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 phosphonamide 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

Materials.—Acetone (Hopkin and Williams, AnalR 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 50.0–50.5°C 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. Benzene (AnalR grade) was refluxed over sodium and then fractionated. Nitromethane was dried over anhydrous magnesium sulfate and fractionated. Amines were dried over potassium hydroxide on a stopper flask and precooled to the desired reaction temperature. Re-action was started by introducing the phosphonochloridate by placing the flask in the constant temperature bath. Re-

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°C for at least 0.5 hr. The solution of the amine in the solvent was placed in a stopped flask and precooled to the desired reaction temperature by placing the flask in the constant temperature bath. Re-

action 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 chloride. The excess acid was then back titrated with a standard solution of triethylamine in toluene using Laemoid indicator.

Isolation of Reaction Products.—A 1.42-g. sample (10 mmol) of ethyl methylphosphonochloridate was added slowly to stirring and cooling to 22 mmol 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 re-

duced pressure. The following compounds were prepared in this way.

**Ethyl N-diethylmethylphosphonamidate (64% yield), b.p. 110–114°C/22 mm.** (Found: C, 46.5; H, 10.0; N, 8.0. C\_1\textsubscript{8}H\_1\textsubscript{8}P\_2O\_2N requires C, 46.9; H, 10.0; N, 7.8.)

**Ethyl N-di-n-butylmethylphosphonamidate (75% yield), b.p. 108–110°C/30 mm.** (Found: C, 56.4; H, 11.8; N, 6.4. P, 14.1. C\_\textsubscript{13}H\_\textsubscript{20}P\_2O\_2N requires C, 56.2; H, 11.9; N, 6.0.)

**Ethyl N-di-sec-butylmethylphosphonamidate (50% yield), b.p. 115–120°C/30 mm.** (Found: C, 55.5; H, 12.4; N, 5.4. C\_\textsubscript{16}H\_\textsubscript{22}P\_2O\_2N requires C, 55.2; H, 11.0; N, 5.0.)

**Ethyl N-butylmethylphosphonamidate (70% yield), b.p. 110–112°C/250 mm.** (Found: C, 46.9; H, 10.0; N, 7.2. P, 18.1. C\_\textsubscript{13}H\_\textsubscript{18}P\_2O\_2N requires C, 46.9; H, 10.0; N, 7.5; P, 17.5.)

**Ethyl N-sec-butylmethylphosphonamidate (47% yield), b.p. 121–125°C/30 mm.** (Found: C, 47.5; H, 10.4; N, 7.0. C\_\textsubscript{15}H\_\textsubscript{20}P\_2O\_2N requires C, 46.5; H, 10.0; N, 7.5.)

**Ethyl N-isobutylmethylphosphonamidate (63% yield), b.p. 134–140°C/26 mm.** (Found: C, 46.8; H, 10.6; N, 6.8. C\_\textsubscript{14}H\_\textsubscript{19}P\_2O\_2N requires C, 46.5; H, 10.0; N, 7.5.)

**Ethyl N-phenylmethylphosphonamidate (52% yield), b.p. 160–165°C/20 mm.** (Found: C, 55.0; H, 6.8; N, 7.3. C\_\textsubscript{16}H\_\textsubscript{18}P\_2O\_2N requires C, 54.0; H, 7.0; N, 7.0.)

The Reactions of α-Bromo Ketones with Primary Amines

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The conversion of α-bromoisobutyrophenone to the corresponding α-hydroxyamines, 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 transformation which suggests a reaction path proceeding via an epoxide (IX) as an intermediate. Apparent anomalous pathways are observed in the reactions of α-bromopropiophenone and 6-bromo-2,2,6-trimethylcyclohexanone with liquid methylamine to yield 1-phenyl-1-methylaminocetone and 6-methylaminoo-2,2,6-trimethylcyclohexanone, respectively.

