the reaction rate and the dielectric constant of the medium.

The nature of the reaction has been demonstrated by the isolation of both the reaction products, the phosphonamidate esters (in 50–70% yield) and the amine hydrochloride (in 81–94% yield), and is a further example of the large part that steric effects play in the reactivity of quadruply connected phosphorus compounds.

Experimental[12]

Materials.—Acetone (Hopkin and Williams, AnalaR grade) was refluxed over anhydrous potassium carbonate for 6 hr. and then fractionated. The distillate was then refluxed over phosphoric oxide for 6 hr. and then fractionated, the fraction boiling at 56.0–56.5° being collected in a flask protected from atmospheric moisture by phosphoric oxide and calcium chloride guard tubes. Dioxane and nitrobenzene were purified using the methods described by Vogel.[13] Benzene (AnalaR grade) was refluxed over sodium and then fractionated. Nitromethane was dried over anhydrous magnesium sulfate and fractionated. Amines were dried over potassium hydroxide pellets, decanted from the solid and distilled from fresh potassium hydroxide pellets. Ethyl methylphosphonochloridate was prepared as described elsewhere.[4]

Determination of Reaction Rates.—A large, well insulated dewar vessel, containing water or aqueous acetone cooled with solid carbon dioxide was used as a constant temperature bath. The temperature was maintained within ±0.1° for at least 0.5 hr. The solution of the amine in the solvent was placed in a stoppered flask and precooled to the desired reaction temperature by placing the flask in the constant temperature bath. Reaction was started by introducing the phosphonochloridate from a weight pipet. The reaction flask was then shaken to ensure complete mixing. Five-milliliter portions were removed at suitable time intervals and added to acetone containing an excess of perchloric acid to stop the reaction as the alkylammonium ion formed does not react with the chloridate. The excess acid was then back titrated with a standard solution of triethylamine in toluene using Lacmoid indicator.

Isolation of Reaction Products.—A 1.42-g. sample (10 mmoles) ethyl methylphosphonochloridate was added slowly with stirring and cooling to 22 mmoles of the appropriate amine in 10 ml. of acetone. After 72 hr. at room temperature, 20 ml. of ether was added and the amine hydrochloride collected by filtration and washed with ether. The solvent was removed from the combined filtrate and washings, and the residue distilled under reduced pressure. The following compounds were prepared in this way.

Ethyl N-diethylmethylphosphonamidate (64% yield), b.p. 110–114°/22 mm. (Found: C, 46.5; H, 10.0; N, 8.0. $C_7H_{18}PO_2N$ requires C, 46.9; H, 10.0; N, 7.8.)

Ethyl N-di-*n*-butylmethylphosphonamidate (75% yield), b.p. 108–110°/30 mm. (Found: C, 56.4; H, 11.8; N, 6.4; P, 14.1. $C_{11}H_{26}PO_2N$ requires C, 56.2; H, 11.9; N, 6.0; P, 13.2.)

Ethyl N-di-*sec*-butylmethylphosphonamidate (50% yield), b.p. 115–120°/30 mm. (Found: C, 55.5; H, 12.4; N, 5.4. $C_{11}H_{26}PO_2N$ requires C, 56.2; H, 11.9; N, 6.0.)

Ethyl N-*n*-butylmethylphosphonamidate (70% yield), b.p. 110–112°/20 mm. (Found: C, 45.9; H, 10.0; N, 7.2; P, 18.1. $C_{17}H_{18}PO_2N$ requires C, 46.9; H, 10.0; N, 7.8; P, 17.3.)

Ethyl N-*sec*-butylmethylphosphonamidate (47% yield), b.p. 121–125°/30 mm. (Found: C, 47.5; H, 10.4; N, 7.5. $C_7H_{18}PO_2N$ requires C, 46.9; H, 10.0; N, 7.8.)

Ethyl N-*tert*-butylmethylphosphonamidate (63% yield), b.p. 134–140°/25 mm. (Found: C, 46.8; H, 10.0; N, 6.8. $C_{17}H_{18}PO_2N$ requires C, 46.9; H, 10.0; N, 7.8.)

Ethyl N-phenylmethylphosphonamidate (52% yield), b.p. 160–165°/20 mm. (Found: C, 55.0; H, 6.8; N, 7.3. $C_9H_{14}PO_2N$ requires C, 54.0; H, 7.0; N, 7.0.)

(12) All melting points and boiling points are uncorrected.

(13) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 2nd ed., Longmans, Green & Co., London, 1951, pp. 173–175.

The Reactions of α-Bromo Ketones with Primary Amines[1]

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Received September 6, 1962

The conversion of α-bromoisobutyrophenone to the corresponding α-hydroxyimines, I, II, and III has been effected in high yield by dissolution in liquid ammonia, methylamine, and ethylamine, respectively. Evidence is cited to support the intramolecular nature of the oxygen migration in the transformation which suggests a reaction path proceeding *via* an epoxyamine (IX) as an intermediate. Apparent anomolous pathways are observed in the reactions of α-bromopropiophenone and 6-bromo-2,2,6-trimethylcyclohexanone with liquid methylamine to yield 1-phenyl-1-methylaminoacetone and 6-methylamino-2,2,6-trimethylcyclohexanone, respectively.

The reactions of α-halo ketones with amines have received considerable attention in the chemical literature.[4] In general, it has been shown that α-halo ketones, whose structures prohibit a Favorskiĭ type rearrangement, undergo substitution and/or dehydrohalogenation where possible, upon treatment with ammonia, primary, or secondary amines.[4,5] Thus α,β-unsaturated ketones and α- and β-amino ketones have been observed as products of such reactions, the latter arising by 1,4-conjugate addition of the amine to the α,β-unsaturated ketone. Of particular interest in the present study is the behavior α-halo ketones toward ammonia and primary amines. The reaction of α-bromoisobutyrophenone with ammonia and methylamine in benzene or ethanol solution has been reported to yield mainly the products of substitution, α-amino-[6] and α - methylaminoisobutyrophenone,[7] respectively. The present work demonstrates that a variation of these reaction conditions can alter the course of the reaction to produce a heretofore unobserved product in high yield.

