

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

Synthesis of 2-Alkylaminoethanols from Ethanolamine

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Certain disadvantages are inherent in the methods which are available for the preparation of 2-alkylaminoethanols, $\text{RNHCH}_2\text{CH}_2\text{OH}$. The reaction of primary amines with ethylene oxide¹ and with ethylene chlorohydrin² produces a mixture of mono and dialkylaminoethanols. The reaction of ethanolamine with alkyl halides³ may lead to either secondary or tertiary amino compounds. The method described by Goldberg and W. F. Whitmore,⁴ in which an alkyl aniline is converted into a dialkylaminoethanol with ethylene oxide, and then cleaved to a monoalkylaminoethanol by nitrosation and hydrolysis, leads to pure products but involves several steps.

We have investigated the preparation of 2-alkylaminoethanols by the reduction of mixtures of ethanolamine with ketones and aldehydes.

The catalytic reduction of mixtures of ethanolamine with various ketones proved to be a remarkably successful method for the preparation of 2-alkylaminoethanols containing secondary alkyl groups. Of the aminoalcohols listed in Table I, seventeen were prepared in this manner, from ketones containing three to ten carbon atoms. The yields in many cases are nearly quantitative. The 2-alkylaminoethanols are produced in a state of exceptional purity, as indicated by constant boiling points and refractive indexes, and uniform agreement between calculated and observed molecular refractions.

Adams platinum oxide-platinum catalyst was used in preparing all of the aminoalcohols. Most of the reductions were exothermic and proceeded rapidly without heating in alcohol solution, the rates of the various reductions corresponding to the reactivity of the ketones. The reductions were much slower in acetic acid, and still slower when palladinized charcoal was used as the catalyst. Raney nickel and copper chromite proved to be suitable catalysts at elevated temperatures and pressures.

(1) Knorr and Matthes, *Ber.*, **31**, 1069 (1898); Knorr and Schmidt, *ibid.*, **31**, 1072 (1898); Matthes, *Ann.*, **315**, 104 (1901); Bain and Pollard, *THIS JOURNAL*, **61**, 2704 (1939).

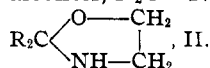
(2) Knorr, *Ber.*, **22**, 2081 (1889); cf. Adams and Segur, *THIS JOURNAL*, **45**, 785 (1923).

(3) Goldberg, U. S. Patent 2,139,818; English Patent 482,886; cf. Fränkel and Cornelius, *Ber.*, **51**, 1660 (1918).

(4) Goldberg and W. F. Whitmore, *THIS JOURNAL*, **59**, 2280 (1937).

Five 2-*primary* alkylaminoethanols were prepared in a similar manner in 60 to 90% yield by reducing mixtures of aldehydes with ethanolamine. By-products were formed from the aldehydes, but they could be removed by distillation, or by dissolving the amino-alcohols in dilute hydrochloric acid and extracting with ether or benzene.

Skita⁵ has prepared a number of amines (different in type from the aminoalcohols herein described) by the reduction of aldehydes and ketones in the presence of ammonia and amines, or by the reduction of the alkylidene amines (Schiff bases) which are the intermediates. We have isolated the products formed by the reaction of four ketones with ethanolamine and found that in three cases the compounds formed by elimination of water are not alkylidene aminoalcohols, $\text{R}_2\text{C}=\text{NCH}_2\text{CH}_2\text{OH}$, I, but oxazolidines,



By refluxing a benzene solution of cyclohexanone and ethanolamine under a constant water separator until the separation of water became very slow, an anhydro compound was formed in about 90% yield. It is very readily hydrolyzed back to ethanolamine and cyclohexanone. Catalytic reduction converts the anhydro compound into 2-cyclohexylaminoethanol. The low boiling point of the anhydro compound [89–90° (16 mm.)] compared to that of 2-cyclohexylaminoethanol [122–123.5 (13 mm.)] suggests a more fundamental change in structure on reduction than simple saturation of a double bond.⁶ The molecular refraction of the anhydro compound (39.55) is in much better agreement with the value calculated for the oxazolidine (40.00) than the calculated value for the alkylidene aminoalcohol (41.48). A similar easily hydrolyzed anhydro compound regarded as an oxazolidine was formed from methyl amyl ketone and ethanolamine; b. p. 88–90° (7 mm.), in contrast to the b. p. of 115–116° (10 mm.) observed for its reduction product, 2-(2-heptylamino)-ethanol; *M_D* found 46.86, calculated for the oxazolidine 46.82, for the alkylidene aminoalcohol 48.30.