The reactions of α-halo ketones with amines have received considerable attention in the chemical literature. In general, it has been shown that α-halo ketones, whose structures prohibit a Favorskii type rearrangement, undergo substitution and/or dehydrohalogenation where possible, upon treatment with ammonia, primary, or secondary amines. 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 and α - methylaminoisobutyrophenone, 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
was readily hydrolyzed in aqueous acid to \( \alpha \)-hydroxyisobutyrophenone (VIII, \( R = CH_3 \)) and reduced catalytically or with sodium borohydride to the known \( \alpha \)-amino alcohol V. On this basis the \( \alpha \)-hydroximine structure I was assigned to the reaction product. The infrared spectrum with strong absorption in the 3-\( \mu \) region (NH/OM) and a strong band at 6.05 \( \mu \) (C\( \equiv \)N) supported the assignment.

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

With a single exception, the isomeric \( \alpha \)-amino ketones could not be detected in the reaction mixtures. Catalytic reduction of a sample of the \( \alpha \)-hydroximine, III, arising from the reaction of \( \alpha \)-bromoisobutyrophenone with ethylamine, led to the formation of the expected \( \alpha \)-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 \( \alpha \)-amino alcohol, 1-phenyl-2-methyl-2-ethylaminopropanol. The latter reduction product must arise from \( \alpha \)-ethylaminoisobutyrophenone, thus indicating that the reaction of \( \alpha \)-bromoisobutyrophenone with ethylamine proceeds to a very minor extent by a substitution course.

\[
\begin{align*}
\text{C}_6\text{H}_6\text{-CH-C-R} & \quad \text{excess } R'\text{-NH}_3 \\
& \quad \text{ HO}^+ \quad \text{C}_6\text{H}_5\text{-CH-C-R} \\
& \quad \text{ OH} \quad \text{VIII} \\
& \quad \text{R'HN} \quad \text{C}_6\text{H}_5\text{-CH-C-R} \\
& \quad \text{NaBH}_4 \quad \text{C}_6\text{H}_5\text{-OH} \quad \text{C}_6\text{H}_5\text{-CH-C-R} \\
\end{align*}
\]

I. \( R = CH_3, R' = H \) \hspace{1cm} V. \( R = CH_3, R' = H \) \\
II. \( R = R' = CH_3 \) \hspace{1cm} VI. \( R = R' = CH_3 \) \\
III. \( R = CH_3, R' = CH_3 \) \hspace{1cm} VII. \( R = CH_3, R' = CH_3 \) \\
IV. \( RR = (CH_3)_2, R' = CH_3 \)

Based upon a consideration of the formation of epoxy ethers from \( \alpha \)-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 \( \alpha \)-hydroximine (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\(^8\) proposed and cited evidence in favor of an epoxyamine intermediate, arising in the manner described above, in the formation of \( \alpha \)-aminoaldehydes from the interaction of \( \alpha \)-haloaldehydes with the secondary amines.

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

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

Although such a mechanism was not considered likely in the present work in view of the high yields of \( \alpha \)-hydroximine obtained, it appeared desirable to establish that water did not play the role of an intermediate in the reaction. The conversion of \( \alpha \)-bromo-cyclohexyl phenyl ketone to the \( \alpha \)-hydroximine 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 \( \alpha \)-hydroximine 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 \( \alpha \)-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\(^1\) who studied the aniline hydrobromide-catalyzed isomerization of \( \alpha \)-anilinoisopropiophenone 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 5) was ruled out on the basis of the observed stability of \( \alpha \)-methylaminoisobutyrophenone under the reaction conditions leading to the formation of the \( \alpha \)-hydroximine II. Dissolution of \( \alpha \)-methylaminoisobutyrophenone in liquid methyamine containing a molar equivalent of methyamine hydrobromide led to an 81% recovery of the starting \( \alpha \) amino ketone.

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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, 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. 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.

An anomalous 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 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.™

(11) Rearrangement of X to XI could possibly proceed via the anediol-type intermediate, CH₃—C—CH₂OH, or via a pinacol-type rearrangement: CH₃—NH OH 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.

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 re-precipitated by filtration and the filtrate concentrated, then redissolved with hexane-petroleum ether (1:1 solution). The resultant solution was filtered once more and the filtrate placed 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 C11H17NO: C, 75.35; H, 8.96. Found: C, 75.70; H, 8.17.

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 30 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. (84%) of α-hydroxyisobutyrophenone, b.p. 87-89° (1.6 mm.), nD 1.5282 (reported, m.p. 127-127.5°).