The dissolution of α-bromoisobutyrophenone in liquid ammonia followed by the gradual evaporation of the solvent led to a product which proved to be neither the result of elimination nor substitution. Elemental analysis indicated the crystalline product, isolated in 80% yield, was isomeric with the substitution product, α-aminoisobutyrophenone. The compound

(1) Presented before the Division of Organic Chemistry at the 141st National Meeting of the American Chemical Society, Washington, D. C., March 26, 1962.

(2) Charles F. Kettering Foundation Fellow, 1958–1960; abstracted in part from the Ph.D. dissertation of P. Blumbergs, Wayne State University, 1962.

(3) Department of Chemistry, Arizona State University, Tempe, Ariz.; supported in part by a Parke, Davis and Co. Fellowship.

(4) See B. Tchoubar, *Bull. soc. chim. France*, 1363 (1955), for a review of the reactions of α-halo ketones with a variety of bases.

(5) N. H. Cromwell and P. H. Hess, *J. Am. Chem. Soc.*, **83**, 1237 (1961).

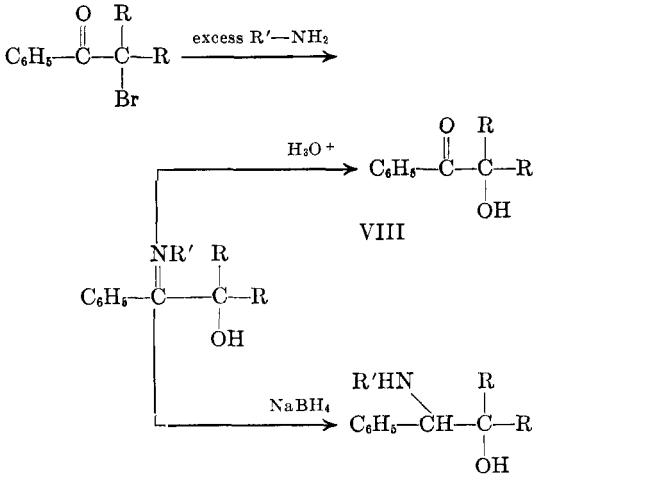
(6) H. Larramona, *Compt. rend.*, **232**, 849 (1951).

(7) C. Mannich and H. Budde, *Arch. Pharm.*, **271**, 51 (1933).

was readily hydrolyzed in aqueous acid to α-hydroxyisobutyrophenone (VIII. R = CH_3) and reduced catalytically or with sodium borohydride to the known α-amino alcohol V. On this basis the α-hydroxyimine structure I was assigned to the reaction product. The infrared spectrum with strong absorption in the 3-μ region (NH/OH) and a strong band at 6.05 μ (C=N) supported the assignment.

The reaction of α-bromoisobutyrophenone with liquid methylamine and ethylamine, and α-bromophenyl cyclohexyl ketone with liquid methylamine under similar reaction conditions resulted in the formation of α-hydroxyimines II, III and IV in 78, 81, and 74% yields, respectively. Structures were assigned on the basis of hydrolysis to the known α-hydroxy ketones and reduction to the corresponding α-amino alcohols.

With a single exception, the isomeric α-amino ketones could not be detected in the reaction mixtures. Catalytic reduction of a sample of the α-hydroxyimine, III, arising from the reaction of α-bromoisobutyrophenone with ethylamine, led to the formation of the expected α-amino alcohol VII in high yield and the isolation of a very small amount of a compound which was shown, by comparison with an authentic sample, to be the isomeric α-amino alcohol, 1-phenyl-2-methyl-2-ethylaminopropanol. The latter reduction product must arise from α-ethylaminoisobutyrophenone, thus indicating that the reaction of α-bromoisobutyrophenone with ethylamine proceeds to a very minor extent by a substitution course.



I. R = CH_3, R' = H
II. R = R' = CH_3
III. R = CH_3, R' = C_2H_5
IV. RR = $(CH_2)_5$, R' = CH_3
V. R = CH_3, R' = H
VI. R = R' = CH_3
VII. R = CH_3, R' = C_2H_5

Based upon a consideration of the formation of epoxy ethers from α-halo ketones[8] a reaction course proceeding *via* an epoxyamine intermediate appeared attractive. Initial attack of nucleophilic ammonia or primary amine at the carbonyl followed by intramolecular displacement of bromide ion by oxygen would result in the formation of the epoxyamine IX. Because of the presence of a mobile hydrogen atom on nitrogen such an intermediate would be expected to rapidly collapse to the observed product, the α-hydroxyimine (scheme 1). Although there are no reported examples of isolated epoxyamines in the literature, the concept of an epoxyamine as an intermediate has been previously invoked.[9,10] Kirrmann[9b] proposed and cited evidence in favor of an epoxyamine intermediate, arising in the manner described above, in the formation of α-aminoaldehydes from the interaction of α-haloaldehydes with the secondary amines.

Two alternate reaction paths required consideration at this stage (schemes 2 and 3).

In the synthesis of α-methylaminoisobutyrophenone by the reaction of α-bromoisobutyrophenone with methylamine in benzene solution Mannich and Budde[7] isolated a significant amount of α-hydroxyisobutyrophenone as a by-product. To rationalize the results these authors suggested that the reaction proceeded in part by the initial formation of an α-haloimine, followed by hydrolysis to the corresponding α-hydroxyimine by the water generated in imine formation (scheme 2). Work-up in aqueous solution accounted for the observed α-hydroxy ketone.

