Aminoketone Rearrangements. II. The Rearrangement of Phenyl α-Aminoketones[1]

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RECEIVED SEPTEMBER 5, 1962
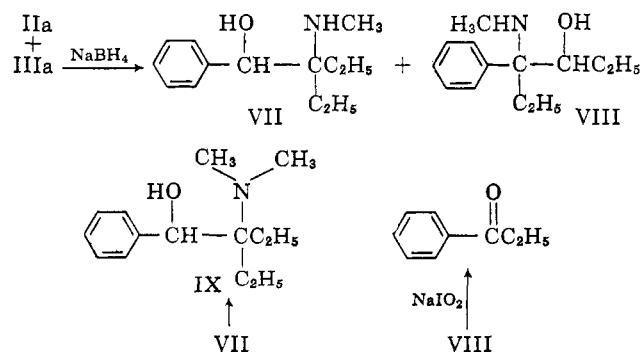
Phenyl α-aminoketones have been shown to undergo carbon skeleton rearrangement to unconjugated amino-ketones when heated at 200–240°. The probable intermediate is an unconjugated hydroxyimine formed by base removal of an amine hydrogen and migration of an alkyl group. The hydroxyimine can subsequently rearrange by base removal of a hydroxyl proton and migration of the phenyl grouping. An amine hydrogen has been shown to be necessary by the inactivity of tertiary aminoketones. Unconjugated hydroxyketones have been synthesized and converted to the corresponding unconjugated aminoketones by heating with methylamine at 200°. This lends evidence to the proposed hydroxyimine intermediate.

It has been found in this Laboratory that the reaction of primary and secondary amines with epoxyethers of type I at elevated temperatures yields phenyl α-aminoketones (II) containing the carbon skeleton of the epoxyethers.[3] In an attempt to increase the yield of the aminoketone IIa from the epoxyether Ia by raising the temperature of the reaction to 240°, an unconjugated aminoketone IIIa was also obtained. The mixture of ketones was separated via their crystalline

Ia, $R_1 = R_2 = C_2H_5$
b, $R_1 = R_2 = CH_3$
c, $R_1 = CH_3$, $R_2 = C_2H_5$

IIa, $R_1 = R_2 = C_2H_5$
b, $R_1 = R_2 = CH_3$
c, $R_1 = CH_3$, $R_2 = C_2H_5$

IIIa, $R_1 = R_2 = C_2H_5$
b, $R_1 = R_2 = CH_3$
c, $R_1 = CH_3$, $R_2 = C_2H_5$

IVa, $R_1 = R_2 = C_2H_5$ V   VIa, $R_1 = R_2 = C_2H$
b, $R_1 = R_2 = CH_3$[5]
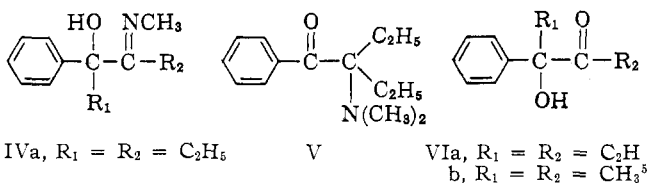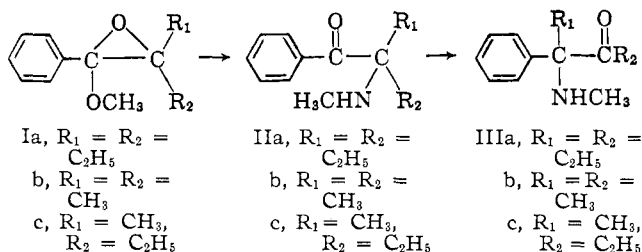
amino alcohols VII and VIII obtained by sodium borohydride reduction. The structure of VII was established by N-methylation to a tertiary amino alcohol IX whose hydrochloride was identical with the hydrochloride of the aminoalcohol derived from the sodium borohydride reduction of the tertiary aminoketone V. The structure of VIII was established by periodate cleavage to yield propiophenone, identified as its 2,4-dinitrophenylhydrazone.

When the aminoketone IIa was heated with methylamine and methanol, it was partially converted into the unconjugated aminoketone IIIa, as shown by infrared analysis. These are the same conditions under which these aminoketones were formed in the original epoxyether reaction. This indicated that IIa was a probable intermediate in the conversion of the epoxyether to the unconjugated aminoketone

Phenyl epoxyethers (I) are known to rearrange to unconjugated methoxyketones in the presence of Lewis acids.[4] However, the possibility that Ia, in the presence of Lewis acid in the walls of the steel autoclave, rearranged to such an unconjugated methoxyketone, which was subsequently transformed to IIIa, was eliminated. When 3-methoxy-3-phenylhexanone-4 was heated with methylamine at 240°, 71% of the starting material was recovered with only a trace of basic material formed.

The problem thus became the determination of the mechanism for the conversion of IIa to IIIa. The infrared spectra of the products obtained from the reaction of IIa with methylamine at 240° showed strong absorption at 5.82 μ, indicating the unconjugated carbonyl of IIIa; an absorption band at 6.05 μ, characteristic of ketone imines; and a slight absorption at 5.93 μ corresponding to the conjugated carbonyl of IIa. After this mixture of bases was hydrolyzed with dilute acid, the ketone imine band disappeared completely and the absorption at 5.93 μ increased considerably. This observation indicated that the low yield of unconjugated aminoketone IIIa might be due in part to the presence of more stable iminoamine in the reaction mixture. Further, cleavage of the conjugated aminoketone IIa by excess methylamine could reduce the yield of the rearranged aminoketone IIIa. Thus, it was felt that conversion of IIa to IIIa might proceed more readily in the absence of methylamine.

When the conjugated aminoketone IIa was heated in a sealed tube in the absence of methylamine, an infrared spectra of the basic material obtained after acid hydrolysis of the reaction mixture showed unconjugated aminoketone with only a small amount of conjugated aminoketone. The aminoketone IIIa was isolated as the hydrochloride in 35% yield.

A mechanism involving the rearrangement of IIa to the hydroxyimine XI via the epoxyamine X[5] followed by conversion to the unconjugated ketone IIIa by a base-catalyzed pinacol-type rearrangement was eliminated. Such a mechanism proceeding through an epoxyamine was proposed by Nelson[6] in the rearrangement of α-anilinopropiophenone to α-phenyl-α-anilino-acetone in the presence of aniline hydrobromide. However, when the hydroxyimine XI was heated to 240°,

(1) Presented before the Division of Organic Chemistry at the 142nd National Meeting of the American Chemical Society in Atlantic City, N. J., September 10, 1962. A preliminary report appeared in J. Am. Chem. Soc., 84, 2272 (1962).

(2) Abstracted in part from the dissertation submitted by Robert D. Elliott in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Wayne State University, 1961.

(3) C. L. Stevens and C. H. Chang, J. Org. Chem., 27, 4392 (1962).

(4) C. L. Stevens and S. D. Dykstra, J. Am. Chem. Soc., 76, 4402 (1954).

(5) C. L. Stevens, P. Blumbergs and M. E. Munk, J. Org. Chem., 28, 331 (1963). A type X intermediate is proposed in the formation of 1-phenyl-1-imino-2-methyl-2-propanol from the reaction of α-bromoisobutyrophenone with methylamine.)

