[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Studies on the Synthesis of Ethyleneimines from Interaction of Ketoximes and Grignard Reagents[1]

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The formation of ethyleneimines from interaction of ketoximes and Grignard reagents has been extended to include aliphatic ketoximes. Whereas interaction of acetophenone oxime with ethylmagnesium bromide might be expected to yield the same product as that from propiophenone oxime and methylmagnesium bromide, actually different ethyleneimines result from these reactions.

The formation of ethyleneimines from ketoximes and Grignard reagents was first reported by Hoch.[3] Subsequently, Campbell *et al.*[4–7] established that alkyl aryl ketoximes react with Grignard reagents in toluene solution at 90–110° to yield ethyleneimines. Vigorous hydrolysis of the reaction mixtures gave α-amino alcohols. Campbell's group prepared 10 ethyleneimine derivatives by this procedure and suggested a sequence of intermediates to account for the products obtained. The present investigation was undertaken with the idea of extending the reaction to purely aliphatic ketoximes and confirming, if possible, the reaction sequence suggested by Campbell.

EXPERIMENTAL[8]

The experimental procedure described by Campbell[6] was employed, modified only by the substitution of an electric heating mantle for the oil bath. Hydrolysis of the ethyleneimines to obtain amino alcohols was also accomplished by Campbell's method.[7]

3-Ethyl-2-phenyl-2-propylethyleneimine. This compound was prepared from interaction of one mole of propylmagnesium bromide and 0.2 mole(32.8 g.) of butyrophenone oxime; b.p. 100–117° (7 mm.); n_D^{20} 1.5150; d_4^{20} 0.9382; mol. refr. calcd.[9] 60.75; summation 60.03; yield 16.3 g. (43%).

Anal. Calcd. for $C_{13}H_{19}N$: N, 7.41. Found: N, 7.44.

This imine formed a hydrochloride, m.p. 140–141° (from ethanol–absolute ether), and a phenylthiourea, m.p. 93–95° (from benzene–Skellysolve B).

Anal. Calcd. for $C_{13}H_{19}N \cdot HCl$: N, 6.06. Found: N, 6.01.

2,2-Diethyl-3-methylethyleneimine. Prepared from interaction of 1 mole of ethylmagnesium bromide and 0.2 mole (20 g.) of diethylketoxime; b.p. 136–142°. n_D^{20} 1.4337; d_4^{20} 0.862; M.R. summation 35.93; M.R. calcd. 36.07; 7.5 g. (14% yield). The product formed a hydrochloride, m.p. 94–95° (from ethanol–absolute ether) and a phenylthiourea, m.p. 97–100° (from benzene–Skellysolve B).

Anal. Calcd. for $C_7H_{15}N \cdot HCl$: N, 9.35. Found: N, 9.73. Calcd. for $C_{14}H_{20}N_2S$: N, 11.28. Found: N, 11.31.

Hydrolysis of this ethyleneimine yielded 2-amino-3-ethyl-3-pentanol, isolated as the hydrochloride, m.p. 143.0–144.5° (from ethanol–absolute ether).

Anal. Calcd. for $C_7H_{17}NO \cdot HCl$: N, 8.36. Found: N, 8.31.

3-Ethyl-2,2-dipropylethyleneimine. Prepared from 0.75 mole of propylmagnesium bromide and 0.25 mole (37 g.) of dipropyl ketoxime; b.p. 70–95° (15 mm.); n_D^{20} 1.4428; d_4^{20} 0.8182; M.R. summation 49.78; M.R. calcd. 50.21; yield 6 g. When the reaction time was increased from 2 hr. to 6 hr., the yield was increased to 11.1 g. (37%).

Anal. Calcd. for $C_{10}H_{21}N$: N, 9.02. Found: N, 9.17.

The compound formed a hydrochloride, m.p. 152–155°.

Anal. Calcd. for $C_{10}H_{23}N \cdot HCl$: N, 7.31. Found: N, 7.66.

Hydrolysis of this imine yielded 3-amino-4-propyl-7-heptanol, isolated as the hydrochloride, m.p. 201.0–201.5° (from ethanol–absolute ether).

Anal. Calcd. for $C_{10}H_{23}NO \cdot HCl$: N, 6.68. Found: N, 6.74.

2-Butyl-2-methylethyleneimine. Prepared from 0.75 mole of butylmagnesium bromide and 0.25 mole (18 g.) of acetoxime; b.p. 81–84°; n_D^{20} 1.4360; d_4^{20} 0.8314; M.R. summation 40.54. M.R. calcd. 40.52, 6 g. (16% yield).

Anal. Calcd. for $C_8H_{17}N$: N, 11.02. Found: N, 10.33.

Hydrolysis of this imine gave 1-amino-2-methyl-2-hexanol, isolated as the phenylthiourea, m.p. 114–116° (from benzene–Skellysolve B).