Although such a mechanism was not considered likely in the present work in view of the high yields of α-hydroxyimine obtained, it appeared desirable to establish that water did not play the role of an intermediate in the reaction. The conversion of α-bromocyclohexyl phenyl ketone to the α-hydroxyimine IV was conducted in liquid methylamine containing a molar equivalent of O^{18} enriched water. A mechanism (scheme 2) analogous to that proposed by Mannich and Budde[7] would require O^{18} incorporation into the product since water is an intermediate; however, the α-hydroxyimine IV demonstrated *no* measurable incorporation of the O^{18} label. This evidence supports the intramolecular nature of the oxygen migration as required by a mechanism proceeding through the epoxyamine as an intermediate.

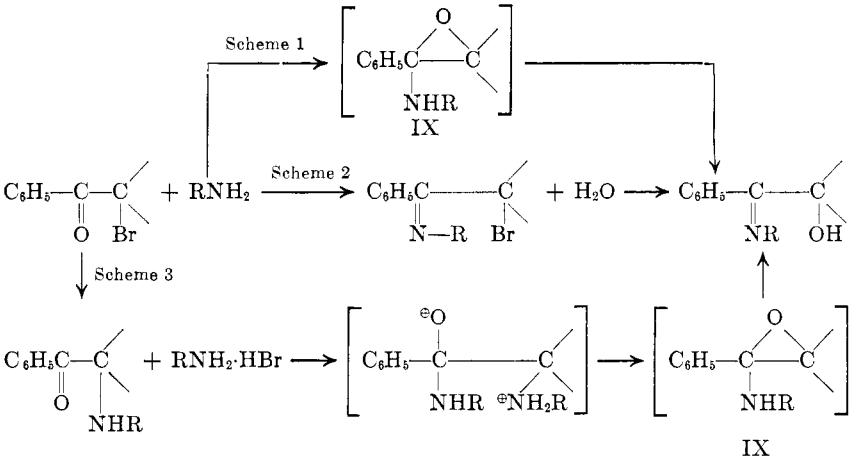
The possible role of the substitution product, an α-amino ketone, as the precursor of the epoxyamine intermediate was also considered. Nucleophilic addition of amine at the carbonyl followed by intramolecular displacement of amine by oxygen would lead to the epoxyamine intermediate IX (scheme 3). The intramolecular displacement by oxygen could be facilitated by the presence of the amine hydrobromide formed in the initial substitution step. The basis for such a mechanism is found in the work of Nelson[10] who studied the aniline hydrobromide-catalyzed isomerization of α-anilinopropiophenone to 1-anilino-1-phenylacetone. Evidence was presented to support the initial formation of an epoxyamine intermediate, in the manner described above, followed by an acid-catalyzed pinacol-type rearrangement to the product.

The intermediacy of the substitution product in the present study (scheme 3) was ruled out on the basis of the observed stability of α-methylaminoisobutyrophenone under the reaction conditions leading to the formation of the α-hydroxyimine II. Dissolution of α-methylaminoisobutyrophenone in liquid methylamine containing a molar equivalent of methylamine hydrobromide led to an 81% recovery of the starting α-amino ketone.

(8) C. L. Stevens, W. Malik, and R. Pratt, *J. Am. Chem. Soc.*, **72**, 4758 (1950).

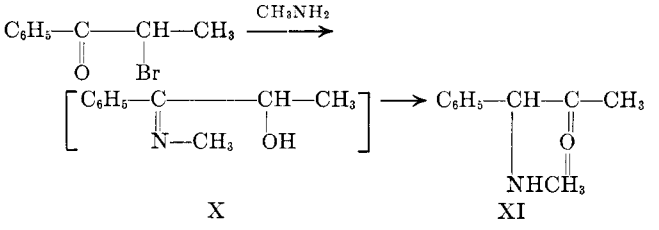
(9) (a) A. Hassner and N. H. Cromwell, *ibid.*, **80**, 903 (1958); (b) A. Kirrman, R. Muths, and J-J. Riehl, *Bull. soc. chim. France*, 1469 (1958).

(10) K. LeRoi Nelson and R. L. Seefeld, *J. Am. Chem. Soc.*, **80**, 5957 (1958); K. LeRoi Nelson, J. C. Robertson, and J. J. Duval, Abstracts, 139th National Meeting of the American Chemical Society, St. Louis, Mo., March 21–30, 1961, p. 32-O.



In summary, the evidence cited suggests that the solvolysis of an α-bromo ketone in liquid ammonia, methylamine, or ethylamine to yield an α-hydroxyimine, proceeds *via* initial formation of an epoxyamine intermediate as outlined in scheme 1.

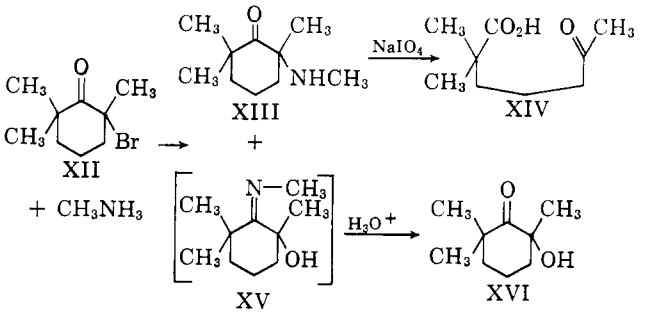
The reaction of α-bromopropiophenone in liquid methylamine failed to produce the expected α-hydroxyimine X, but led to the isolation of 1-methylamino-1-phenylacetone (XI) in good yield. Inspection of the infrared spectrum of the once distilled reaction product (65% yield) indicated the presence of a small amount of a conjugated carbonyl containing component, presumably the substitution product, α-methylaminopropiophenone. The pure α-amino ketone XI showed a single sharp absorption peak at 5.80 μ (unconjugated carbonyl). The α-amino ketone XI, although known, was further characterized by treatment with methylmagnesium iodide to yield the same α-amino alcohol VI as was obtained from the reduction of the α-hydroxyimine II.