(6) K. L. Nelson and R. L. Seefeld, J. Am. Chem. Soc., 80, 5957 (1958).
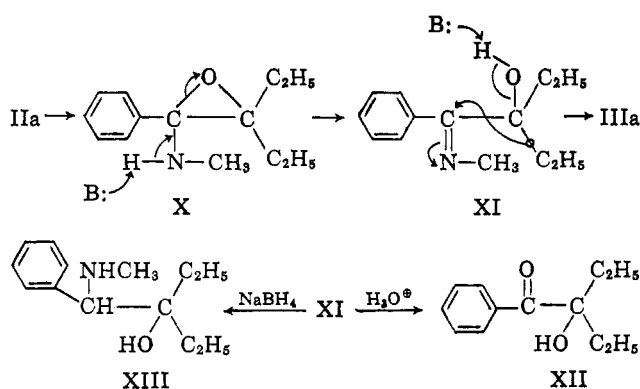
only a 7% yield of IIIa hydrochloride was obtained as compared to a 35% yield of the same product from the thermal rearrangement of IIa. Thus, the hydroxyimine XI is not an intermediate in the formation of IIIa. The structure of XI was established by hydrolysis to the known hydroxyketone XII.[7] Infrared data, analysis and sodium borohydride reduction to the aminoalcohol XIII also supported this structure assignment.

The mechanism proposed to explain the rearrangement of IIa to IIIa involves base abstraction of the amine proton and migration of an ethyl group to form the hydroxyimine IVa. The hydroxyimine can, by a similar base abstraction of the hydroxyl proton and migration of the phenyl group, be converted to IIIa. The aminoketone itself can act as the base; alternatively, one or both of the rearrangements can involve a cyclic intramolecular mechanism.
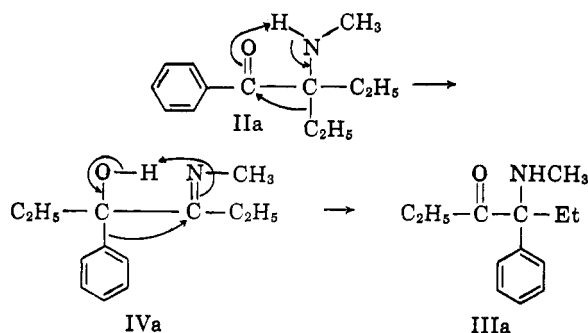
A similar mechanism has been proposed to explain the base-catalyzed isomerization of α-hydroxyketones.[8-13] In addition, Eastham[13] has shown by use of C^{14}-tracer studies that migration results, even in the absence of conditions favorable to rearrangement, such as release of steric strain. The starting ketone recovered after treatment of C^{14}-labeled p-anisylanisoin with base showed a statistical distribution of C^{14}-label.

The rearrangements considered here differ from the α-hydroxyketone rearrangements in that a discrete intermediate, the hydroxyimine, occurs between the initial aminoketone and the final isomeric aminoketone.

The necessity of the amine hydrogen was demonstrated in an attempted rearrangement of the tertiary aminoketone V at 265°. The absence of unconjugated carbonyl in the infrared spectra and the recovery of the

starting aminoketone in 70% yield indicated that no rearrangement had occurred.

In order to test the validity of the proposed hydroxyimine mechanism, the hydroxyimine IVa was prepared by heating the hydroxyketone VIa with methylamine at 100°. The ketone absorption band in the infrared was converted almost entirely to the imine absorption band at 6.05 μ. When the pure iminoalcohol IVa was heated in a sealed tube at 200°, a 32% yield of the rearranged aminoketone IIIa was obtained. Likewise, when the hydroxyketone VIa was heated directly with methylamine at 200°, the rearranged aminoketone IIIa was obtained in 32.4% yield. These experimental results lend support to the proposed mechanism. An analogous hydroxyimine rearrangement has been studied by Witkop and Patrick.[14] These authors have shown that the hydroxyimine XIV rearranges readily in the presence of acid, base or heat to the aminoketone XV.
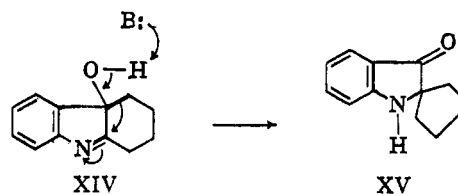
The generality of the rearrangement of hydroxyimines was further demonstrated by the similar conversion of hydroxyketones VIb and XVI to the aminoketones IIIb and XVII in 39% and 36% yield, respectively. The structure of the aminoketone XVII was established by the formation of acetophenone (isolated as its 2 4-dinitrophenylhydrazone) upon periodate cleavage of the aminoalcohol obtained from sodium borohydride reduction of XVII.
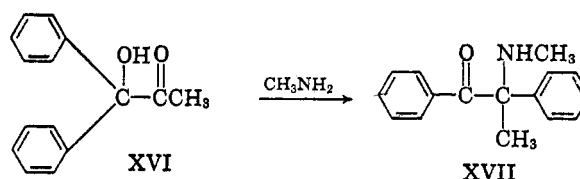
A mechanism involving direct displacement of the hydroxyl group of XVI by methylamine followed by rearrangement of the resulting aminoketone XVIII via its iminoamine was also eliminated. This aminoketone was synthesized independently by the treatment of the corresponding α-bromoketone with methylamine in benzene and then subjected to the conditions of the rearrangement. The only isolable product, N-methylbenzhydrylamine, was obtained in 82% yield. Thus, the α-aminoketone XVIII could not be an intermediate in the rearrangement.

A previous attempt to prepare XVIII by heating methylbenzoin XIX with methylamine resulted in a single isolable product, N-methylbenzhydrylamine being obtained in 4% yield. Thus, some initial rearrangement to the aminoketone XVIII had probably occurred. Confirmation of the structure of XVIII was obtained by the isolation of the 2,4-dinitrophenylhydrazones of benzophenone and acetaldehyde following the periodate cleavage of the aminoalcohol.

To show further the scope and generality of the rearrangement of phenyl α-aminoketones and phenyl-α-hydroxyimines, several other series of compounds were studied. For example, when 2-methyl-2-methylaminobutyrophenone (IIc) was heated in a sealed tube at 185°, a 32% yield of 2-methylamino-2-phenyl-3-pentanone (IIIc) was obtained. Structural assignment of

(7) H. Larramona, Compt. rend., **237**, 192 (1953).

(8) I. Elphimoff-Felkin, G. LeMyet, and B. Tchoubar, Bull. soc. chim. France, 522 (1958).

(9) D. Y. Curtin and A. Bradley, J. Am. Chem. Soc., **76**, 5778 (1954).

(10) D. Y. Curtin and S. Leskowitz, ibid., **73**, 2633 (1951).

(11) C. W. Shoppee and D. A. Prins, Helv. Chim. Acta, **26**, 185 (1943), and succeeding papers.
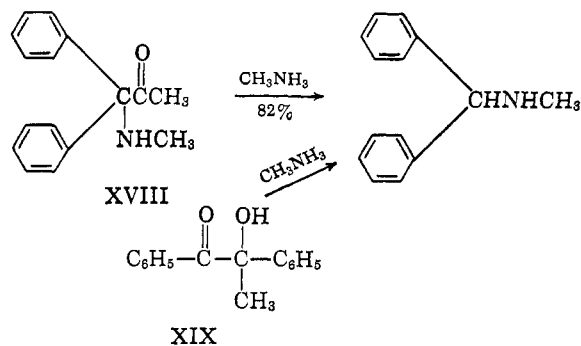
(12) H. E. Stavely, J. Am. Chem. Soc., **62**, 489 (1940).

(13) J. F. Eastham, J. E. Huffaker, V. F. Raaen and C. J. Collins, ibid., **78**, 4323 (1956).

(14) B. Witkop and J. B. Patrick, ibid., **73**, 2196 (1951).

