodium methoxide in methanol.



The structure of II was fully supported by the infrared absorption spectrum which showed no absorption indicative of a carbonyl or of an hydroxyl group. Bands characteristic of an aliphatic ether (1075 cm.$^{-1}$) and an oxirane ring (1220 and 1280 cm.$^{-1}$) were present in the spectrum of II.

For comparison, 1-methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIV) was prepared by the chlorination of IIIa. The base of XIV was found to be stable and resistant to reaction with sodium hydroxide in ether, but the reaction of XIV with sodium methoxide in methanol gave II.

Unlike the epoxyether (I) of Stevens, II was readily converted to the hydroxyketone (XV) by aqueous mineral acid and formed ketoesters with organic acids.[13] Attempts to prepare the picrate or methiodide of II failed, and only the corresponding derivative of the hydroxyketone (XV) was isolated. It is therefore evident that the acid resistance of I results from a shielding of the epoxy ring created by the chain containing the ammonium group assuming the conformation which places the positive nitrogen in the vicinity of the epoxide ring. The fact that the amino nitrogen of II is in a ring prevents the ammonium ion formed in acid from interfering with attack of acid on the oxirane ring.

EXPERIMENTAL

4-Benzoylpyridine (VIII). A suspension of 26 g. of selenium dioxide and 31.2 g. of 4-benzylpyridine (VII) in 125 ml. of glacial acetic acid was heated carefully until a highly exothermic reaction began. After the initial boiling ceased, the mixture was heated for 0.5 hr. The selenium was removed by filtration, and the solution was concentrated under reduced pressure. Water was added, and the reaction mixture

(9) K. E. Crook and S. M. McElvain, *J. Am. Chem. Soc.*, **52**, 4008 (1930).

(10) F. C. Teague, *J. Am. Chem. Soc.*, **69**, 714 (1947).

(11) G. H. Warner, University of New Hampshire, unpublished results.

(12) G. Scheuing and L. Winterhalder, *Ann.*, **473**, 126 (1929).

(13) R. E. Lyle, H. J. Troscianiec, and G. H. Warner, *J. Org. Chem.*, 338 (1959).

was neutralized with sodium hydroxide solution. The solid which precipitated was isolated by filtration, washed with water, and dried to give 27.5 g. (81%) of 4-benzoylpyridine (VIII), m.p. 69–75°, lit.[14] m.p. 72–75°.

4-Benzoylpyridine methiodide (IXa). A solution of 32.9 g. of 4-benzoylpyridine (VIII) and 52 g. of methyl iodide in 150 ml. of dry methanol was heated under reflux for 2 hr. The solvent was removed by distillation under reduced pressure, and the residue crystallized on addition of acetone giving 56 g. (96%) of IXa, m.p. 174–176°, lit.[5] m.p. 80–180°.

Anal. Calcd. for $C_{13}H_{12}INO$: I, 39.03. Found: I, 39.08, 39.15.

4-Benzoylpyridine methobromide (IXb). To a solution of 3 g. of 4-benzoylpyridine (VIII) in 15 ml. of acetone was added 5 ml. of liquid methyl bromide, and the flask was stoppered tightly. The precipitated salt, 3.8 g. (82%), was collected by filtration. Recrystallization from acetone and drying under reduced pressure gave 4-benzoylpyridine methobromide, (IXb), m.p. 165–168°.

Anal. Calcd. for $C_{13}H_{12}BrNO$: Br, 28.73. Found Br, 28.93, 28.61.

4-Pyridylphenylcarbinol methiodide. The hydrogenation of 10.8 g. of 4-benzoylpyridine methiodide (IXa) in 200 ml. of methanol over 0.2 g. of platinum oxide was stopped after 3 hr. The catalyst was removed by filtration, and the filtrate was concentrated. The residue, after washing with anhydrous ether, partially crystallized. The solid was removed by filtration and discarded, and the filtrate was warmed, treated with ethyl acetate, and cooled to give 1.8 g. (17%) of 4-pyridylphenylcarbinol methiodide, m.p. 143–144°. The melting point of this compound was not depressed on mixing with an authentic sample prepared from 4-pyridylphenylcarbinol.[14] Solutions containing 4-pyridylphenylcarbinol methiodide turned dark blue on addition of base.

Anal. Calcd. for $C_{13}H_{14}INO$: I, 38.79. Found: I, 38.94.

Reduction of 4-benzoylpyridine (VIII). The hydrogenation of 15 g. of VIII in 100 ml. of methanol over 1.0 g. of Raney nickel catalyst at 130° and 50 atm. of pressure of hydrogen for 6 hr. gave an oily solid after evaporation of the solvent. The residue was triturated with petroleum ether extracting 2.18 g. of 4-benzylpyridine (VII). The solid remaining after the trituration was dissolved in water by the addition of acetic acid. Base was added to adjust the *p*H to approximately 6 causing the precipitation of 3.4 g. of 4-pyridylphenylcarbinol, m.p. 112–118°; lit.[14] m.p. 123–125°. The filtrate from the isolation of 4-pyridylphenylcarbinol was made strongly basic giving 8.0 g. of 4-piperidylphenylcarbinol, m.p. 154–159°; lit.[9] m.p. 166–167°. Recrystallization of the solids raised the melting points to the corresponding literature values.

4-Piperidylphenylcarbinol (2.0 g.) was converted to 2.0 g. of 1-benzoyl-4-piperidylphenylcarbinol, m.p. 103–105°, by reaction with 2 g. of benzoyl chloride in aqueous sodium hydroxide. Recrystallization from ethyl acetate gave an analytical sample of 1-benzoyl-4-piperidylphenylcarbinol, m.p. 112–114°.