It is suggested that the observed product, 1-methylamino-1-phenylacetone (XI) arises *via* a facile rearrangement of the expected α-hydroxyimine X.[11] An attempt to detect the presence of C=N by infrared analysis (absorption at 6.00 μ) of the crude reaction product immediately after removal of solvent (maximum operating temperature < 20°) failed. An absorption band at 5.90 μ (conjugated carbonyl) was attributed to the presence of the substitution product. Thus, if the α-hydroxyimine X is an intermediate in the formation of the α-amino ketone XI, it readily rearranges under the mild conditions employed.

(11) Rearrangement of X to XI could possibly proceed *via* the enediol-type intermediate, $C_6H_5-C(=CH-CH_3)-OH$, or *via* a pinacol-type rearrangement; see C. L. Stevens, *et al.*, *J. Am. Chem. Soc.*, **84**, 2272 (1962). A pinacol-type rearrangement might occur in the case of the hydroxyimine X and yet not be an important reaction course in the case of hydroxyimines I–IV since in the former example a group, hydrogen, with a significantly greater migratory aptitude than an alkyl group is involved in the rearrangement.

An anomolous reaction course was observed upon solvolysis of 2-bromo-2,6,6-trimethylcyclohexanone in liquid methylamine. The unexpected substitution product, 2-methylamino-2,6,6-trimethylcyclohexanone (XIII) was isolated in 57% yield. The α-amino ketone XIII was characterized by elemental analysis and periodate oxidation to the known geronic acid (XIV). Some evidence was obtained to indicate the presence of the expected α-hydroxyimine XV among the reaction products. The infrared spectrum of the crude reaction mixture showed a strong absorption band at 5.85 μ, characteristic of a cyclic carbonyl, and a relatively weak band at 5.95 μ which could be attributed to the C=N of the α-hydroxyimine. Although no α-hydroxyimine XV was isolated, acid hydrolysis of the crude reaction mixture led to the formation of a 16% yield of 2-hydroxy-2,6,6-trimethylcyclohexanone (XVI) in addition to the α-amino ketone XIII. The fact that the α-hydroxy ketone XVI arose from hydrolysis of the α-hydroxyimine XV and not unchanged α-bromo ketone XII was established by the isolation of a quantitative yield of methylamine hydrobromide prior to acid hydrolysis.



The result described above is striking in view of the other solvolyses described in this paper in which little or no substitution product could be detected. It is interesting to note that the treatment of the same α-bromo ketone XII with methanol-free sodium methoxide in liquid ammonia led to the exclusive formation of the substitution product, 2-methoxy-2,6,6-trimethylcyclohexanone whereas treatment of α-bromoisobutyrophenone under identical conditions led to the formation of the epoxy ether in good yield.[12]

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

Experimental

1-Phenyl-1-imino-2-methyl-2-propanol (I).—In a 100-ml. three-neck flask, equipped with a stirrer and a reflux condenser, were placed 50 ml. anhydrous liquid ammonia and 5 g. (0.022 mole) of α-bromoisobutyrophenone. The reaction mixture was stirred for 0.5 hr. At the end of this period the reaction flask was warmed gently to remove the ammonia which was replaced with anhydrous ether. The ammonium bromide which precipitated was removed by filtration and the filtrate concentrated, then rediluted with hexane–petroleum ether (1:1 solution). The resultant solution was filtered once more and the filtrate placed in in the refrigerator. A white crystalline material was obtained. The mother liquor was concentrated to yield additional product. The total yield of the α-hydroxyimine I was 2.9 g. (80%), m.p. 82.5–84°. Two recrystallizations from ether–hexane gave an analytically pure product, m.p. 83.5–85°.

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03. Found: C, 73.70; H, 8.10.

Hydrolysis of I.—Four grams (0.025 mole) of I was dissolved in 30 ml. of dilute hydrochloric acid and heated on the steam bath for 20 min. At the end of this period the mixture was extracted with three 10-ml. portions of ether, the ether extracts were combined, dried over anhydrous potassium carbonate, and concentrated under reduced pressure (aspirator–steam bath). The residue was fractionated *in vacuo* to yield 2.63 g. (64%) of α-hydroxyisobutyrophenone, b.p. 87–89° (1.6 mm.), $n^{25}D$ 1.5282 (reported[13] $n^{25}D$ 1.5271–1.5279).

The semicarbazone derivative was prepared by the method of Shriner and Fuson,[14] m.p. 185°. There was no depression in melting point upon admixture with an authentic[13] sample of α-hydroxyisobutyrophenone semicarbazone.

2-Phenyl-2-amino-1,1-dimethylethanol (V). A. By Hydrogenation of I.—A solution of 1.0 g. (0.0061 mole) of the α-hydroxyimine I in 60 ml. of anhydrous ethyl acetate containing 0.05 g. of prereduced platinum oxide was stirred under an atmosphere of hydrogen. The hydrogen uptake ceased after 1 mole (15–20 min.). The solution was filtered and concentrated under reduced pressure (aspirator–steam bath). The residue crystallized and was recrystallized from ether–petroleum ether to yield 0.83 g. (82%) of material, m.p. 84–85° (reported,[15] m.p. 82.5–83.5°).