XVIII

XIX

IIIc was based on sodium borohydride reduction of IIIc to diastereoisomeric aminoalcohols followed by periodate cleavage of one of the diastereosiomers to give acetophenone and propionaldehyde, identified as their 2,4-dinitrophenylhydrazones.

Rearrangements that lead to ring expansion or ring contraction have also been observed. When 1-methyl-amino-cyclopentyl phenyl ketone (XX) was heated at 220° in a se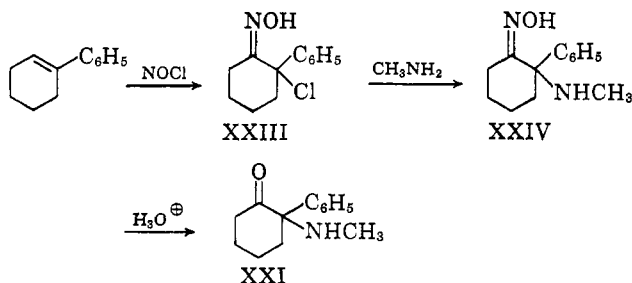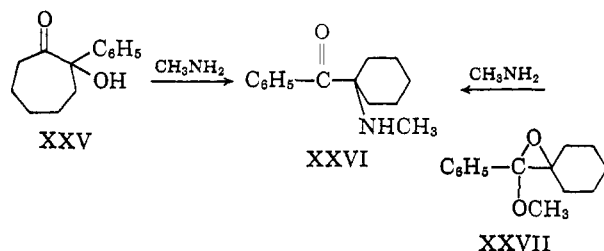aled tube, 2-methylamino-2-phenylcyclo-hexanone (XXI) was isolated. Infrared and ultra-violet spectra of XXI showed absorption peaks indicative of an unconjugated carbonyl. Sodium borohydride

XX   XXI   XXII
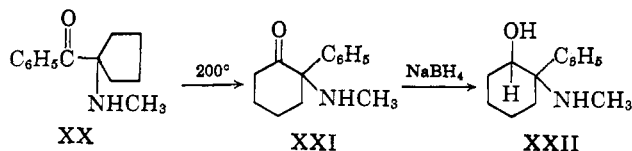
reduction of XXI gave the aminoalcohol XXII. The structure of XXI was established by independent synthesis. Using the procedure of Koelsch,[15] a 47% yield of 2-chloro-2-phenylcyclohexanone oxime (XXIII) was obtained from the reaction of 1-phenylcyclohexene and nitrosyl chloride. The chlorine atom of XXIII was replaced with methylamine to give 2-methylamino-2-phenyl-cyclohexanone oxime (XXIV). Acid hydrolysis of XXIV gave a product that was identical in every respect with that obtained by the thermal rearrangement of XX. The possibility that 2-phenyl-2-cyclohexenone oxime[15] had been formed from the

XXIII   XXIV

XXI

α-chloro oxime XXIII under the basic reaction conditions, followed by a Michael addition of methylamine to give 3-methylamino-2-phenylcyclohexanone oxime, was eliminated. Reaction of the unsaturated oxime with methylamine gave no amino oxime under the conditions used for the preparation of XXIV.

XXV   XXVI   XXVII

(15) C. F. Koelsch, J. Am. Chem. Soc., 73, 2951 (1951).

When 2-hydroxy-2-phenylcycloheptanone (XXV) was heated at 200° in a sealed tube with methylamine, 1-methylaminocyclohexyl phenyl ketone (XXVI) resulted. Structure proof of XXVI was by independent synthesis involving treatment of the epoxyether XXVII with methylamine.

Experimental

1,2-Epoxy-2-ethyl-1-methoxy-1-phenylbutane (Ia).—Using the procedures of Stevens and Weinheimer,[16] 39 g. (97%) of epoxyether Ia,[17] b.p. 52–53° (0.22 mm.), $n^{27}D$ 1.4897, was obtained from the reaction of 50 g. (0.20 mole) of 2-bromo-2-ethylbutyrophenone and one equivalent of freshly prepared sodium methoxide.

2-Ethyl-2-methylaminobutyrophenone (IIa).—A steel autoclave containing 15.8 g. (0.077 mole) of epoxyether Ia in 60 ml. of liquid methylamine was heated at 140° for 12 hours. The excess methylamine was removed on a steam-bath in vacuo. The residue was heated on a steam-bath for 1 hour with 30 ml. of 3 N hydrochloric acid. The resulting solution was washed with ether, made basic with dilute sodium hydroxide solution and then extracted with ether. The ether fraction was dried over anhydrous potassium carbonate, filtered, and the ether removed in vacuo. Fractional distillation of the residue on an 8-inch Vigreux column gave 9.9 g. (63%) of the aminoketone IIa, b.p. 74–76° (0.12 mm.), $n^{25}D$ 1.5227.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33. Found: C, 75.83; H, 9.52.

A portion of the aminoketone was converted to the hydrochloride, m.p. 204.5–205°.

Anal. Calcd. for $C_{13}H_{20}ClNO$: C, 64.59; H, 8.34. Found: C, 64.63; H, 8.26.

α-(1-Ethyl-1-methylaminopropyl)-benzyl Alcohol (VII).—A solution of 0.035 g. (0.00015 mole) of IIa hydrochloride was made basic with dilute sodium hydroxide and extracted with ether. The ether layer was dried over anhydrous potassium carbonate, filtered, and the ether removed in vacuo. To a solution of the residue in 4 ml. of methanol was added 0.010 g. (0.00027 mole) of sodium borohydride. After the solution had stood for 6 hours, the methanol was removed in vacuo and the residue was dissolved in dilute hydrochloric acid. The acid solution was washed with ether, then made basic with dilute sodium hydroxide and extracted with ether. Addition of a saturated solution of hydrogen chloride in 2-propanol[18] to the dried ether extract gave 0.021 g. (61%) of the aminoalcohol hydrochloride, m.p. 254–255°. Recrystallization from ethanol–ether gave an analytical sample, m.p. 259°.

Anal. Calcd. for $C_{13}H_{22}ClNO$: C, 64.05; H, 9.10. Found: C, 64.29; H, 9.10.

The free base had m.p. 50°.

Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.32; H, 10.21. Found: C, 75.37; H, 10.03.

Reaction of 1,2-Epoxy-2-ethyl-1-methoxy-1-phenylbutane (Ia) with Methylamine at 240°.—A steel autoclave containing 30.5 g. (0.148 mole) of epoxyether Ia and 150 ml. of methylamine was heated at 240° for 11 hours. The excess methylamine was removed in vacuo and the residue flash distilled. An infrared spectrum of the distillate showed strong absorption at 1730 and 1653 cm.$^{-1}$ indicative of unconjugated carbonyl and carbon–nitrogen double bonds, respectively. The distillate, 25.4 g., was heated on a steam-bath with 60 ml. of 6 N hydrochloric acid for 4 hours. The acid solution was washed with ether, made basic with dilute sodium hydroxide, and extracted with ether. The ether layer was dried over anhydrous sodium sulfate, filtered, and the ether removed in vacuo. The residue was flash distilled to give 15.3 g. (51%) of a mixture of aminoketones IIa and IIIa. An infrared spectrum of this distillate showed approximately equal absorption at 1730 and 1678 cm.$^{-1}$, indicative of unconjugated and conjugated carbonyl groups, respectively. To the mixture of aminoketones in 45 ml. of methanol was added 2.7 g. (0.075 mole) of sodium borohydride. The solution was allowed to stand for 12 hours, made acidic with dilute hydrochloric acid, and the methanol then removed in vacuo. The aqueous fraction was made basic and extracted with chloroform. The chloroform layer was dried and the solvent removed in vacuo. Crystallization of the residue from 13 ml. of hexane gave 6.4 g. (21%) of aminoalcohol VIII, m.p. 120–121°.

Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.78; O, 7.72. Found: C, 75.30; H, 10.18; N, 6.69; O, 7.81.

(16) C. L. Stevens and A. J. Weinheimer, ibid., 80, 4072 (1958).

(17) C. L. Stevens and T. H. Coffield, ibid., 80, 1920 (1958).

(18) All of the amine hydrochlorides were prepared in this manner unless otherwise indicated.

The residue obtained after evaporation of the mother liquor was dissolved in 25 ml. of 3 N hydrochloric acid. The hydrochloride of VII crystallized and was filtered. The mother liquor was concentrated and allowed to crystallize until no further solid appeared. A total yield of 6.1 g. (17%) of VII hydrochloride, m.p. 251–252°, was obtained. A mixture melting point with a sample of VII hydrochloride obtained from the reduction of the conjugated aminoketone IIa showed no depression.

α-(1-Dimethylamino-1-ethylpropyl)-benzyl Alcohol (IX). A.— To a 50-ml. flask containing 0.33 g. (0.0015 mole) of aminoketone V[3] in 15 ml. of methanol was added 0.057 g. (0.0015 mole) of sodium borohydride. The mixture was allowed to stand overnight, acidified, and the methanol removed *in vacuo*. The acid solution was made basic and extracted with ether. The ether extract was dried over anhydrous potassium carbonate, filtered, and the ether removed *in vacuo*. A solid residue was obtained which was recrystallized from hexane to give 0.26 g. (76%) of aminoalcohol IX, m.p. 81–82°.

Anal. Calcd. for $C_{14}H_{23}NO$: C, 75.97; H, 10.47. Found: C, 76.09; H, 10.36.

A portion of the amine was converted to the hydrochloride, m.p. 233° dec.

Anal. Calcd. for $C_{14}H_{24}ClNO$: C, 65.25; H, 9.38. Found: C, 65.28; H, 9.00.

B.—Aminoalcohol VII was converted to its N,N-dimethyl derivative by the Eschweiler–Clarke procedure. The crude product, however, showed the presence of amide absorption in its infrared spectrum (probably due to the N-formyl side product). The aminoalcohol was purified by treatment of the crude product with lithium aluminum hydride in ether to give a 74% yield of the N,N-dimethylaminoalcohol isolated as its hydrochloride, m.p. 232° dec. A mixture melting point with the hydrochloride obtained from the reduction of V showed no depression.

Periodate Oxidation of α,β-Diethyl-β-methylaminophenethyl Alcohol (VIII).—To a solution of 0.20 g. (0.00094 mole) of VIII in 6 ml. of methanol was added 11 ml. (0.0011 mole) of 0.1 M sodium metaperiodate solution. The solution was allowed to stand at room temperature for 2 days, then was steam distilled into a solution of 2,4-dinitrophenylhydrazine hydrochloride in methanol. The precipitate was heated with 40 ml. of benzene on a steam-bath, filtered, and the filtrate was passed over a column containing 20 g. of neutral alumina, followed by elution with benzene. The residue obtained after removal of the solvent *in vacuo* was recrystallized from ethanol and ethyl acetate to give 0.14 g. (50.2%) of propiophenone 2,4-dinitrophenylhydrazone, m.p. 189–190°. A mixture melting point with an authentic sample showed no depression.

Attempted Rearrangement of 3-Methoxy-3-phenyl-4-hexanone. —Using the procedure of Stevens and Dykstra,[4] 5.0 g. (0.24 mole) of epoxyether Ia was rearranged in the presence of magnesium bromide to give 4.5 g. (91%) of the unconjugated methoxyketone, b.p. 50–52° (0.06 mm.), $n^{26}D$ 1.5019.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.60; H, 8.53.

An autoclave containing 3.86 g. (0.0187 mole) of the methoxyketone and 50 ml. of methylamine was heated at 240° for 10 hours. The starting methoxyketone was recovered in 71% yield. The only basic material isolated (0.06 g.) showed no infrared absorption at 1730 cm.$^{-1}$ (unconjugated carbonyl).

Reaction of 2-Ethyl-2-methylaminobutyrophenone (IIa) with Methylamine and Methanol at 240°.—An autoclave containing 4.1 g. (0.020 mole) of aminoketone IIa, 0.62 g. (0.020 mole) of methanol and 20 ml. of methylamine was heated under the same conditions as was the epoxyether Ia previously described.

The infrared spectrum of the flash distillate showed absorption peaks at 1730 and 1653 cm.$^{-1}$ in the same intensity ratio (approximately 1:1) as that obtained from the reaction of Ia with methylamine. An infrared spectrum of the aminoketone obtained after acid hydrolysis and flash distillation also showed carbonyl absorption peaks at 1730 and 1680 cm.$^{-1}$, again in the same ratio as that from the epoxyether reaction.

Thermal Rearrangement of 2-Ethyl-2-methylaminobutyrophenone (IIa).—A sealed tube containing 1.83 g. (0.0089 mole) of conjugated aminoketone IIa was placed in an autoclave and surrounded with 15 ml. of toluene to counteract any pressure which might develop in the tube. The autoclave was heated at 250° for 10 hours. The product, after flash distillation, was dissolved in dilute hydrochloric acid and washed with ether. The acid solution was made basic and extracted with ether. The ether layer was dried and the ether removed *in vacuo*. The residue was microdistilled to give 0.88 g. of a pale yellow liquid whose infrared spectrum showed strong absorption at 1730 cm.$^{-1}$ with only slight absorption at 1678 cm.$^{-1}$. The crude 3-methylamino-3-phenyl-4-hexanone (IIIa) was isolated as its hydrochloride. The precipitated hydrochloride was recrystallized from ethanol and ether to give 0.75 g. (35%) of colorless crystals, m.p. 209–

210°. Recrystallization provided an analytical sample, m.p. 210.5–211°.

Anal. Calcd. for $C_{13}H_{20}ClNO$: C, 64.59; H, 8.34; N, 5.79. Found: C, 64.77; H, 8.44; N, 5.98.

A portion of IIIa hydrochloride was converted in 98% yield to the free amine, b.p. 60–65° (0.03 mm.), $n^{23.5}D$ 1.5135, d^{25}_4 0.9972.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33. Found: C, 76.06; H, 9.10.

α,β-Diethyl-β-methylaminophenethyl Alcohol (VIII).—Using the procedure for the reduction of V, 0.76 g. (0.0037 mole) of IIIa was reduced with 0.28 g. (0.0074 mole) of sodium borohydride. Crystallization of the product from hexane gave 0.43 g. (56%) of aminoalcohol VIII, m.p. 120.5–121.5°. A mixture melting point with the aminoalcohol, m.p. 120–121°, obtained in the reaction of Ia with methylamine showed no depression.

A portion of the aminoalcohol was converted to its hydrochloride, m.p. 188°.

Anal. Calcd. for $C_{13}H_{22}ClNO$: C, 64.05; H, 9.10. Found: C, 63.87; H, 8.97.

Attempted Rearrangement of 2-Dimethylamino-2-ethylbutyrophenone (V).—When 1.16 g. (0.0053 mole) of V was heated in a sealed tube at 265° for 10 hours, an infrared spectrum of the basic material obtained by the usual procedure showed no rearranged aminoketone (no absorption in the 1730 cm.$^{-1}$ region). The starting material was recovered in 76% yield.