(5) Skita and Keil, *Ber.*, **61**, 1452 (1928), and subsequent papers.

(6) Alkylidene amines derived from citral (ref. 5) boil *higher* than the corresponding saturated amines.

TABLE I: 2-ALKYLAMINOETHANOLS, RNHCH₂CH₂OH

Alkyl group	Prepared from (ketone or aldehyde)	Yield, %	Boiling point, °C. (uncorr.) mm.	n _D ²⁰	d ₄ ²⁰	Molecular refraction		Formula	Nitrogen, % Calcd. Found ^f	Picrate, m. p., °C. (uncorr.) ^{5a}	Formula	Nitrogen, % Calcd. Found ^f
						Calcd.	Found					
Isopropyl ^{1c}	Acetone	95	76-77	1.4390	0.8977	30.42	30.29	C ₈ H ₁₅ ON	11.96	11.80	C ₁₈ H ₁₉ O ₃ N ₄	16.18
s-Butyl	Methyl ethyl ketone	98	88-88.5	1.4435	.8953	35.04	34.82	C ₉ H ₁₇ ON	10.68	10.74	C ₁₉ H ₂₁ O ₃ N ₄	15.55
3-Pentyl	Methyl propyl ketone	95	98-99	1.4445	.8968	39.66	39.44	C ₁₀ H ₁₉ ON	10.68	10.67	C ₂₀ H ₂₃ O ₃ N ₄	15.55
2-Pentyl	Diethyl ketone	97	85-85.5	1.4463	.8931	39.66	39.32	C ₁₀ H ₁₉ ON	9.65	9.41	C ₁₈ H ₂₁ O ₃ N ₄	14.97
2-(4-Methylpentyl)	Methyl isobutyl ketone	98	102-102.5	1.4440	.8770	44.28	44.12	C ₁₁ H ₂₁ ON	8.79	8.64	C ₁₉ H ₂₃ O ₃ N ₄	14.43
2-Heptyl	Methyl amyl ketone	98	115-116	1.4485	.8791	48.90	48.69	C ₁₂ H ₂₃ ON	8.79	8.96	C ₂₀ H ₂₅ O ₃ N ₄	14.43
4-Heptyl	Dipropyl ketone	96	104-105	1.4479	.8788	48.90	48.65	C ₁₂ H ₂₃ ON	8.08	8.03	C ₁₉ H ₂₃ O ₃ N ₄	13.93
2-Octyl	Methyl hexyl ketone	96	130-130.5	1.4501	.8751	53.52	53.57	C ₁₃ H ₂₅ ON	7.48	7.50	C ₂₀ H ₂₅ O ₃ N ₄	13.46
2-Nonyl	Methyl heptyl ketone	92	138-139	1.4516	.8729	58.14	58.02	C ₁₄ H ₂₇ ON	7.48	7.50	C ₂₁ H ₂₇ O ₃ N ₄	13.46
5-Nonyl	Dibutyl ketone	94	130.5-131	1.4509	.8732	58.14	57.92	C ₁₄ H ₂₇ ON	6.96	7.05	C ₁₉ H ₂₃ O ₃ N ₄	13.05
2-Decyl	Diisobutyl ketone	94	113-114	1.4456	.8639	58.14	57.95	C ₁₄ H ₂₇ ON	7.48	7.50	C ₂₂ H ₂₉ O ₃ N ₄	15.02
Cyclohexyl ^d	Methyl octyl ketone	97	149-150	1.4528	.8712	62.76	62.62	C ₁₅ H ₂₉ ON	9.78	9.84	C ₂₁ H ₂₇ O ₃ N ₄	14.49
2-Methylcyclohexyl	Cyclohexanone	96	122-123.5 ^d	1.4843	.9811	42.08	41.87	C ₁₂ H ₂₃ ON	8.91	8.86	C ₁₈ H ₂₁ O ₃ N ₄	14.49
4-Methylcyclohexyl	2-Methylcyclohexanone	88	123.5-124	1.4827	.9714	46.70	46.34	C ₁₃ H ₂₅ ON	8.91	8.99	C ₁₉ H ₂₃ O ₃ N ₄	13.52
2,2,6-Trimethylcyclohexyl	4-Methylcyclohexanone	98	129.5-130	1.4792	.9607	46.70	46.57	C ₁₃ H ₂₅ ON	7.56	7.53	C ₁₈ H ₂₁ O ₃ N ₄	13.88
1-(1-Phenylethyl)	2,2,6-Trimethylcyclohexanone	80	134.5-136	1.4779	.9393	60.56	60.23	C ₁₄ H ₂₇ ON	8.48	8.37	C ₂₂ H ₂₉ O ₃ N ₄	16.18
Butyl ^e	l-Menthone	95	139-140	1.5326	1.0311	49.91	49.85	C ₁₀ H ₁₉ ON	10.68	10.57	C ₁₉ H ₂₃ O ₃ N ₄	15.55
Isobutyl ^f	Acetylaldehyde	68	91-92	1.4427	0.8905	35.04	34.97	C ₈ H ₁₅ ON	8.79	8.68	C ₁₈ H ₂₁ O ₃ N ₄	14.43
Amyl ^g	Isobutyraldehyde	62	89-90	1.4389	.8834	39.66	39.62	C ₉ H ₁₇ ON	8.08	7.88	C ₁₉ H ₂₃ O ₃ N ₄	13.93
Heptyl	Valeraldehyde	70	114-115	1.4446	.8884	48.90	48.77	C ₁₀ H ₁₉ ON	10.68	10.57	C ₂₀ H ₂₅ O ₃ N ₄	16.25
1-(2-Ethylhexyl)	Heptaldehyde	71	120-121 ^e	1.4488	.8782	53.52	53.22	C ₁₁ H ₂₁ ON	8.79	8.68	C ₂₁ H ₂₇ O ₃ N ₄	15.48
	2-Ethylhexanal	91	119-120	1.4519	.8808	53.52	53.22	C ₁₁ H ₂₁ ON	8.08	7.88	C ₂₂ H ₂₉ O ₃ N ₄	16.25