The hydrochloride salt was prepared by addition of isopropyl alcohol saturated with dry hydrogen chloride to an ether solution of the amino alcohol V. The product was recrystallized from methanol–ether to yield colorless plates, m.p. 181.5–183° (reported,[15] m.p. 173–175°).

Anal. Calcd. for $C_{10}H_{16}ClNO$: C, 59.55; H, 8.00. Found: C, 59.71; H, 8.17.

B. By Sodium Borohydride Reduction of I.—In 15 ml. of absolute ethanol were placed 0.60 g. (0.0037 mole) of the α-hydroxyimine I and 0.20 g. (0.0053 mole) of sodium borohydride, and the reaction allowed to proceed for 2 hr. at room temperature. At the end of this period the borohydride complex was decomposed with dilute hydrochloric acid, the aqueous acid solution extracted with ether, and the ether extract discarded. The aqueous portion was made basic, extracted with ether, and the ether extract dried over anhydrous magnesium sulfate. To the ether solution was added isopropyl alcohol saturated with dry hydrogen chloride until the formation of a precipitate ceased. The white solid was collected by filtration and recrystallized twice from ethanol–ether to yield white plates, 0.51 g. (69%), m.p. 181–182.5°. A depression in melting point was not observed on admixture with the amino alcohol hydrochloride obtained by catalytic hydrogenation.

1,1-Dimethyl-2-phenyl-2-methyliminoethanol (II).—In a 100-ml. three-neck flask equipped with stirrer and reflux condenser was placed 50 ml. anhydrous methylamine, followed by the gradual addition of 15 g. (0.066 mole) of α-bromoisobutyrophenone. The reaction was stirred for 30 min. and then gently warmed to facilitate the evaporation of excess amine. Ether–hexane solution was added to the residue, the resulting mixture filtered to remove methylamine hydrobromide and concentrated under reduced pressure. The residue was flash distilled and then fractionated *in vacuo*. A clear colorless liquid, 9.20 g. (78.6%), b.p. 73–75° (1.0 mm.), $n^{25}D$ 1.5130, d^{25}_4 0.991, was obtained.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.56; H, 8.26.

Hydrolysis of II.—The hydrolysis of II was performed in a manner similar to the hydrolysis of I. Four grams (0.023 mole) of II was hydrolyzed to yield 3.05 g. (82%) of material, b.p. 75–77° (0.8 mm.), $n^{25}D$ 1.5283. A semicarbazone derivative, m.p. 184–185°, was shown to be identical with an authentic sample of α-hydroxyisobutyrophenone semicarbazone by mixture melting point determination.

Reaction of α-Methylaminoisobutyrophenone with Methylamine.—Four grams (0.023 mole) of α-methylaminoisobutyrophenone,[16a] b.p. 70–71° (0.3 mm.), $n^{25}D$ 1.5246, and 2.58 g. (0.023 mole) of methylamine hydrobromide were dissolved in 25 ml. of anhydrous methylamine and the solution stirred for 1 hr. Methylamine was removed by gentle warming and the residue treated with ether–hexane (1:1 solution). The solution was filtered and the solvents removed under reduced pressure. The residual oil was dissolved in dilute hydrochloric acid, the solution heated on the steam bath for 15 min., cooled, extracted with ether, and the ether extracts discarded. The aqueous portion was made basic with dilute sodium hydroxide solution and extracted with several portions of ether. The combined ether extracts were dried over anhydrous potassium carbonate, filtered, and the ether was removed under reduced pressure. The residue was fractionated *in vacuo* and 3.24 g. (81%) of the starting material, b.p. 66–68° (0.25 mm.), $n^{23}D$ 1.5248, was recovered.

1,1-Dimethyl-2-phenyl-2-methylaminoethanol (VI). A. By Catalytic Hydrogenation of II.—The hydrogenation was performed in a similar manner to that described for I. Two grams (0.011 mole) of II gave 1.91 g. (94%) of VI, m.p. 57–58° after recrystallization from ether–hexane.

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70: H, 9.56. Found: C, 73.70; H, 9.39.

The hydrochloride salt, recrystallized from methanol–ether, melted at 241–242°.

Anal. Calcd. for $C_{11}H_{18}ClNO$: C, 61.24: H, 8.41. Found: C, 61.48; H, 8.31.

B. By Sodium Borohydride Reduction of II.—The same procedure was used as for the reduction of the α-hydroxyimine I. From 6.5 g. (0.0366 mole) of the starting material, 6.79 g. (86%) of amino alcohol VI hydrochloride salt was obtained, m.p. 241–242°.

1,1-Dimethyl-2-phenyl-2-ethyliminoethanol (III).—The procedure described for the preparation of II was followed with two minor modifications. The reaction was carried out at 0° and the reaction period was extended to 1 hr. The crude reaction product was flash distilled and then fractionated *in vacuo*. From 16 g. (0.071 mole) of α-bromoisobutyrophenone, 10.9 g. (81%) of material, b.p. 55–58° (0.15 mm.), was obtained. The liquid crystallized on standing to yield a solid, m.p. 36.5–38°.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35: H, 8.96. Found: C, 75.26; H, 8.87.

Hydrolysis of III.—The α-hydroxyimine III, 4 g. (0.021 mole), was hydrolyzed in the same manner as described previously to yield 2.70 g. (74%) of α-hydroxyisobutyrophenone, b.p. 91–93° (1.7 mm.), $n^{25}D$ 1.5276. The semicarbazone was prepared in 83% yield, m.p. 183.5–185°. There was no depression in melting point on admixture with an authentic sample of α-hydroxyisobutyrophenone semicarbazone.