Thermal Rearrangement of α,α-Diethyl-β-methyliminophenethyl Alcohol (XI).—2-Bromo-2-ethylbutyrophenone (30.4 g.) was converted to the iminoalcohol XI in 94.2% yield, b.p. 68–70°, $n^{25}D$ 1.5131, using the procedure of Stevens, Blumbergs and Munk.[5] An infrared spectrum of the product showed absorption at 3390 and 1675 cm.$^{-1}$ corresponding to hydroxyl and carbon–nitrogen double bond absorption.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.32. Found: C, 76.04; H, 9.07.

A hydrochloride was prepared, m.p. 184–186°.

Anal. Calcd. for $C_{13}H_{20}ClNO$: C, 64.58; H, 8.34; Cl, 14.67. Found: C, 65.05; H, 8.04; Cl, 14.67.

A sealed tube containing 1.6 g. (0.0076 mole) of the iminoalcohol was heated at 240° for 14 hours and worked up using the procedure described for the rearrangement of IIa. From the reaction mixture was isolated 0.13 g. (7.1%) of IIIa hydrochloride, m.p. 208–210°.

The rearrangement was repeated using methylamine as a solvent. The unconjugated aminoketone IIIa was obtained in 6% and 7% yield in two separate experiments.

Hydrolysis of α,α-Diethyl-β-methyliminophenethyl Alcohol (XI).—One gram (0.0049 mole) of XI was heated on a steambath with 15 ml. of 6 N hydrochloric acid for 24 hours. An ether extract of the reaction mixture was dried and the ether removed *in vacuo*. The residue was microdistilled to give 0.85 g. (91%) of 2-ethyl-2-hydroxybutyrophenone (XII), b.p. 68° (0.03 mm.), $n^{28}D$ 1.5200 (lit.[7] $n^{23}D$ 1.5210). The hydroxyketone was converted to its semicarbazone derivative, m.p. 185–186° (lit.[7] 196–197°), in 81% yield.

Anal. Calcd. for $C_{13}H_{19}N_3O_2$: C, 62.63; H, 7.68. Found: C, 62.46; H, 7.97.

α,α-Diethyl-β-methylaminophenethyl Alcohol (XIII).—Eight grams (0.039 mole) of the iminoalcohol XI was reduced with 1.84 g. (0.049 mole) of sodium borohydride to the aminoalcohol XIII using the procedure for the reduction of aminoketone V. The aminoalcohol XIII was isolated by fractional distillation to give 6.9 g. (86%) of a colorless liquid, b.p. 78–81° (0.2 mm.). The liquid crystallized from pentane at Dry Ice–acetone temperature to give the aminoalcohol XIII, m.p. 32–33°.

Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.32; H, 10.21. Found: C, 75.14; H, 10.28.

Five grams of XIII was converted in 99% yield to the hydrochloride, m.p. 161–162°. Recrystallization from ethanol–ether provided an analytical sample, m.p. 163–165°.

Anal. Calcd. for $C_{13}H_{22}ClNO$: C, 64.05; H, 9.10. Found: C, 63.89; H, 9.25.

Three-tenths gram of XIII was converted in 98% yield to its picrate, m.p. 142–143°.

Anal. Calcd. for $C_{19}H_{24}N_4O_8$: C, 52.29; H, 5.54. Found: C, 52.51; H, 5.63.

3-Hydroxy-3-phenyl-4-hexanone (VIa).—2-Ethyl-2-hydroxybutyrophenone (XII),[7] prepared in 96% yield from the epoxyether Ia by the procedure of Stevens and Farkas,[19] was isomerized to the unconjugated hydroxyketone VIa by a modification of the procedure of Tchoubar.[8] A solution of 27 g. (0.14 mole) of the conjugated hydroxyketone in 200 ml. of 6 N sodium hydroxide solution and 100 ml. of ethanol was heated at the reflux temperature for 48 hours. The solution was diluted with

(19) C. L. Stevens and E. Farkas, *J. Am. Chem. Soc.*, **74**, 618 (1952).

300 ml. of water and extracted with ether. The ether layer was dried and the solvent removed *in vacuo*. The residue was flash distilled to give a colorless oil whose infrared spectrum indicated chiefly unconjugated ketone. This crude product was converted to its semicarbazone. There was obtained 20.4 g. (58% over-all yield) of white crystals, m.p. 134–136°. Recrystallization from ethanol–water gave an analytical sample, m.p. 136–137°.

Anal. Calcd. for $C_{13}H_{19}N_3O_2$: C, 62.63; H, 7.68. Found: C, 62.71; H, 7.92.

Following the procedure of Hey and Morris,[20] 20.4 g. (0.082 mole) of the semicarbazone was hydrolyzed with 15% oxalic acid to give 13.8 g. (89%) of hydroxyketone VIa, b.p. 67°(0.22 mm.). An infrared spectrum of the product showed strong absorption at 1720 cm.$^{-1}$ indicative of an unconjugated carbonyl. The spectrum showed no trace of conjugated carbonyl.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.80; H, 8.63.

α-Ethyl-α-(1-methyliminopropyl)-benzyl Alcohol (IVa).—An autoclave containing 13.6 g. (0.071 mole) of hydroxyketone VIa and 75 ml. of methylamine was heated at 100° for 10 hours. The product obtained after removal of excess methylamine *in vacuo* was flash distilled. The distillate, which showed strong absorption in the infrared at 3322 and 1660 cm.$^{-1}$, was dissolved in 500 ml. of anhydrous ether and filtered. Anhydrous hydrogen chloride was bubbled through the filtrate until no further precipitation occurred. The supernatant liquid was siphoned off through a sintered glass filter. To the hydrochloride was added 500 ml. of anhydrous pentane and 20 ml. (0.14 mole) of anhydrous triethylamine. The suspension was stirred at room temperature overnight. The supernatent liquid was siphoned off through a sintered glass filter. The solvent was removed *in vacuo* and the residue flash distilled to give 8.8 g. (61%) of colorless iminoalcohol, b.p. 82–83.5° (0.14 mm.), n^{21}D 1.5215. An infrared spectrum of the product showed no carbonyl impurity.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.00; H, 9.53; N, 7.06.

Thermal Rearrangement of α-Ethyl-α-(1-methyliminopropyl)-benzyl Alcohol (IVa).—A sealed tube containing 2.9 g. (0.014 mole) of the iminoalcohol IVa was heated at 200° for 10 hours. Using the procedure previously described for the rearrangement of IIa, 1.09 g. (32%) of 3-methylamino-3-phenyl-4-hexanone (IIIa) was isolated as its hydrochloride, m.p. 211–212°.

Thermal Rearrangement of 3-Hydroxy-3-phenyl-4-hexanone (VIa) with Methylamine.—Four grams (0.021 mole) of hydroxyketone VIa and 30 ml. of methylamine were heated in an autoclave at 200° for 10 hours. After removal of excess methylamine, the basic fraction was isolated, using the procedure previously described for the rearrangement of IIa. From the basic fraction was obtained 1.44 g. (32%) of the unconjugated aminoketone IIIa as the hydrochloride, m.p. 210.5–211°.

Thermal Rearrangement of 3-Hydroxy-3-phenyl-2-butanone (VIb) with Methylamine.—Five grams (0.030 mole) of VIb[21] and 25 ml. of methylamine were heated in an autoclave at 200° for 10 hours. Using the procedure previously described for the rearrangement of IIa, 2.5 g. (39%) of 3-methylamino-3-phenyl-2-butanone (IIIb) was obtained as the hydrochloride, m.p. 211–212°. Recrystallization from ethanol–ether gave an analytical sample, m.p. 213.5°.