The semicarbazone derivative was prepared by the method of Shriner and Fusan. The white solid was collected by filtration and recrystallized from ethyl alcohol with an authentic sample of the I semicarbazone semicarbazide. The melting point upon admixture with an authentic sample of the l-phenyl-l-dimethyl-2-methylaminoethanol semicarbazide.

1,1-Dimethyl-2-phenyl-2-methyliminoethanol (V).—A. By Hydrogenation of I.—A solution of 1.0 g. (0.006 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. Twenty-five milliliters of anhydrous methanol-ether was added isopropyl alcohol saturated with dry ammonia. The reaction was allowed to proceed for 2 hr. at room temperature. The white solid was collected by filtration and recrystallized from ethyl alcohol with an authentic sample of the I1 semicarbazone semicarbazide.


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


B. By Sodium Borohydride Reduction of I.—In 15 ml. of absolute ethanol were placed 0.55 g. (0.003 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 reaction flask was warmed gently to remove the ammonia which was replaced with an atmosphere of nitrogen. Two recrystallizations from ether-hexane gave an analytically pure product, m.p. 83.5-85°.

C. By Acetaldehyde Reduction of I.—The reaction of 2 g. (0.023 mole) of α-hydroxyisobutyrophenone with acetaldehyde was carried out at 0° and the reaction product was flash distilled and then fractionated in vacuo. A clear colorless liquid, 9.20 g. (78.6%), b.p. 73-75° (1.0 mm.), nD 1.5130, d4° 0.991, was obtained.


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


B. By Sodium Borohydride Reduction of I.—The same procedure was used for the reduction of the α-hydroxyimine I. From 6.5 g. (0.036 mole) of the starting material, 6.79 g. (86%) of amino alcohol VI hydrochloride salt was obtained, m.p. 241-242°.


Catalytic Hydrogenation of II.—The same procedure was used for the preparation of I. Two grams (0.011 mole) of II gave 1.91 g. (94%) of VI, m.p. 57-58° after recrystallization from ether-hexane.

The same procedure gave an oil which was fractionated in vacuo, and a depression in melting point was not observed in the crude reaction product. The crude reaction product was flash distilled and then fractionated in vacuo. A total yield of material was 7.25 g. (89%). Fractionation of the material gave six fractions: (1) 0.48 g., b.p. 51° (0.02 mm.), nD 1.5111; (2) 1.37 g., b.p. 51° (0.02 mm.), nD 1.5111; (3) 2.46 g., b.p. 51° (0.02 mm.), nD 1.5112; (4) 1.37 g., b.p. 51° (0.02 mm.), nD 1.5112; (5) 1.00 g., b.p. 51-51.5° (0.02 mm.), nD 1.5116; (6) 0.57 g., b.p. 51.5-55° (0.02 mm.), nD 1.5118. The total yield of material was 7.4 g. (85%). Fraction 2 was used for density measurements: d4° 0.9847. Fraction 3 was used for an analytical sample.


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

(16) (a) This compound was prepared by the reaction of 1-phenyl-1-methoxy-2,2-dimethylbutylenoxide 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-dimethylbutylenoxide with ethylamine followed by reduction. K. G. Taylor, Wayne State University, private communication.
A. In Presence of O18 Enriched Water (Sample B).—Identical reaction conditions and amounts of materials were used with the exception that 0.2 g. (0.011 mole) of O18 enriched water (6 atom% excess O18) was added to the mixture before addition of the bromo ketone. The same yield of product was obtained with an identical melting point and undepressed mixture melting point.

O18 Analysis—Sample A, atom% O18, 0.203; 0.203; atom% excess O18, 0.00; sample B, atom% O18, 0.126, 0.201; atom% excess O18, 0.00. Required atom% excess O18 (4) 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 to vacuo to yield an oily residue which was crystallized from hexane, 0.52 g. (75%), m.p. 47.5-48.5° (reported10 m.p. 48-49°). Recrystallization of the red aqueous portion containing an additional portion 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 = (CH3)2].

B. In Presence of O18 Enriched Water (Sample A).—The ether extract was dried over anhydrous sodium sulfate, the ether extract discarded, and the concentrate was dissolved in anhydrous ether and washed. Isopropyl alcohol saturated with hydrogen chloride was added to the concentrate until the formation of a precipitate ceased. The solid was recrystallized from methanol-ether to yield 1.60 g. (74%), m.p. 199°.