1,1-Dimethyl-2-phenyl-2-ethylaminoethanol (VII).—The hydrogenation of 8 g. (0.042 mole) of III by the previously described procedure gave an oil which was fractionated *in vacuo*. The material was collected in six fractions: (1) 0.48 g., b.p. 51° (0.02 mm.), $n^{26}D$ 1.5110; (2) 1.37 g., b.p. 51° (0.02 mm.), $n^{26}D$ 1.5111; (3) 2.46 g., b.p. 51° (0.02 mm.), $n^{26}D$ 1.5112; (4) 1.37 g., b.p. 51° (0.02 mm.), $n^{26}D$ 1.5114; (5) 1.00 g., b.p. 51–51.5° (0.02 mm.), $n^{26}D$ 1.5116; (6) 0.57 g., b.p. 51.5–55° (0.02 mm.,) 1.5118. The total yield of material was 7.25 g. (89%). Fraction 2 was used for density measurements: d^{25}_4 0.9847. Fraction 3 was used for an analytical sample.

(13) C. L. Stevens, R. L. McLean, and A. J. Weinheimer, *J. Am. Chem. Soc.*, **80**, 2276 (1958).

(14) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956.

(15) A. McKenzie and M. S. Leslie, *Ber.*, **62B**, 288 (1929).

(16) (a) This compound was prepared by the reaction of 1-phenyl-1-methoxy-2,2-dimethylethylene oxide with methylamine employing the general reaction conditions described by C. L. Stevens and C. H. Chang, *J. Org. Chem.*, in press; (b) An authentic sample of this material was obtained by the reaction of 1-phenyl-1-methoxy-2,2-dimethylethylene oxide with ethylamine followed by reduction. K. G. Taylor, Wayne State University, private communication.

Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.57; H, 9.91. Found: C, 74.72; H, 9.91.

After the fractionation a small amount (approximately 0.1 g.) of solid formed in the distilling head. When fractions 3, 4, 5, and 6 of the amino alcohol were seeded with this solid, crystals formed in fraction 6, and a very small amount in fraction 5. Fractions 3 and 4 did not yield any solid. The solid was purified by vacuum sublimation, m.p. 117–120°. The material was shown to be 1-phenyl-2-ethylamino-2,2-dimethylethanol by elemental analysis and by a mixture melting point determination with an authentic sample.[16]

Anal. Calcd. for $C_{12}H_{19}NO$: N, 7.25. Found: N, 7.52.

One gram (0.0052 mole) of the material from fraction 3 was dissolved in ether, and isopropyl alcohol saturated with anhydrous hydrogen chloride was added to this solution until the formation of a precipitate ceased. The white solid was collected by filtration and recrystallized from methanol–ether to yield 1.10 g. (92%) of material, m.p. 197–198°. The good yield of a sharp melting hydrochloride salt is indicative of the high purity of fraction 3. The analytical sample was recrystallized twice from methanol–ether, m.p. 198–199°.

Anal. Calcd. for $C_{12}H_{20}ClNO$: C, 62.73; H, 8.77. Found: C, 62.52; H, 8.96.

The sodium borohydride reduction of III gave a 75% yield of amino alcohol VII, isolated as the hydrochloride salt, m.p. 198–199°. None of the hydrochloride of the isomeric amino alcohol, 1-phenyl-2-ethylamino-2,2-dimethylethanol, was isolated.

α-Hydroxycyclohexyl-phenyl-*N*-methylimine (IV). A. In Absence of O^{18} Enriched Water (Sample A).—To 30 ml. of anhydrous methylamine was added 2.67 g. (0.01 mole) of α-bromocyclohexyl phenyl ketone,[17] and the reaction mixture cooled somewhat in a Dry Ice–acetone bath until solution was complete. The flask was then allowed to warm to room temperature with stirring until most of the methylamine had evaporated. The remaining methylamine was removed under reduced pressure (aspirator). The residue was taken up in several small portions of hot hexane and filtered. The filtrate was treated with decolorizing charcoal, concentrated to a small volume and allowed to cool to room temperature. Crystals were deposited, 1.60 g. (74%), m.p. 116–117°. Recrystallization from hexane gave 1.30 g., m.p. 116–117°.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.24; H, 8.99; N, 6.33.

B. In Presence of O^{18} Enriched Water (Sample B).—Identical reaction conditions and amounts of materials were used with the exception that 0.2 g. (0.011 mole) of O^{18} enriched water (6 atom % O^{18})[18] was added to the methylamine before addition of the bromo ketone. The same yield of product was obtained with an identical melting point and undepressed mixture melting point.

O^{18} Analysis[19].—Sample A, atom % O^{18}, 0.203, 0.203; atom % excess O^{18}, 0.00; sample B, atom % O^{18}, 0.199, 0.201; atom % excess O^{18}, 0.00. Required atom % excess O^{18} (1) for 100% incorporation, 2.90%, (2) for 5% incorporation, 0.28%.

Hydrolysis of IV.—Seven-tenths of a gram (0.0032 mole) of IV was dissolved in 15 ml. of 1 *N* hydrochloric acid and the solution was warmed on the steam bath for 10 min. and then allowed to stand at room temperature for 5 hr. The turbid solution was extracted three times with chloroform, the extracts combined, washed with water, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated *in vacuo* to yield an oily residue which was crystallized from hexane, 0.52 g. (78%), m.p. 47.5–48.5° (reported,[17] m.p. 48–49°). Recrystallization of the residue from the mother liquors produced an additional 70 mg. of product, m.p. 48–49°, bringing the total yield to 89%. There was no observed depression in melting point upon admixture with an authentic sample of the hydroxy ketone VIII [RR = $-(CH_2)_5$].