Anal. Calcd. for $C_{15}H_{24}N_2OS$: N, 10.00. Found: N,10.06.

2-Methyl-3-phenyl-3-propylethyleneimine. Interaction of 3 moles of propylmagnesium bromide with 0.52 mole (81 g.) of propiophenone yielded 53.3 g. of basic material boiling at 80–110° (3 mm.); n_D^{20} 1.5299; d_4^{20} 0.9445; M.R. summation 55.41; M.R. calcd. 56.33. Fractionation of this material through a 15 cm. Widmer column gave 14 ml. with principal fraction boiling at 107–108° (9 mm.); n_D^{20} 1.5155; d_4^{20} 0.9448; M.R. calcd. 55.91.

Anal. Calcd. for $C_{13}H_{17}N$: N, 8.00. Found: N, 8.25.

The lower boiling fractions of the reaction contained 6.64–7.54% N. The principal fraction formed a phenylthiourea derivative, m.p. 112–113° (from benzene–Skellysolve B); the lower boiling fractions yielded the same material (m.p. 112–113°, mixture melting point with derivative from main fraction, 112–113°), thus the fractionation is indicated as being incomplete.

Anal. Calcd. for $C_{19}H_{22}N_2S$: N, 9.02. Found: N, 9.17.

Hydrolysis of the principal fraction yielded 2-amino-3-phenyl-3-hexanol, n_D^{20} 1.5267.

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(1) Taken in part from the dissertation submitted by W. D. Compton in partial fulfillment of the requirements for the Ph.D. degree at The University of Texas, January 1956.

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(7) K. N. Campbell, B. K. Campbell, L. G. Hess and I. J. Schaffner, *J. Org. Chem.*, **9**, 184 (1944).

(8) Melting points are corrected unless otherwise noted; boiling points are uncorrected.

(9) Molar refraction (M.R.) "calculated" is obtained by substitution of experimental data into the Lorentz-Lorenz equation; molar refraction "summation" is obtained by appropriate summing of the atomic refractivities and of those for linkages in the molecule.

Anal. Calcd. for $C_{12}H_{19}NO$: N, 7.25. Found: N, 7.15.

On reaction with phenyl isothiocyanate, the hydrolysis product formed a phenylthiourea derivative, m.p. 148–151° (from benzene–Skellysolve B).

Anal. Calcd. for $C_{19}H_{24}N_2OS$: N, 8.53. Found: N, 8.60.

2-Amino-3-phenyl-3-hexanol was synthesized from α-aminopropiophenone hydrochloride and propylmagnesium bromide; b.p. 145–150° (17 mm.); n_D^{20} 1.5212; d_4^{20} 1.002; this product reacted with phenyl isothiocyanate to form a derivative of m.p. 153–154° (from benzene–Skellysolve B) which did not alter the melting point of the derivative of the hydrolysis product described above. This sample of the amino alcohol yielded a hydrochloride, m.p. 231° (dec.) (from ethanol–absolute ether).

Anal. Calcd. for $C_{19}H_{24}N_2OS$: N, 6.10. Found: N, 5.96.

Anal. Calcd. for $C_{12}H_{19}NO \cdot HCl$: N, 8.53. Found: N, 8.37.

Reaction of propiophenone oxime with methylmagnesium bromide. From 0.75 mole of methylmagnesium bromide and 0.25 mole (35 g.) of propiophenone oxime there was obtained about 10 g. of a basic product; b.p. 85–95° (10 mm.); n_D^{20} 1.5288; d_4^{20} 0.9885; M.R. summation (for 2-ethyl-2-phenylethyleneimine or an isomer) 46.18; M.R. calcd. 45.82.

Anal. Calcd. for $C_{10}H_{13}N$: C, 81.59; H, 8.89; N, 9.25. Found: C, 81.12; H, 9.02; N, 9.34.

The imine formed a phenylthiourea derivative, m.p. 122–123° (from benzene-Skellysolve B).

Anal. Calcd. for $C_{17}H_{18}N_2S$: N, 9.92. Found: N, 10.17.

Hydrolysis of this imine yielded a basic product which was isolated as the hydrochloride, m.p. 234° (dec.) (from ethanol–absolute ether).

Anal. Calcd. for $C_{10}H_{15}NO \cdot HCl$: N, 6.95. Found: N, 6.88.

The physical properties of this imine and the melting points of its derivatives and of those of its hydrolysis product differ significantly from those reported[7] for the expected imine, namely, 2-ethyl-2-phenylethyleneimine. An authentic sample of the latter showed significant differences from the product of this reaction outlined above. The phenylthiourea derivative of authentic 2-ethyl-2-phenylethyleneimine melts at 100–102°; a mixture of it with the phenylthiourea of the new product (m.p. 122–123°) melted at 88–115°. Hydrolysis of authentic 2-ethyl-2-phenylethyleneimine gave a product the hydrochloride of which melted at 180–182°. The latter melting point is to be contrasted with that of 234° (dec.) for the hydrochloride of the hydrolysis product of the isomeric imine; the melting point of a mixture of the two hydrochlorides was 161–186°.

Since 3-amino-2-phenyl-2-butanol could not be obtained directly from hydrolysis of 2-ethyl-2-phenylethyleneimine, but could be from 2,3-dimethyl-2-phenylethyleneimine, it was concluded that interaction of propiophenone oxime and methylmagnesium bromide yields 2,3-dimethyl-2-phenylethyleneimine rather than the 2-ethyl isomer.

Reaction of acetoxime with butylmagnesium bromide. After interaction of 0.1 mole (18 g.) of acetoxime and 0.75 mole of butylmagnesium bromide, treatment of the reaction mixture with diluted acid, drying, and removal of the organic solvent left 13.5 g. of a red-brown liquid. Fractionation of the latter gave 5.5 g. (17% yield) of product, b.p. 60–70° (30 mm.), n_D^{20} 1.4341; d_4^{20} 0.8294; M.R. summation (for 2-butyl-2-methylethyleneimine) 35.93; M.R. calcd. 35.49; the product did not yield a derivative either with hydrogen chloride or with phenyl isothiocyanate.

Anal. Calcd. for $C_7H_{15}N$: N, 12.38. Found: N, 11.60.

A portion of the product was subjected to hydrolysis with dilute sulfuric acid, but attempts to isolate the hydrolysis product as the phenylthiourea yielded a liquid which could not be caused to crystallize.

Reaction of acetoxime with amylmagnesium bromide. One-fourth mole (18 g.) of acetoxime and 0.75 mole of amylmagnesium bromide were allowed to react; after the usual procedure, 11 g. of red-brown liquid was subjected to fractionation. Fraction 1: b.p. 81–84° (30 mm.); n_D^{20} 1.4360; d_4^{20} 0.8134; M.R. calcd. 40.52. Fraction 2: b.p. 84–90° (30 mm.); n_D^{20} 1.4375; d_4^{20} 0.8173; M.R. calcd. 40.75; M.R. summation (for 2-amyl-2-methylethyleneimine) 40.54.

Neither fraction yielded a solid derivative with either hydrogen chloride or phenyl isothiocyanate. The two fractions were recombined and refractionated to obtain a sample for analysis.

Anal. Calcd. for $C_8H_{17}N$: N, 11.02. Found: N, 10.33.

The basic reaction product was hydrolyzed in sulfuric acid solution to give a liquid; the latter reacted with phenyl isocyanate to yield a difficultly crystallizable solid; m.p. 114–116°.

Anal. Calcd. for $C_{15}H_{24}N_2OS$: N, 10.00. Found: N, 10.06.

Reaction of diethyl ketoxime with phenylmagnesium bromide. From interaction of 0.25 mole (25 g.) of diethylketoxime and one mole of phenylmagnesium bromide, and subsequent hydrolysis, there remained about 25 g. of a dark yellow liquid. Vacuum distillation of the product gave considerable volatile material (collected in the Dry Ice–acetone cold trap) and only a small amount of distillate of b.p. 90–92° (5 mm.); n_D^{20} 1.5173. Attempts to prepare solid derivatives of this material were unsuccessful.

The experiment was repeated and 9 g. of distilled product was obtained; it, too, failed to form the usual ethyleneimine derivatives. It was fractionated; b.p. 70–78° (3 mm.); n_D^{20} 1.5160; d_4^{20} 0.9679; M.R. calcd. 50.2; [the expected product, 2-ethyl-3-methyl-2-phenylethyleneimine, had previously been found to possess quite different physical properties, namely; b.p. 88–90° (5 mm.); n_D^{20} 1.5202; d_4^{20} 0.9572; M.R. summation 50.8; M.R. calcd. 51.2]. The preparation was repeated again and yielded a liquid of b.p. 80–90° (4 mm.); n_D^{21} 1.5160. These products, too, failed to yield a solid hydrochloride of phenylthiourea derivative.

Anal.[10] Calcd. for $C_{11}H_{15}N$: C, 81.95; H, 9.37; N, 8.70. Found: C, 79.35; H, 9.69; N,[11] 7.14.

The product could be shown to contain an "active hydrogen," but was completely destroyed by boiling with dilute hydrochloric acid solution. The infrared absorption spectrum of this reaction product was determined and compared with that of an authentic sample of 2-ethyl-3-methyl-2-phenylethyleneimine. The high degree of similarity of the two spectra suggested that the reaction product represented a slightly impure sample of the anticipated imine.

DISCUSSION

The formation of ethyleneimines from ketoxime and Grignard reagents has been extended in this investigation to include dialkyl ketoximes. The latter appear to give poorer yields than do alkyl aryl ketoximes; this fact is attributed to the production of an insoluble intermediate, probably of the type $R_2C{=}NOMgBr$, which is formed in considerable amounts from the dialkyl ketoximes. This insoluble material is infusible, contains magnesium and bromine, and in one case was hydrolyzed by ice and water to regenerate the dialkyl ketoxime. An analogous material could be obtained from interaction of equimolecular quantities of propiophenone oxime and ethylmagnesium bromide, and, also, when the Grignard reagent was added to the oxime ("inverse addition"). In this latter case, further addition of the Grignard reagent caused the insoluble material to redissolve.

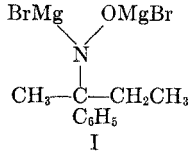
The facts observed tend to support, in general,

(10) Analyses made by Huffman Analytical Laboratories, Wheatridge, Colo.

(11) Two analyses on freshly prepared and fractionated material yielded N, 8.47 and 8.88.

the reaction sequence proposed by Campbell *et al.*,[6] which involves (1) replacement of the active hydrogen of the oxime by MgBr, (2) addition of RMgBr to the C=N linkage, (3) elimination of Mg(OH)Br by closure of the ethyleneimine ring at an α-carbon, and (4) formation of the free imine by hydrolysis. The only modification of this sequence seemingly necessitated by the present work is some accounting for the unidirectional ring closure.

According to Campbell, the same intermediate, I, should be obtained from either of two pairs of



I

reactants, acetophenone oxime and ethylmagnesium bromide or propiophenone oxime and methylmagnesium bromide. But actually, these two pairs of reactants, after mixing and hydrolysis, yield different products; in each instance the alkyl side chain of the oxime becomes incorporated into the ethyleneimine nucleus. Quite probably this directional influence is a result of steric hindrance in the intermediate product of reaction—inspection of molecular models suggests such hindrance. The results seem to be explainable on the basis that the OMgBr grouping is in close proximity to the side chain of the oxime, and are thus dependent upon the configuration of the oxime. Ring closure, therefore, is favored in a unidirectional manner; at least it appears to take place exclusively in that sense.

During the course of this investigation, hydrolysis of 2-ethyl-3-methyl-2-phenylethyleneimine was carried out and yielded 2-amino-3-phenyl-3-pentanol. The latter was described by Campbell[7] as being a liquid, but, in our experience, the once-distilled liquid crystallized slowly on standing. The solid, after repeated recrystallization from ether, melted at 98–99°. Its hydrochloride melted at 225–226°, in agreement with the melting point of 228° recorded by Campbell.

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Syntheses of *N*-Substituted Isoindolines. I. Derivatives of Phthalimide

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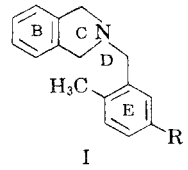
A series of four *N*-benzyl isoindolines has been prepared *via* alkylation of potassium phthalimide and reduction of the resulting *N*-benzylphthalimides with lithium aluminum hydride. Basic hydrolysis of the intermediate phthalimides has been shown to yield *N*-benzylphthalamic acids. A new infrared band characteristic of *N*-benzylphthalimides is reported.

Recent advances in the chemistry and pharmacology of reserpine and its derivatives have spurred interest in the synthesis of heterocycles bearing some of the structural features present in these natural products, in the hope that useful ataractics might result. The isoindolines discussed herein contain a basic tertiary amine bound to an aromatic system and to a benzyl group carrying a labile *meta*-substituent. This grouping may be considered to be roughly analogous to that found in the B, C, D, and E rings of reserpine, as shown in structure I.

It was necessary to develop an improved synthesis for the 2-methyl-5-nitrobenzyl chloride (II),[2] which was required for the Gabriel reaction. It was condensed with potassium phthalimide in refluxing ethanol-acetone. Reduction of the product, *N*-(2-methyl-5-nitrobenzyl)phthalimide, III, over Adams' catalyst afforded a high yield of *N*-(2-methyl-5-aminobenzyl)phthalimide, VI. Curiously, compound VI was bright yellow as obtained from the reaction mixture, but the crystals became colorless when suspended in dilute hydrochloric acid, presumably because of formation of a colorless, insoluble hydrochloride at the crystal surface. Basification regenerated the original yellow color. These observations suggested the possibility that the product was not VI, but was instead 3-(2′-methyl-5′-aminophenyl)-1,2,3,4-tetrahydroisoquinoline-1,4-dione. Gabriel[3] demonstrated conclusively that certain *N*-substituted-phthalimides may be rearranged to 3-substituted-1,2,3,4-tetrahydroisoquinoline 1,4-



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