Reaction of XI with Methylmagnesium Iodide.—One gram (0.005 mole) of 1-phenyl-1-methylamino-2-methyl-2-propanone hydrochloride dissolved in water was made basic and extracted with ether. The ether extract was dried over anhydrous sodium sulfate, the ether extract discarded, and the concentrate was dissolved in anhydrous ether and washed. Isopropyl alcohol saturated with hydrogen chloride was added to the concentrate until the formation of a precipitate ceased. The solid was recrystallized and washed and then heated on the steam bath for 10 min., extracted with ether, and filtered. 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. The reaction 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, filtered, and concentrated under reduced pressure (aspirator). The resulting mixture was refluxed for 1 hr. During this period the excess methylamine was removed under reduced pressure and replaced with O18 enriched water (6 atom% excess O18) for 1 hr., then allowed to stand at room temperature for 5 hr. The resulting solution was extracted with chloroform, the extracts combined, washed with water, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to vacuo to yield an authentic sample of the hydroxy ketone VIII [RR = (CH3)2].

1-Phenyl-1-methylaminoacetone (XI).—To 10 ml. of anhydrous liquid methylamine was added 10 g. (0.047 mole) of 1-bromo-1-phenylethanol. The resulting solution was stirred for 20-30 min., during which time the temperature was allowed to rise to the boiling point of methylamine (6-6.5°). 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 product indicated that this point was reached when an intense band at 5.90 μ [unconjugated carbonyl] and a weaker band at 7.90 μ [conjugated carbonyl] had disappeared and the residue was flash distilled to yield 5.00 g. (65%) of a liquid, b.p. 60-62° (0.66 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 oil and turned to a solid. Several 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. (94%) of solid, m.p. 211-213° with charring (reported11 m.p. 210-211°). The hydrochloride salt showed a single carbonyl absorption band in the infrared at 5.55 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 salt 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. The reaction 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, filtered, and concentrated under reduced pressure (aspirator). A depression in melting point was noted upon admixture with 1-phenyl-1-methylamino-2-methyl-2-propanone 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 5.0 (0.024 mole) of 6-bromo-2,2,6-trimethylcyclohexanone.15 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 O18 enriched water (6 atom% excess O18) for 1 hr., then allowed to stand at room temperature for 5 hr. The resulting solution was extracted with chloroform, the extracts combined, washed with water, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to vacuo to yield an authentic sample of the hydroxyketone VIII [RR = (CH3)2].

(19) We are indebted to J. H. Swinehart, Department of Chemistry, University of Chicago, for the O18 analyses.
to a 2,4-dinitrophenylhydrazone, m.p. 221-222° (reported,11 m.p. 224-225°), which showed no depression in melting point upon admixture with an authentic sample11 of the hydroxy ketone 2,4-dinitrophenylhydrazone derivative.

The aqueous 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 under reduced pressure (aspirator-steam bath) and the residue was fractionated. It is necessary only to allow a solution of the amino ketone XIII, 2.22 g. (57%), was obtained as an oil. b.p. 82-86° (8 mm.), nD25 1.4611, d34 0.9481. The infrared spectra indicated a single carbonyl absorption band at 5.85 μ.


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


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

The use of cyclohexylamine in the cyanoethylation of vantage of giving a more easily controllable reaction, and Shimo have recently reported liquid ammonia-catalyzed Michael additions of nitroparaffins4 and of in synthesis. Since it might be expected to have the advantage 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% C6H10OH-50% H2O > C2H5OH > (CH3)2CHOH >


C2H5OH

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 nitroparaffins4 and of derivatives of malonic and cyanoacetic acid5 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 yields obtained are reported in Table I. 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% C6H10OH-50% H2O > C2H5OH > (CH3)2CHOH > (CH3)COH

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

(CH3CO)2CH + (CH3)2N → (CH3CO)2CH-N+ + (CH3)2NH+

(CH3CO)2CH-N- + CH3=CHCN →

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

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

(CH3CHO)2CH2 + (C2H5)2N → (CH3CHO)2CH2-N+ + (C2H5)2NH+


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


(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, 5420 (1956). It is essentially the same as that given by Wakamatsu (ref. 3).