1-Phenyl-1-methylaminoacetone (XI).—To 70 ml. of anhydrous liquid methylamine, collected at Dry Ice–acetone bath temperature, was added 10 g. (0.047 mole) of 1-bromopropiophenone. The resultant solution was stirred for 20–30 min. during which time the temperature was allowed to rise to the boiling point of methylamine (−6.5°). At the end of this period the excess methylamine was removed under reduced pressure (aspirator), and replaced with anhydrous ether–hexane solution. The methylamine hydrobromide which precipitated was removed by filtration, washed with ether–hexane and the combined filtrate and washings were concentrated under reduced pressure without the application of heat. Infrared analysis of the crude reaction mixture at this point revealed an intense band at 5.80 μ (unconjugated carbonyl) and a weaker band at 5.90 μ (conjugated carbonyl). The residue was flash distilled to yield 5.00 g. (65%) of a liquid, b.p. 60–62° (0.06 mm.), which partially solidified on cooling. A small amount of the oily solid was recrystallized from hexane to yield a product m.p. 41–42°, which oiled and turned brown when attempts were made to purify this material further by repeated crystallizations. The flash distilled product also was quite unstable and could be stored only in a tightly sealed flask in the refrigerator. The recrystallized solid in chloroform solution showed a single sharp carbonyl absorption band in the infrared at 5.80 μ.

Hydrochloride Salt.—Two grams (0.012 mole) of the flash distilled material was dissolved in anhydrous ether, and isopropyl alcohol saturated with dry hydrogen chloride was added to the solution until the formation of a precipitate ceased. The solid was filtered and recrystallized from methanol–ether to yield 1.57 g. (64%) of solid, m.p. 211–213° with charring (reported,[20] m.p. 210–211°). The hydrochloride salt showed a single carbonyl absorption band in the infrared at 5.85 μ.

Sixty-five milligrams of the recrystallized amino ketone XI, m.p. 41–42°, was converted to the hydrochloride salt in the manner described above to yield 52 mg. (65%) of solid m.p. 212–213° after two recrystallizations from methanol–ether. There was no depression in melting point when this hydrochloride was mixed with the hydrochloride salt obtained from the flash distillation product.

Reaction of XI with Methylmagnesium Iodide.—One gram (0.005 mole) of 1-phenyl-1-methylaminoacetone hydrochloride dissolved in water was made basic and extracted with ether. The ether extract was dried over anhydrous potassium carbonate, filtered, and concentrated under reduced pressure (aspirator). The concentrated solution, 10 ml., was added slowly to 20 ml. of an ether solution of methylmagnesium iodide prepared from 0.72 g. (0.03 g.-atom) of magnesium metal and 4.26 g. (0.03 mole) of methyl iodide. When the addition was complete, the ether was removed by distillation and replaced with benzene. The resultant mixture was refluxed for 12 hr. At the end of this period the reaction mixture was cautiously poured into dilute hydrochloric acid, the solution extracted with ether, and the ether extract discarded. The aqueous portion was made basic, extracted with ether, the ether extract dried over anhydrous potassium carbonate and concentrated to a small volume under reduced pressure. Isopropyl alcohol saturated with hydrogen chloride was added to the concentrate and the solid obtained was filtered and recrystallized twice from methanol–ether to yield 0.57 g. (53%) of material, m.p. 242°. A depression in melting point was not observed upon admixture with 1-phenyl-1-methylamino-2-methyl-2-propanol hydrochloride obtained from the reduction of the α-hydroxyimine II.

Reaction of 6-Bromo-2,2,6-Trimethylcyclohexanone with Methylamine.—In a 50-ml. three-neck flask, equipped with a stirrer and a reflux condenser were placed 35 ml. of anhydrous liquid methylamine, collected at Dry Ice–acetone bath temperature, and 5 g. (0.023 mole) of 6-bromo-2,2,6-trimethylcyclohexanone.[12] The resultant solution was stirred for 1 hr. during which time the temperature was allowed to rise to the boiling point of methylamine (−6.5°). At the end of this period the excess methylamine was removed under reduced pressure and replaced with ether. The methylamine hydrobromide which precipitated was removed by filtration, washed with ether and amounted to 100%. The filtrate and washings were combined and concentrated under reduced pressure. A sample was removed at this point for infrared analysis (see discussion). The concentrate was dissolved in dilute hydrochloric acid, allowed to stand at room temperature for 1 hr., then heated on the steam bath for 10 min., extracted with ether, the ether extract dried over anhydrous sodium sulfate, and the ether removed under reduced pressure (aspirator–steam bath) to yield 0.57 g. (16%) of 6-hydroxy-2,2,6-trimethylcyclohexanone (XVI). The infrared absorption spectrum was identical with that of an authentic sample.[12] The crude hydroxy ketone was distilled in a sublimation apparatus to yield a colorless oil, $n^{27}D$ 1.4603 (reported[12] $n^{25}D$ 1.4599). The ketone was converted

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

(18) 20th Century Electronics Ltd., New Addington, Surrey, England.

(19) We are indebted to J. H. Swinehart, Department of Chemistry, University of Chicago, for the O^{18} analyses.

(20) H. Emde and E. Runno, *Arch. Pharm.*, **249**, 366 (1911).

to a 2,4-dinitrophenylhydrazone, m.p. 221–222° (reported,[12,21] m.p. 224–225°), which showed no depression in melting point upon admixture with an authentic sample[12] of the hydroxy ketone 2,4-dinitrophenylhydrazone derivative.

The aqueous acid solution obtained from the above hydrolysis was made basic and extracted with ether. The ether extract was dried over anhydrous potassium carbonate, the ether removed under reduced pressure (aspirator–steam bath) and the residue was fractionated *in vacuo*. The amino ketone XIII, 2.22 g. (57%), was obtained as an oil, b.p. 82–86° (8 mm.), $n^{32}D$ 1.4611, d^{25}_4 0.9481. The infrared spectra indicated a single carbonyl absorption band at 5.85 μ.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.31. Found: C, 70.66; H, 11.55.

The hydrochloride salt was recrystallized from methanol–ether, m.p. 158.5–160°.

Anal. Calcd. for $C_{10}H_{20}ClNO$: C, 58.38; H, 9.80. Found: C, 58.64; H, 9.84.

Oxidation of Amino Ketone XIII to Geronic Acid.—Two-tenths gram (0.0012 mole) of XIII was dissolved in 24 ml. of 2 *N* sodium metaperiodate solution. The reaction mixture was allowed to stand at room temperature for 20 hr. At the end of this period the periodate solution was made strongly alkaline, extracted with ether, and the ether extract discarded. The aqueous portion was acidified, and extracted twice with ether and once with chloroform. The extracts were combined, dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. The residue was treated with 2,4-dinitrophenylhydrazine to yield 0.26 g. (62%) of the derivative, m.p. 135.5–137° (reported m.p. 135.5–137°[22] or 139.5–140°[12]). A depression in melting point was not observed upon admixture with an authentic sample[12] of geronic acid, 2,4-dinitrophenylhydrazone.

(21) A. Bell, T. H. Stickland, and G. F. Wright, *J. Org. Chem.*, **16**, 1742 (1961); K. R. Bharucha, H. L. Cohen, and G. F. Wright, *ibid.*, **19**, 1097 (1954).

(22) H. H. Strain, *J. Am. Chem. Soc.*, **57**, 758 (1935).

Cyanoethylation. I. Weakly Basic Catalysts in the Reaction of Acrylonitrile with Active Methylene Compounds[1]

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Received August 6, 1962

Cyanoethylation of some active methylene compounds has been shown to proceed in the presence of triethylamine, often in high yields. With this catalyst at 25° the cyanoethylation of acetylacetone is greatly affected by the nature of the solvent. Little or no reaction occurs in tetrahydrofuran or dioxane, and the rate of the reaction varies with the nature of the solvent in this manner: *t*-butyl alcohol < isopropyl alcohol < 95% ethanol < "50% ethanol." The cyanoethylation of α-cyanoacetamide in the presence of triethylamine gave the expected product at 20°, but an isomer (VIII) at 65–70°. Studies on VIII have enabled us to formulate it as 3-cyano-3-(2′-cyanoethyl)-6-imino-2-piperidone.

Strong bases, such as benzyltrimethylammonium hydroxide and potassium hydroxide, are ordinarily used as catalysts in the cyanoethylation reaction.[2] However, the use of cyclohexylamine in the cyanoethylation of ethyl cyanoacetate has been reported.[3] Wakamatsu and Shimo have recently reported liquid ammonia-catalyzed Michael additions of nitroparaffins[4] and of derivatives of malonic and cyanoacetic acids[5,6] to acrylonitrile and other acceptors. Nevertheless, the use of such catalysts has not generally been exploited in synthesis. Since it might be expected to have the advantage of giving a more easily controllable reaction, the employment of triethylamine in the cyanoethylation of some active methylene compounds has been investigated.

The results obtained are reported in Table I. The yields can be quite high and the method is very convenient. It is necessary only to allow a solution of the active methylene compound, acrylonitrile, and triethylamine in a suitable solvent to stand at room temperature whereupon the product, if solid, separates from the reaction mixture.

In the course of the work, it was noted that the nature of the solvent had a great effect on the rate of the reaction and on the ultimate yields obtainable. In nonhydroxylic solvents such as dioxane and tetrahydrofuran the reaction took place extremely slowly if at all while it did proceed at a reasonable rate in alcohols.

This factor was therefore investigated more thoroughly by conducting the cyanoethylation of acetylacetone in various solvents at 25°. The ultimate yield of product was determined, and, as a rough indicator of the reaction rate, the time required to obtain one half of the ultimate yield. The results are shown in Table II.

That the reaction rate increases with the solvating ability of the solvent is shown by the order of reactivity in the solvents studied.

$$50\%\ C_2H_5OH\text{–}50\%\ H_2O > C_2H_5OH > (CH_3)_2CHOH > (CH_3)_3COH$$

The following explanation can be given for our results. The monocyanoethylation of acetylacetone in the presence of triethylamine proceeds as follows:

$$(CH_3CO)_2CH_2 + (C_2H_5)_3N \longrightarrow (CH_3CO)_2CH^- + (C_2H_5)_3NH^+$$

$$(CH_3CO)_2CH^- + CH_2{=}CHCN \longrightarrow (CH_3CO)_2CH{-}CH_2CH{-}CN$$

VI

where HA is an acidic species such as acetylacetone, triethylammonium ion, or possibly even solvent.[7] Since the reaction involves formation of the ionic species VI and triethylammonium from neutral molecules, the observed dependence of the rate on the solvent is expected.

(1) The support of this work by the Robert A. Welch Foundation is gratefully acknowledged.

(2) H. A. Bruson, *Org. Reactions*, **5**, 81 (1949).

(3) G. Wiest and H. Glaser, U.S. Patent 2,396,626 (March 12, 1946).

(4) S. Wakamatsu and K. Shimo, *J. Org. Chem.*, **27**, 1609 (1962).

(5) S. Wakamatsu, *ibid.*, **27**, 1285 (1962).

(6) K. Shimo and S. Wakamatsu, *ibid.*, **26**, 3788 (1961).

(7) This mechanism is a modification of the one given for the hydroxide ion-catalyzed cyanoethylation of acetylacetone by Y. Ogata, M. Okano, Y. Furuya, and I. Tabushi, *J. Am. Chem. Soc.*, **78**, 5426 (1956). It is essentially the same as that given by Wakamatsu (ref. 5).