Anal. Calcd. for $C_{11}H_{16}ClNO$: C, 61.82; H, 7.53. Found: C, 61.55; H, 7.51.

Thermal Rearrangement of 1,1-Diphenyl-1-hydroxy-2-propanone (XVI) with Methylamine.—Six-tenths of a gram (0.0027 mole) of XVI[22] and 5 ml. of methylamine were sealed in a Pyrex tube and placed in an autoclave with 50 ml. of methylamine to counteract any pressure developed in the sealed tube. The autoclave was heated at 200° for 10 hours and 0.27 g. (36%) of 2-methylamino-2-phenylpropiophenone (XVII) was isolated as the hydrochloride, m.p. 215.5–216°, by the usual procedure. An infrared spectrum of the aminoketone showed only conjugated carbonyl group absorption.

Anal. Calcd. for $C_{16}H_{18}ClNO$: C, 69.69; H, 6.58. Found: C, 69.90; H, 6.80.

β-Methyl-β-methylamino-α-phenylphenethyl Alcohol.—Using the procedure for the reduction of IIa, 0.49 g. (0.0018 mole) of pure crystalline XVII hydrochloride was converted to the free amine and reduced with 0.14 g. (0.0036 mole) of sodium borohydride. Fractional crystallization of the product from hexane at ice-box temperature gave 0.12 g. (28%) of aminoalcohol, m.p. 114–115°. Recrystallization gave an analytical sample, m.p. 122°.

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.93. Found: C, 79.41; H, 7.64.

Concentration of the mother liquors gave 0.18 g. (42%) of the diastereomeric amino alcohol, m.p. 90–91°. Recrystallization gave an analytical sample, m.p. 90–91°.

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.93. Found: C, 79.66; H, 7.68.

A mixture melting point of the two isomers showed a melting range of 80–115°. The infrared spectra of the two isomers in chloroform were identical except for minor variations between 1000 and 1100 cm.$^{-1}$.

Periodate Oxidation of β-Methyl-β-methylamino-α-phenylphenethyl Alcohol.—The hydrochloride of XVII (0.15 g., 0.00054 mole) was converted to the aminoalcohol as described above. To a solution of the aminoalcohol in 5 ml. of methanol was added 7 ml. (0.0007 mole) of 0.1 *M* sodium metaperiodate solution. After standing for 24-hours at room temperature, the solution was extracted with ether and the ether layer was extracted with 40% sodium bisulfite solution. No benzaldehyde was isolated from the sodium bisulfite solution; however, the ether layer, after removal of solvent, gave a 51% yield of acetophenone, isolated as its 2,4-dinitrophenylhydrazone (0.082 g., m.p. 240°). A mixture melting point with an authentic sample showed no depression.

Pyrolysis of Methylbenzoin (XIX)[23] with Methylamine.—An autoclave containing 8.0 g. (0.035 mole) of methylbenzoin and 50 ml. of methylamine was heated at 200° for 10 hours. From the reaction mixture was obtained by the usual procedure 0.3 g. (4%) of N-methylbenzhydrylamine as its hydrochloride, m.p. 240°. A mixture melting point with an authentic sample showed no depression.

1,1-Diphenyl-1-methylamino-2-propanone (XVIII).—Aminoketone XVIII was prepared by a modification of the procedure of Emde and Runne.[24] To a solution of 10 g. (0.035 mole) of 1-bromo-1,1-diphenyl-2-propanone[25] in 50 ml. of cold benzene was added 2.3 g. (0.076 mole) of methylamine in 50 ml. of cold benzene. After the solution was allowed to stand at room temperature for 2 days, it was filtered to give a 97% yield of methylamine hydrobromide, showing almost complete reaction. The filtrate was extracted with 0.5 N hydrochloric acid. The aqueous layer was made basic, extracted and the solvent removed *in vacuo* on a steam-bath. The brown residue of XVIII was converted to the hydrochloride and recrystallized from methanol–ether to give 1.08 g. (11.3%) of white crystals, m.p. 210–212°. Recrystallization gave an analytical sample, m.p. 214–115°.

Anal. Calcd. for $C_{16}H_{18}ClNO$: C, 69.69; H, 6.58. Found: C, 69.57; H, 6.63.

Pyrolysis of 1,1-Diphenyl-1-methylamino-2-propanone (XVIII) with Methylamine.—Seven-tenths of a gram (0.0025 mole) of the hydrochloride of XVIII was converted to the free amine and heated in a sealed tube with 5 ml. of methylamine at 200° for 10 hours. From the reaction mixture was isolated by the usual procedure 0.49 g. (82%) of N-methyl-benzhydrylamine as its hydrochloride, m.p. 226–228°. Recrystallization from methanol–ether raised the melting point to 238° (lit.[26] m.p. 238°). A mixture melting point with an authentic sample showed no depression.

α-Methyl-β-methylamino-β-phenylphenethyl Alcohol.—Using the procedure for the reduction of IIa, 0.25 g. (0.00091 mole) of XVIII hydrochloride was converted to the free amine and reduced with sodium borohydride. From the reaction was obtained 0.19 g. (87%) of the aminoalcohol, m.p. 76–76.5°.

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.93. Found: C, 79.47; H, 7.87.

Periodate Oxidation of α-Methyl-β-methylamino-β-phenylphenethyl Alcohol.—Sixteen-hundredths gram (0.00053 mole) of XVIII hydrochloride was reduced to the aminoalcohol as described above. To a solution of the aminoalcohol in 5 ml. of methanol was added 7 ml. (0.0007 mole) of 0.1 *M* sodium metaperiodate solution. After standing for 24 hours, excess barium hydroxide solution was added to the reaction mixture, which was then filtered. The filtrate was acidified with dilute sulfuric acid and extracted with ether. From the ether layer was obtained 0.0704 g. (35%) of benzophenone, isolated as its 2,4-dinitrophenylhydrazone, m.p. 236°. A mixture melting point with an authentic sample showed no depression. The dilute sulfuric acid layer remaining after extraction with ether was steam distilled into an ethanolic solution of 2,4-dinitrophenylhydrazine hydrochloride to give 0.010 g. (8%) of the 2,4-dinitrophenylhydrazone of acetaldehyde, m.p. 147–148°. Recrystallization raised the melting point to 161–162°. A mixture melting point determination with an authentic sample showed no depression.

1,2-Epoxy-1-methoxy-2-methyl-1-phenylbutane (Ic).—To 83 g. (0.7 mole) of commercial sodium methylate in 200 ml. of absolute methanol was added, dropwise and with stirring, 150 g. (0.624

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mole) of α-bromo-α-methylbutyrophenone[27] dissolved in 100 ml. of absolute methanol. The solution was not cooled during the 1.5-hr. addition period. The stirring was continued for 45 minutes, and the solution was then refluxed for 15 minutes before 200 ml. of ice-water was added. Immediate extraction of the solution with three 100-ml. portions of petroleum ether followed. The petroleum ether extracts were combined, dried over sodium sulfate, and the solvent removed. Distillation of the residue through a 30-cm. Vigreux column using a reflux ratio of 5:1 yielded 116.1 g. (97%) of the epoxyether, b.p. 49° (0.1 mm.), n^{25}D 1.4890.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.83; H, 8.66.

2-Methyl-2-methylaminobutyrophenone (IIc).—1,2-Epoxy-1-methoxy-2-methyl-1-phenylbutane (Ic) was converted to the aminoketone IIc, b.p. 79° (0.4 mm.), n^{25}D 1.5423, in 87% yield using the procedure previously described for the preparation of aminoketone IIa.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96. Found: C, 75.45; H, 9.19.

A portion of the aminoketone was converted to the hydrochloride, m.p. 177–178°.

Anal. Calcd. for $C_{12}H_{18}ClNO$: C, 63.29; H, 7.97. Found: C, 63.20; H, 7.78.

Thermal Rearrangement of 2-Methyl-2-methylaminobutyrophenone (IIc).—A sealed tube containing 5 g. (0.026 mole) of the conjugated amino-ketone IIc was heated at 185° for 10 hours and worked up using the procedure for the rearrangement of IIa. From the reaction was isolated 4.26 g. of crude 2-methylamino-2-phenyl-3-pentanone (IIIc), b.p 59–60° (0.1 mm.). The aminoketone was converted to the hydrochloride and crystallized from ethanol–ether to give 1.93 g. (32.4%) of white crystals, m.p. 192–193°.

Anal. Calcd. for $C_{12}H_{18}ClNO$: C, 63.29; H, 7.97. Found: C, 63.06; H, 7.81.

α-Ethyl-β-methyl-β-methylaminophenethyl Alcohol.—Using the procedure for the reduction of IIa hydrochloride, 1 g. (0.0044 mole) of pure IIIc hydrochloride (showing no trace of conjugated carbonyl in its infrared spectrum) was reduced with 0.33 g. (0.0088 mole) of sodium borohydride. Fractional crystallization of the product from hexane at ice-box temperature gave 0.32 g. (38%) of aminoalcohol, m.p. 115–116°.

Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.56; H, 9.91. Found: C, 74.50; H, 9.70.

Concentration of the mother liquors gave 0.39 g. (46%) of the diastereomeric aminoalcohol, m.p. 72–73°. Recrystallization from hexane gave an analytical sample, m.p. 75–76°.

Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.56; H, 9.91. Found: C, 74.78; H, 9.81.

A mixture melting point of the high and low melting aminoalcohols melted over a range of 66–107°. Infrared spectra of the two alcohols were identical. α-(1-Methylamino-1-methylpropyl)-benzyl alcohol is a liquid, thus eliminating the possibility that one of the diastereomers could be the reduction product of the unrearranged aminoketone IIc.

Periodate Oxidation of α-Ethyl-β-methyl-β-methylaminophenethyl Alcohol.—To a solution of 0.19 g. (0.00096 mole) of the low melting aminoalcohol in 10 ml. of methanol was added 20 ml. (0.002 mole) of 0.1 *M* sodium metaperiodate solution. After the solution was allowed to stand overnight, it was extracted with ether and distilled from Drierite on a steam-bath. From the residue obtained after flash distillation was isolated 0.17 g. (59%) of acetophenone as its 2,4-dinitrophenylhydrazone derivative, m.p. 238–239°. A mixture melting point with an authentic sample showed no depression. From the distillate was isolated 0.2 g. (88%) of propionaldehyde as its 2,4-dinitrophenylhydrazone derivative, m.p. 140–141°. Recrystallization raised the melting point to 146°. A mixture melting point with an authentic sample showed no depression.

1-Bromocyclopentyl phenyl ketone was prepared by direct bromination of cyclopentyl phenyl ketone[28] in carbon tetrachloride. Decomposition occurred upon attempted distillation of the product; however, upon treatment of the combined distillate and undistilled material with activated charcoal and crystallization from petroleum ether, a 64% yield of the 1-bromoketone was obtained, m.p. 29–30°.

Anal. Calcd. for $C_{12}H_{13}BrO$: C, 56.93; H, 5.18. Found: C, 57.17; H, 5.28.

2-Methoxy-2-phenyl-1-oxaspiro[2.4]heptane.—1-Bromocyclopentyl phenyl ketone was converted in 96% yield to epoxyether,

b.p. 62–64° (0.05 mm.), n^{25}D 1.5136, according to the procedure of Stevens and Weinheimer.[16]

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.34; H, 7.98.

1-Methylaminocyclopentyl Phenyl Ketone (XX).—A steel autoclave containing 6.13 g. (0.0395 mole) of 2-methoxy-2-phenyl-1-oxaspiro[2.4]heptane and 40 ml. of liquid methylamine was heated at 130° for 10 hours. Using the procedure for the preparation of IIa, 4.05 g. (57%) of aminoketone XX was obtained as the hydrochloride, m.p. 113–114°.

Anal. Calcd. for $C_{13}H_{18}ClNO$: C, 65.13; H, 7.56. Found: C, 65.18; H, 7.80.

A portion of the hydrochloride was converted in 96% yield to the free aminoketone, b.p. 74–76° (0.03 mm.), n^{29}D 1.5441.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.48. Found: C, 76.88; H, 8.43.

Thermal Rearrangement of 1-Methylaminocyclopentyl Phenyl Ketone (XX).—A sealed tube containing 2.31 g. (0.0114 mole) of XX was heated at 220° for 10 hours. Using the procedure for the rearrangement of IIa, 0.54 g. (20%) of 2-methylamino-2-phenylcyclohexanone (XXI) was isolated as its hydrochloride, m.p. 256°.

Anal. Calcd. for $C_{13}H_{18}ClNO$: C, 65.13; H, 7.57. Found: C, 65.26; H, 7.75.

2-Methylamino-2-phenylcyclohexanol (XXII).—Using the procedure for the reduction of IIa, 0.38 g. (0.0016 mole) of pure crystalline XXI hydrochloride was converted to the free amine and reduced with sodium borohydride. From the reaction was obtained 0.27 g. (82%) of the aminoalcohol XXII, m.p. 89–96°. Recrystallization gave colorless crystals, m.p. 90.5–103°, indicating a probable mixture of diastereoisomers.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33. Found: C, 76.17; H, 9.39.

2-Methylamino-2-phenylcyclohexanone Oxime (XXIV).—To 30 ml. of anhydrous benzene was added 1.32 g. (0.0059 mole) of 2-chloro-2-phenylcyclohexanone oxime (XXIII) prepared in 47% yield by addition of nitrosyl chloride to 1-phenylcyclohexene.[15] To this benzene solution was added a solution of 0.76 g. (0.024 mole) of methylamine in 30 ml. of cold anhydrous benzene. The solution was allowed to stand overnight at room temperature. The benzene solution was washed with water and extracted with 2 *N* hydrochloric acid. The acid layer was washed with ether, then made basic and extracted with ether. The ether extract was dried and the solvent removed *in vacuo*. The residue of crude XXIV was converted to the amine hydrochloride and recrystallized from ethanol–ether to give 0.16 g. (11%) of colorless needles, m.p. 245° dec.

Anal. Calcd. for $C_{13}H_{19}ClN_2O$: C, 61.29; H, 7.52. Found: C, 61.10; H, 7.61.

Hydrolysis of 2-Methylamino-2-phenylcyclohexanone Oxime (XXIV).—A solution containing 0.155 g. (0.000609 mole) of XXIV in 6 ml. of 8 *N* hydrochloric acid was heated on a steambath for 14 hours. The resulting solution was washed with ether, made basic, and extracted with ether. The extract was dried and the ether removed *in vacuo*. The residue was converted to the hydrochloride and crystallized from ethanol–ether to give 0.12 g. (82%) of 2-methylamino-2-phenylcyclohexanone hydrochloride, m.p. 255°. A mixture melting point with the product from the rearrangement of XX showed no depression.

Attempted Addition of Methylamine to 2-Phenyl-2-cyclohexenone Oxime.—To a solution of 0.58 g. (0.0031 mole) of the α,β-unsaturated oxime[15] in 50 ml. of anhydrous benzene was added a solution of 1.5 g. (0.048 mole) of methylamine in 15 ml. of cold anhydrous benzene. The solution was allowed to stand at room temperature for 3 days. The product was worked up using the procedure for the reaction of methylamine with the α-chloro oxime XXIII. No basic material other than methylamine was isolated. The starting oxime was recovered in 95% yield, m.p. 154–155°.

Thermal Rearrangement of 2-Hydroxy-2-phenylcycloheptanone (XXV) with Methylamine.—The hydroxyketone XXV (6.0 g.) and 15 ml. of methylamine were placed in a bomb and heated for 10 hours at 200°. The product, 1-methylaminocyclohexyl phenyl ketone (XXVI), was isolated as its hydrochloride in 14% yield by the usual procedure. The hydrochloride after recrystallization from alcohol had m.p. 221–224°.

1-Methylaminocyclohexyl Phenyl Ketone (XXVI).—A steel autoclave containing 11.27 g. (0.0516 mole) of 2-methoxy-2-phenyl-1-oxaspiro[2.5]octane (XXVII)[19] and 50 ml. of liquid methylamine was heated at 130° for 10 hours. Using the procedure for the preparation of IIa, 10.55 g. of aminoketone XXVI was obtained as the hydrochloride, m.p. 225–226°. A portion

(27) T. I. Temnikova, A. K. Petryaeva and S. S. Skorokhodov, *Zhur. Obshch. Khim.*, **25**, 1575 (1955).

(28) D. H. Hey and O. C. Musgrave, *J. Chem. Soc.*, 3162 (1949).

of the hydrochloride was converted in 90% yield to the free aminoketone, b.p. 104–106° (0.09 mm.), $n^{27.5}$D 1.5438.

(29) I. Elphimoff-Felkin, *Bull. soc. chim. France*, 653 (1962), reports the ring expansion

The reaction was carried out in 96% formic acid at 100° for 5 hours.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.37; H, 8.81. Found: C, 77.23; H, 8.73.

A mixture melting point between the hydrochloride of the aminoketone XXVI obtained by reaction of methylamine with the epoxyether XXVII and that obtained by the thermal rearrangement of 2-hydroxy-2-phenylcycloheptanone (XXV) with methylamine was undepressed.[29,30]

(30) Paper I in this series, C. L. Stevens, R. D. Elliott, B. L. Winch and I. L. Klundt, *J. Am. Chem. Soc.*, **84**, 2272 (1962).

# The Effect of Pressure on the Homogeneous Alkylation of Phenoxide Ion

BY W. J. le Noble

The homogeneous reaction of phenoxide ion with allyl chloride in the solvents water, methanol and 1,2-dimethoxyethane has been studied in the pressure range 1–7000 atm. In water, the yield of *p*-allylphenol increases at the expense of allyl phenyl ether as the pressure is increased. In methanol, C-alkylation is observed at high pressure but not at 1 atm. In 1,2-dimethoxyethane, only O-alkylation is observed in the entire range of pressures studied. These results are consistent with Kornblum's hypothesis regarding the solvent effect in this reaction, and furthermore suggest that the *o*- to *p*-ratio is similarly affected. The differences in molar volume between the three transition states were calculated.

The homogeneous reaction of allyl chloride with sodium phenoxide in most organic solvents gives excellent yields of allyl phenyl ether; in fact, usually no other alkylation products can be found.[1] Recently, however, it has been reported[2] that in certain solvents considerable amounts of *o*- and *p*-allylphenols are also obtained.
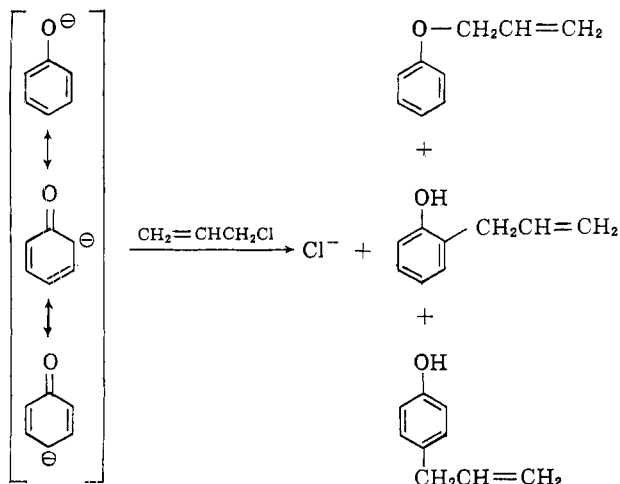
O-Alkylation alone was found to take place in ethers, unsubstituted aliphatic alcohols and N,N-dimethylformamide; C-alkylation occurs to the extent of 40–75% in water, phenol and fluorinated alcohols. On the basis of this solvent effect and of kinetic studies Kornblum concluded that O-alkylation of the phenoxide ion takes place exclusively unless the reaction occurs in a solvent highly effective as a proton donor in hydrogen bonding. It appears that the oxygen atom, where the charge is largely concentrated, is intensely solvated in such solvents, and that this solvation sphere hinders the approach of the alkylating agent to that position, but not to the *o*- and *p*-carbon atoms. An alternative way to state this explanation is to say that of the three transition states the one leading to O-alkylation is favored in a non-polar solvent since the oxygen atom carries most of the charge, but those leading to ring alkylation are favored in an effectively solvating medium because they require the least interference with solvation.

One question invited by this interpretation is concerned with the fact that no C-alkylation is observed at all when unsubstituted aliphatic alcohols are used, since these solvents are also capable of H-bonding. Apparently these hydrogen bonds are much less effective. There appears to be some evidence for this. If the acid strengths may be regarded as a rough measure of H-bonding ability, the following correlation is found to exist: phenol, pK_a 9.9, 75% C-alkylation; 2,2,3,3-tetrafluoropropanol, pK_a^3 11.3, 50% C-alkylation; methanol, pK_a^3 15.9, 0% C-alkylation. On this basis, however, it is surprising that water (pK_a 15.7) is so effective in promoting C-alkylation (45%). Perhaps water, with its ability to form two H-bonds, allows the formation of an extensive (rather than a tightly bound) solvation sphere, thus interfering with the approach to the oxygen atom of phenoxide ion. A second question concerns the ratio of *o*- to *p*-alkylation; the greater proximity of the *o*-carbon atom to the solvated oxygen might be expected to affect that ratio also.

One of the methods available for approaching problems of this type is a study of the effect of hydrostatic pressure. It is known that immersion of an ion in a dielectric causes a decrease in the total volume (electrostriction).[4] The solvent near the ion becomes oriented and compressed into a smaller volume. Conversely, the application of pressure always enhances solvation. If therefore the interpretation quoted above for the solvent effect is correct, it should be expected that C-alkylation will be increased in effective H-bonding solvents if pressure is applied. Similarly, some C-alkylation might be observed in an ineffectively H-bonding solvent such as methanol under pressure, but not in a non-protonic solvent such as 1,2-dimethoxyethane. Finally, if the solvation sphere is large enough, the *o*- to *p*-ratio will be observed to diminish as the pressure is increased. To test these predictions the product distribution in this reaction was measured in several solvents as a function of the external pressure.

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(3) P. B. Allinger and F. A. Long, *J. Am. Chem. Soc.*, **82**, 795 (1960).

(4) S. D. Hamann, "Physico-chemical Effects of Pressure," Academic Press, Inc., New York, N. Y., 1957, Chap. IX.