^a Previously prepared by Matthes (ref. 1). ^b Matthes (ref. 1) reports m. p. 98°. M. p. of the picrolonate 211-213°, in fairly good agreement with the value of 218° reported by Matthes. ^c Reported by Goldberg (ref. 4) as having b. p. 214-216°; refractive index (conditions unspecified) 1.4508; sp. gr. 0.8814; picrate m. p. 57-58°. ^d Reported by Bain and Pollard (ref. 1), whose physical constants are in good agreement with ours. Our sample solidified on standing, m. p. 40-41°. Physical constants were determined on the supercooled liquid. ^e Solidified on standing, m. p. 30-32°. Physical constants were determined on the supercooled liquid. ^f We are indebted to Mr. C. S. Miller and Mr. J. P. Lutz for semi-micro Kjeldahl analyses.

The reaction of methyl propyl ketone and ethanolamine also gave an anhydro compound with physical properties indicating an oxazolidine structure; b. p. 62-62.5° (16 mm.) compared to 98-99° (15 mm.) for its reduction product; *M_D* found 37.06, calculated for the oxazolidine 37.58, for the alkylidene aminoalcohol 39.06. The refractive index of this compound increased rapidly on standing for a few hours from an initial value of 1.4400 to a final value of 1.4502, which remained practically constant for two months. Redistillation reconverted the material into the form with the original refractive index, which again increased to 1.4502 on standing. These data are interpreted as meaning that this particular anhydro compound exists as an oxazolidine (II) in fairly mobile equilibrium with an alkylidene aminoalcohol (I). The freshly distilled material is the lower boiling oxazolidine, which reaches an equilibrium with I on standing. The conversion is apparently not complete, for the molecular refraction of the material at equilibrium is 37.81, a value too low for structure I.

The condensation of diisobutyl ketone with ethanolamine produced an anhydro compound which boiled only slightly lower than its reduction product [110-111° (8 mm.)] compared to [113-114 (7 mm.)], and had a molecular refraction (57.21) closer to the value for the alkylidene aminoalcohol (57.54) than the oxazolidine (56.06). Presumably it is largely or completely in the form of the alkylidene aminoalcohol.

It is of interest to note that the three anhydro compounds which appear to exist predominantly in the form of oxazolidines are derived from the three reactive, relatively unhindered ketones. Presumably the first step in the reaction is the formation of an addition product, R₂C(OH)NHCH₂CH₂OH. Whether the oxazolidines are formed directly from these intermediates by the elimina-

tion of water, or whether the reaction takes the course of dehydration to an alkylidene aminoalcohol followed by an intramolecular addition to give the oxazolidines, the presence of large branched alkyl groups would be expected to retard or prevent their formation.

Knorr and Matthes⁷ have prepared anhydro compounds from aldehydes and ethanolamine, and considered that their low boiling points and ease of hydrolysis proved them to be oxazolidines. Knorr and Rössler⁸ obtained anhydro compounds formulated as oxazolidines from the reaction of ethanolamine with acetyl acetone and acetoacetic ester. They did not obtain pure products from either acetone or acetophenone. Oxazolidines derived from ketones and ethanolamine are mentioned as intermediates in the patent literature,⁹ but were not isolated.

Experimental Part

Most of the ketones and all of the aldehydes listed in Table I were obtained from commercial sources and purified by distillation before use. Methyl heptyl ketone was prepared from caprylyl chloride and methyl zinc iodide; dibutyl ketone from valerionitrile and butylmagnesium bromide; methyl octyl ketone from ethyl *n*-heptylacetate; 2,2,6-trimethylcyclohexanone by reducing isophorone in the presence of palladinized charcoal.

Preparation of 2-*s*-Alkylaminoethanols.—Details of the preparation of 2-(2-octylamino)-ethanol may be cited to illustrate the method used for the 2-*s*-alkylaminoethanols listed in Table I, with one exception. Platinum oxide catalyst (0.5 g.) was placed in a one-liter bottle containing 50 cc. of absolute alcohol and reduced to platinum by shaking in an atmosphere of hydrogen. Ethanolamine (61 g., 1 mole) was dissolved in 100 cc. of absolute alcohol and methyl hexyl ketone (166 g., 1.3 mole) was added. The mixture became warm from the heat of reaction. The solution was rinsed into the bottle containing the platinum catalyst with 50 cc. of alcohol and reduced by shaking with hydrogen at one to two atmospheres pressure for seven hours. The reduction was rapid and exothermic. The catalyst was removed by filtration and the bottle and catalyst rinsed with 75 cc. of benzene. The benzene and alcohol were removed from the filtrate by distillation at atmospheric pressure, and the residue was distilled in vacuum through a Widmer column. The excess ketone was recovered as a fore-run. There was practically no distillation residue.

Mixtures of ethanolamine with all of the methyl ketones except acetophenone reduced rapidly, preparations of one-half to one mole requiring three to ten hours for completion. The cyclic ketones, except *l*-menthone, gave equally rapid reductions. The reduction was slightly slower in the case of diethyl ketone, but went to completion without heating. The mixtures of ethanolamine and acetophe-

none, dipropyl ketone, dibutyl ketone and *l*-menthone were heated to 50 to 60°, and complete reduction of one-half mole quantities required 20 to 30 hours. No reduction occurred with diisobutyl ketone under these conditions. An excess of ketone was used in each reduction in order to eliminate the possibility that the products might be contaminated with ethanolamine. It is noteworthy that no dialkylaminoethanols were formed through further reaction of the monoalkylaminoethanols with the ketones present in excess.

The following facts concerning the reductions were established during the development of the procedure illustrated above. It is advantageous to reduce the catalyst separately before adding the mixture of ethanolamine and carbonyl compound, in order to avoid a long induction period which otherwise occurs before the catalyst reduces. Palladinized charcoal¹⁰ is a much less effective catalyst for the reduction. Thus a half-mole preparation of 2-*s*-butylaminoethanol required a total of 3 g. of palladinized charcoal added in three portions and thirty-one hours for complete reduction at 60°. A number of reductions were carried out in acetic acid (2 moles per mole of ethanolamine). With platinum catalyst under these conditions the reductions required twenty to thirty hours at 60°, while palladium gave even slower reductions. The yields were also 10 to 20% lower than those obtained by the above procedure, due to the loss of the aminoalcohols which occurred because of their solubility in water when they were liberated from their acetate salts by treatment with alkali. Raney nickel and copper chromite are satisfactory catalysts for the reductions either in alcohol solution or without a solvent. Thus the reduction of 28 g. of methyl ethyl ketone and 18 g. of ethanolamine in the presence of 3 g. of Raney nickel at 150° and 1000 to 2000 lb. hydrogen pressure gave 27.2 g. (86%) of 2-*s*-butylaminoethanol. A similar reduction in the presence of 1 g. of copper-barium chromite¹¹ at 160° gave 28.5 g. (88%) of the aminoalcohol.

Preparation of 2-*primary*-Alkylaminoethanols.—The method described in detail above was followed, except that the alcohol solution of ethanolamine was cooled in ice while the aldehyde (15% molar excess) was added slowly, in order to avoid polymerization. One attempt to prepare 2-butylaminoethanol in acetic acid solution was unsuccessful due to extensive polymerization of the aldehyde under these conditions.

The picrates described in Table I were prepared by heating to boiling alcohol solutions of the aminoalcohols with equivalent quantities of picric acid, followed by cooling. Water was added if necessary. They were recrystallized from alcohol or alcohol and water.

Condensation of Ketones with Ethanolamine. Spiro-[cyclohexane-1,2'-oxazolidine].—A mixture of 30.5 g. of ethanolamine, 63.7 g. of cyclohexanone and 100 cc. of benzene was refluxed under a constant water separator¹² for thirty minutes, while 9.4 cc. of water collected. The benzene was removed in vacuum and the residue distilled in vacuum through a Widmer column. The yield of spiro-[cyclohexane-1,2'-oxazolidine] was 66.8 g. (94%); b. p.

(10) Hartung, *THIS JOURNAL*, **50**, 3372 (1928).

(11) Connor, Folkers and Adkins, *ibid.*, **54**, 1140 (1932).

(12) Cope, Hofmann, Wyckoff and Hardenbergh, *ibid.*, **63**, 3452 (1941).

(7) Knorr and Matthes, *Ber.*, **34**, 3484 (1901).

(8) Knorr and Rössler, *ibid.*, **36**, 1282 (1903).

(9) French Patent 730,760; English Patent 388,874.

89–90° (16 mm.); n_D^{25} 1.4803; d_{25}^{25} 1.0178; M_D calcd. 40.00, found 39.55.¹³

Anal. Calcd. for $C_8H_{15}ON$: N, 9.92. Found: N, 9.81.

Reduction of 28.2 g. of the oxazolidine in 40 cc. of alcohol with the platinum from 0.3 g. of platinum oxide gave 26.3 g. (92%) of 2-cyclohexylaminoethanol.

2-Methyl-2-amyloxazolidine.—Ethanamine (30.5 g.), methyl amyl ketone (74 g.) and 100 cc. of benzene were refluxed under a water separator. After thirty-five minutes 9.2 cc. of water had collected. Distillation gave 50 g. (64%) of the oxazolidine; b. p. 88–90° (7 mm.); n_D^{25} 1.4501; d_{25}^{25} 0.9047; M_D calcd. 46.82, found 46.86.

Anal. Calcd. for $C_9H_{19}ON$: N, 8.92. Found: N, 9.16.

2-Methyl-2-propyloxazolidine.—Ethanamine (30.5 g.), methyl propyl ketone (56 g.) and 100 cc. of benzene were refluxed under a water separator for one hour, when 9.0 cc. of water had collected. Distillation gave 49.5 g. (85%) of the oxazolidine; b. p. 62–62.5° (16 mm.); n_D^{25} 1.4400; d_{25}^{25} 0.9215; M_D calcd. 37.58, found 37.06.

Anal. Calcd. for $C_7H_{15}ON$: N, 10.84. Found: N, 11.01.

The refractive index of this oxazolidine increased noticeably on the refractometer. After one day its refractive index was 1.4502, after two months, 1.4510. The density remained constant; d_{25}^{25} 0.9216. Redistillation converted the sample without appreciable loss into material with n_D^{25} of 1.4400, which again increased to 1.4502 after standing for one day.

In a quantitative reduction with platinum catalyst 2.50 g. of this oxazolidine took up 99.3% of one molecular equivalent of hydrogen. Distillation gave 2.0 g. of 2-(2-pentylamino)-ethanol, identified by its physical properties and the melting point of its picrate.

2-[4-(2,6-Dimethylheptylidene)-amino]-ethanol.—A mixture of 30.6 g. of ethanamine, 92 g. of diisobutyl ketone and 150 cc. of benzene was refluxed under a constant water separator for thirteen hours, during which time 12.4 cc. of water collected. The mixture was not homogeneous at the beginning of the reaction, but was at the end. The water which collected in the separator contained some ethanamine. After the benzene had been removed in vacuum, the residue was distilled through a Widmer

(13) The following atomic refractions were used in obtaining calculated molecular refractions: nitrogen in the oxazolidines, 2.50 as in secondary amines; Eisenlohr, *Z. phys. Chem.*, **79**, 134 (1912). Double bond-nitrogen in the Schiff bases, 4.10 as in alkyldene amines; von Auwers, *ibid.*, **147**, 436 (1930). Other values (C, 2.42; H, 1.10; O, 1.64) are the usual Eisenlohr values; *ibid.*, **75**, 605 (1910). "Optical depression" is frequently observed in (unsaturated) heterocyclic compounds [see Brühl, *ibid.*, **79**, 38 (1912); von Auwers, *Ber.*, **57**, 461 (1924)]. Consequently it is probable that the low molecular refractions observed for spiro[cyclohexane-1,2'-oxazolidine] (deviation -0.45) and 2-methyl-2-propyl-oxazolidine (-0.52) are characteristic of the oxazolidine ring system, while the agreement of calculated and found values for 2-methyl-2-amyloxazolidine (deviation +0.04) is fortuitous and may indicate the presence of some of the corresponding Schiff base.

column. The yield of the alkyldene aminoalcohol was 52 g. (56%); b. p. 110–111° (8 mm.); n_D^{25} 1.4568; d_{25}^{25} 0.8844; M_D calcd. 57.54, found 57.21.

Anal. Calcd. for $C_{11}H_{23}ON$: N, 7.56. Found: N, 7.66.

Reduction of 29.6 g. of the above anhydro compound with platinum catalyst in alcohol solution gave 28 g. (94%) of 2-[4-(2,6-dimethylheptyl)-amino]-ethanol (Table I).

All of the above anhydro compounds were very readily hydrolyzed. Samples which were freshly distilled or stored in sealed containers had a distinct amine-like odor, but after exposure to moist air for a few minutes the odor of the ketones appeared.

Methyl hexyl ketone and acetophenone were also condensed with ethanamine in benzene solution. A molecular equivalent of water was formed in both cases, but the condensation products did not have constant boiling points and appeared to polymerize slightly on distillation in vacuum.

In order to determine whether condensation products could be prepared from ketones and 2-alkylaminoethanols, 32.8 g. of 2-(2-pentylamino)-ethanol, 28 g. of methyl propyl ketone, 1.5 g. of acetic acid and 50 cc. of benzene were refluxed under a constant water separator for 48 hours. Although 1.4 cc. of water collected, on distillation 29 g. (88%) of the aminoalcohol was recovered.

Summary

The reduction of mixtures of ethanamine with ketones and with aldehydes provides a convenient synthesis for 2-alkylaminoethanols. Nearly quantitative yields of 2-*s*-alkylaminoethanols are obtained from ketones and ethanamine.

The substances which are presumably intermediates in this synthesis were isolated in four cases by condensing four ketones with ethanamine. The condensation products obtained from cyclohexanone and methyl amyl ketone had physical properties which indicated that they were not alkyldene aminoalcohols (I) but oxazolidines (II). The product obtained from methyl propyl ketone and ethanamine had the properties of an oxazolidine when distilled, but rapidly changed in refractive index on standing, probably because of ring-chain tautomerism and the establishment of an equilibrium between I and II. The condensation product obtained from diisobutyl ketone and ethanamine had physical properties indicating that it was largely in the alkyldene aminoalcohol form.

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