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.25; H, 7.17; N, 4.74. Found: C, 76.70, 76.69; H, 6.97, 7.21; N, 4.70, 4.78.

1-Methyl-4-piperidylphenylcarbinol (X) *from 4-piperidylphenylcarbinol.* A solution of 4 g. of 4-piperidylphenylcarbinol in 7 ml. of formic acid and 4 ml. of formalin was heated at 100° for 7 hr. The reaction mixture was neutralized while cooling to give 3.95 g. (93%) of 1-methyl-4-piperidylphenylcarbinol, m.p. 149–152°. The melting point was depressed by mixing with the starting material but was not depressed by mixing with authentic 1-methyl-4-piperidylphenylcarbinol (X), m.p. 160–161°.

1-Methyl-4-piperidylphenylcarbinol (X) *from 4-benzoylpyridine methobromide* (IXb). A solution of 15.9 g. of 4-benzoylpyridine methobromide (IXb) in 55 ml. of water was reduced at low pressure over 0.3 g. of platinum oxide for 24 hr. The catalyst was removed by filtration, and the filtrate was neutralized with 50 ml. of 20% potassium hydroxide with cooling. The solid which separated was collected to give 11.0 g. (94%) of 1-methyl-4-piperidylphenylcarbinol (X), m.p. 153–156°, lit.[5] m.p. 157–159°.

The reduction of 10 g. of IXb in 40 ml. of methanol over 0.2 g. of platinum oxide for 4 hr. gave, after removal of the catalyst and solvent, 8.8 g. (85.5%) of 1-methyl-4-piperidylphenylcarbinol hydrobromide, m.p. 133–141°.

Anal. Calcd. for $C_{13}H_{20}BrNO$: Br, 27.92. Found, Br. 27.35, 27.39.

1-Methyl-4-piperidyl phenyl ketone (III). A mixture of 32.5 g. of 1-methyl-4-piperidylphenylcarbinol (X), 13.3 g. of chromic acid anhydride, and 650 ml. of acetic acid was heated at 100° for 1 hr. The solvent was removed by distillation under reduced pressure, and the residue was diluted with 100 ml. of water and basified with 400 ml. of 25% sodium hydroxide solution. The oily layer which separated was dissolved in ether, and the aqueous layer was extracted 3 times with ether. The combined extracts were dried over potassium carbonate and fractionally distilled under reduced pressure. 1-Methyl-4-piperidyl phenyl ketone (III) (27.5 g., 85%) was collected as the fraction boiling at 190° at 21 mm.; lit.[4] b.p. 130–137° at 2 mm.

1-Methyl-4-piperidyl phenyl ketone hydrobromide (IIIb). The reaction of 33 g. of X and 13.5 g. of chromic acid anhydride in 650 ml. of glacial acetic acid was effected as above. After removal of the solvent the green residue was dissolved in chloroform, and the solution was saturated with hydrogen bromide. The chloroform was removed by distillation, and the residue was suspended in hot isopropyl alcohol and filtered. On cooling the filtrate, the hydrobromide (IIIb) precipitated yielding 29.3 g. (65%), m.p. 198–204°, lit.[15] m.p., 211–212°.

1-Methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIII). A solution of 25 g. of 1-methyl-4-piperidyl phenyl ketone hydrobromide (IIIb) in 90 ml. of chloroform was treated with 12 ml. of bromine. The reaction mixture was allowed to stand for 12 hr. at room temperature, and the solvent was removed under reduced pressure. The residue was dissolved in a solution containing 6.5 g. of phenol in 100 ml. of methanol, and the solution was diluted with anhydrous ether precipitating 28.0 g. (93%) of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIII), m.p. 155–156° (dec.).

Anal. Calcd. for $C_{13}H_{17}Br_2NO$: 1 Br, 22.1; 2 Br, 44.2. Found: Br (Volhard), 22.2, 22.4; Br (Stepanow), 44.3, 44.2.

1-Methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIV). 1-Methyl-4-piperidyl phenyl ketone hydrochloride (IIIa) was prepared in quantitative yield from the base (III) by precipitation from a solution of hydrogen chloride in ether. The hydrochloride (IIIa) melted at 201–205° after recrystallization from methanol chloroform. A chloroform solution of 6.4 g. of IIIa was saturated with chlorine and allowed to stand for 12 hr. The solvent was removed under reduced pressure, and the residue was dissolved in methanol and treated with phenol. After filtration, the solution was diluted with anhydrous ether precipitating 5.3 g. (73%) of 1-methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIV), m.p. 179–180° (dec.).

Anal. Calcd. for $C_{13}H_{17}Cl_2NO$: 1 Cl, 12.9. Found: Cl, 12.88, 12.67.

Reactions of 1-methyl-4-halo-4-piperidyl phenyl ketone hydrohalide in alcohol. (a) 1-Methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIII) (3.6 g.) dissolved in 50 ml. of absolute methanol was added dropwise to a refluxing solution of 3.2 g. of sodium in 100 ml. of methanol (or an equivalent amount of commercial sodium methoxide

(14) M. R. Kegelman and F. V. Brown, *J. Am. Chem. Soc.*, **75**, 4649 (1953).

(15) C. A. Grob and E. Renk, *Helv. Chim. Acta*, **37**, 1672 (1954).

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°.

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

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

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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: