

[CONTRIBUTION FROM THE U. S. NAVAL RESEARCH LABORATORY]

## Alkylation of Amines with Alcohols Catalyzed by Raney Nickel. II. Aliphatic Amines

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Heating Raney nickel in ethanol with butylamine and dibutylamine gave 54 and 42% yields, respectively, of *N*-ethyl-dibutylamine. Butylamine, 1-propanol and Raney nickel gave a 57% yield of *N*-propylbutylamine. The reaction of 1,6-diaminohexane with 1,4-butanediol in the presence of Raney nickel afforded a 15% yield of *N*-(4-hydroxybutyl)hexahydroazepine (I) plus an unidentified viscous oil. The structure of I was established by an independent synthesis.

In a previous publication<sup>2</sup> we have reported the *N*-alkylation of aniline and benzidine with various aliphatic alcohols catalyzed by Raney nickel. Subsequently other investigators<sup>3-5</sup> described similar alkylations. The present communication is concerned with some reactions of butylamine with ethanol and 1-propanol, and a novel reaction of 1,6-diaminohexane with 1,4-butanediol, all in the presence of Raney nickel.

*Alkylation products from butylamine.* When a mixture of butylamine and Raney nickel in a large excess of ethanol was heated under reflux for 16 hr., a 54% yield of *N*-ethyl-dibutylamine was obtained. Substitution of dibutylamine for butylamine gave a 42% yield of *N*-ethyl-dibutylamine. A similar reaction mixture of butylamine, Raney nickel, and 1-propanol afforded a 57% yield of *N*-propylbutylamine.

The *N*-ethyl-dibutylamine was identified by an independent synthesis from dibutylamine and ethyl bromide. Picrates prepared from this tertiary amine obtained by the three different reaction paths were found to melt identically, both alone and in admixture.

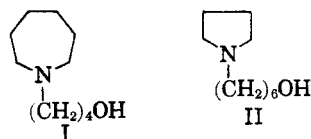
The above results contrast somewhat with those of Kao, Tilak, and Venkataraman,<sup>3</sup> who obtained unspecified yields of both *N*-ethylbutylamine and dibutylamine, along with a trace of *N,N*-diethylbutylamine, by heating under reflux for 3.5 hr. a mixture of butylamine, Raney nickel and excess ethanol. When the reaction was carried out at 30° for 20 hr., only *N*-ethylbutylamine and dibutylamine (unspecified yields) were obtained. *N*-Ethyl-dibutylamine was not reported as a product of either reaction mixture.

It appears, therefore, that the *N*-alkylation reaction, which apparently is specific when carried out with primary arylamines to yield only *N*-alkyl-

arylamines, is not selective when applied to aliphatic amines.

*Reaction of 1,6-diaminohexane with 1,4-butanediol.* When an equimolar mixture of 1,6-diaminohexane with 1,4-butanediol in toluene was heated under reflux in the presence of Raney nickel, a considerable amount of ammonia was evolved. Although two liquid products were isolated from the reaction mixture, only the lower boiling product was identified. Attempts to distil the residual viscous oil resulted in decomposition. These properties suggest that the oil may be the expected polyamine.

The volatile component was indicated to be either *N*-(4-hydroxybutyl)hexahydroazepine (I) or the isomeric *N*-(6-hydroxyhexyl)pyrrolidine (II) on



the basis of results of elemental analyses, molecular weight determination, and standard qualitative tests. The formation of II is considered to be improbable since its mode of formation necessitates the replacement of an amine by an hydroxyl group. This replacement is not required in the formation of I.

The final decision in favor of the more logical structure I was made on the basis of an independent synthesis. The procedure of Moffett,<sup>6</sup> by which had been prepared *N*-(1,1-dimethyl-2-hydroxyethyl)pyrrolidine from the condensation of 1,4-dibromobutane with 2-amino-2-methylpropanol-1, was followed resulting in a 3% yield of I by the reaction of 1,6-dibromohexane with 4-aminobutanol-1. The two products (I) were shown to be the same by the identities of their infrared spectra and the melting points of their methiodide derivatives. Compound II was eliminated from consideration when it was synthesized by the reaction of 1,4-dibromobutane with 6-aminohexanol-1 and shown to have properties different from those of I obtained by the diamine-diol reaction.

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(2) R. G. Rice and E. J. Kohn, *J. Am. Chem. Soc.*, **77**, 4052 (1955).

(3) G. N. Kao, B. D. Tilak, and K. Venkataraman, *J. Sci. Ind. Research (India)*, **14B**, 624 (1955).

(4) C. Ainsworth, *J. Am. Chem. Soc.*, **78**, 1635 (1956).

(5) J. Horyna and O. Černý, *Chem. Listy*, **50**, 381 (1956); *Collection Czech. Chem. Commun.*, **21**, 906 (1956).

(6) R. B. Moffett, *J. Org. Chem.*, **14**, 866 (1949).

A somewhat similar condensation was carried out by Kao, Tilak, and Venkataraman<sup>3</sup> by heating *o*-phenylenediamine and ethylene glycol in the presence of Raney nickel. They obtained 1,2,3,4-tetrahydroquinoxaline in 20% yield together with an unidentified liquid. The yield of I obtained in the present investigation from the reaction of 1,6-diaminohexane and 1,4-butanediol was 15%.

**Mechanisms of the reactions.** Several logical reaction paths can be devised to explain the formation of the various products obtained. These involve dehydrogenation, addition-elimination, dehydration and hydrogenation reactions of types described elsewhere.<sup>3-5,7,8</sup> The limited experimental evidence obtained, however, does not permit a choice between these several possible reaction routes.

The formation of *N*-ethyl dibutylamine from both butyl- and dibutylamines would seem to suggest that perhaps dibutylamine is an intermediate in condensations involving butylamine. At the same time, however, this view is negated by the fact that the reaction of butylamine with 1-propanol produced *N*-propylbutylamine and not *N*-propyldibutylamine.

**Discussion of infrared spectra.** The infrared spectra of the compound I prepared by the two methods described earlier, are identical in the 2-15  $\mu$  region, and are different from the spectrum of II. These spectra are presented in Figure 1. It is of interest that the infrared spectrum of 1-pentanol<sup>9</sup> is closely similar to, but not identical with, that of I. Apparently the seven membered heterocyclic ring adds no intense group absorption bands to the spectrum of the straight chain alcohol portion of I.

The spectrum of I indicates the presence of tertiary amine and hydroxyl groups which are hydrogen bonded. In solutions of carbon tetrachloride the position of the hydroxyl band in I is shifted to lower frequencies (3450  $\text{cm}^{-1}$  in the liquid state, 3150  $\text{cm}^{-1}$  in  $\text{CCl}_4$  solution), which is in a direction opposite to that usually observed with hydrogen bonded hydroxyl groups. The explanation for this shift has not yet been determined. The results of dilution studies on this band, however, appear to be normal. An eight-fold dilution of the carbon tetrachloride solution is exactly compensated by an eight fold increase in cell thickness. Thus it may be concluded that the hydrogen bonding in I is intramolecular.

The spectrum of II is similar to that of the straight chain alcohol 1-heptanol, although the similarity is not so striking as in the previous case. Hydrogen bonding again is evident. The free hydroxyl group frequency at 3620  $\text{cm}^{-1}$  appears in carbon tetrachloride solutions of II, so that the hydrogen bonding in this case must be intermolec-

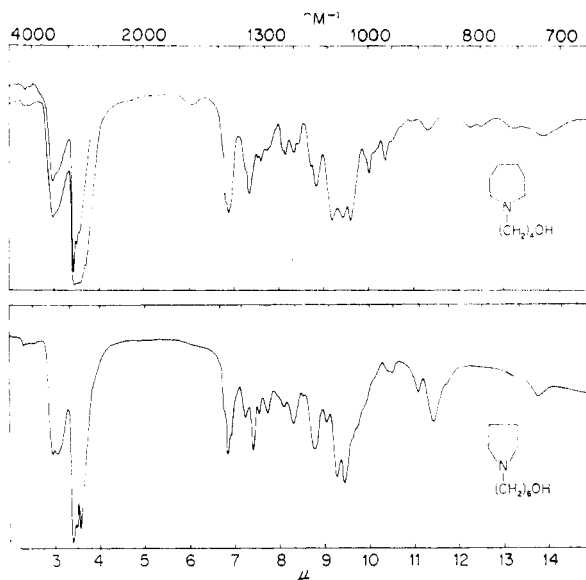


Fig. 1. Infrared spectra of I and II

ular. It is possible that the differences in modes of hydrogen bonding in the two compounds can be explained on the basis of ring size. The intramolecularly bonded I embraces a seven-membered ring, whereas nine members are required for II. The nine-membered intramolecularly bonded ring is expected to be less stable than the intermolecularly bonded form.

#### EXPERIMENTAL<sup>10</sup>

**Reagents.** All chemicals used were of reagent grade. Raney nickel was prepared by the method of Mozingo,<sup>11</sup> stored under 95% ethanol, then washed with the appropriate alcohol immediately prior to use. 4-Aminobutan-1 was obtained from Sapon Laboratories, Valley Stream, N. Y., and 1,6-dibromohexane and 1,4-dibromobutane were obtained from Columbia Organic Chemicals Co., Inc., Columbia, S. C.

**Infrared measurements.** The spectra in the range 2-15  $\mu$  were obtained with a Perkin-Elmer Model 21 Infrared Spectrophotometer equipped with sodium chloride optics.

**Alkylation products involving butylamines.** The following standard procedure was employed: A mixture of 25 ml. of redistilled amine, 75 ml. of anhydrous alcohol, and 15 g. of Raney nickel was stirred and heated at reflux for 15 hrs. The nickel was filtered off and washed with 95% ethanol. After the filtrate and washings were combined, the solvents were removed by distillation at atmospheric pressure, then the residue was distilled *in vacuo*. In this manner butylamine and ethanol gave 10.80 g. (54% yield based upon butylamine) of *N*-ethyl dibutylamine, b.p. 75-79° (30 mm.),  $n_D^{25}$  1.4199; dibutylamine and ethanol gave 9.55 g. (42% yield based upon dibutylamine) of *N*-ethyl dibutylamine, b.p. 169-170°. The picrate, recrystallized from 95% ethanol, in each case melted at 83.0-84.0°, both alone and in admixture. The methiodide, recrystallized from ethyl acetate, melted at 156.5-158.5° (uncorr.). Butylamine and 1-propanol gave 16.55 g. (57% yield) of *N*-propylbutylamine, b.p. 78-79° (30 mm.),  $n_D^{25}$  1.4278. The hydrochloride

(7) E. J. Schwoegler and H. Adkins, *J. Am. Chem. Soc.*, **61**, 3499 (1939).

(8) W. S. Emerson in *Org. Reactions*, **IV**, 174 (1948).

(9) American Petroleum Institute Collection of Infrared Spectra, No. 751.

(10) Analyses by Prof. M. Kathryn Gerdeman of the University of Maryland, College Park, Md. Melting points are corrected, except where otherwise noted; boiling points are uncorrected.

(11) R. Mozingo, *Org. Syntheses*, **21**, 15 (1941).

melted at 266–267° (dec.) [lit.<sup>12</sup> 267–268° (dec.)]; however, the melting point of the  $\alpha$ -naphthylthiourea (128.5–129.0°) failed to agree with the previously reported value<sup>12</sup> (136–137°) even after repeated recrystallization from 95% ethanol.

The molecular weight of *N*-ethyl dibutylamine was 156 as determined by titration with standard hydrochloric acid using phenolphthalein indicator. The theoretical molecular weight is 157.3.

The absence of both primary and secondary amines was shown by the Hinsberg test.<sup>13</sup>

*Independent synthesis of N-ethyl dibutylamine.* To 55 ml. (0.77 mole) of refluxing ethyl bromide was added with stirring 83 ml. (0.49 mole) of redistilled dibutylamine over a period of 2 hr. The mixture was refluxed an additional hr., cooled to room temperature and poured into 200 ml. of water. After extraction with ether the aqueous solution was made alkaline with 20% sodium hydroxide and the liberated oil extracted into ether. These extracts were dried over anhydrous magnesium sulfate, the ether removed under reduced pressure and the residue distilled. There was obtained 32.7 g. (42% yield based on dibutylamine) of crude *N*-ethyl dibutylamine, b.p. 69–71° (32 mm.),  $n_D^{25}$  1.4162. Residual secondary amine was removed by treating a portion of the crude product with benzoyl chloride, water, and sodium hydroxide under the conditions of the Schotten-Baumann reaction.<sup>13</sup> The aqueous mixture was extracted with ether, the ether solution extracted with 10% hydrochloric acid, the acid extracts made alkaline with 20% sodium hydroxide, and the resultant oil extracted into ether. Drying of the ethereal solution over anhydrous magnesium sulfate followed by removal of the solvent and distillation of the residue afforded *N*-ethyl dibutylamine, b.p. 72–76° (26 mm.),  $n_D^{25}$  1.4197.

*Reaction of 1,6-diaminohexane with 1,4-butanediol.* A mixture of 263 g. (2.26 moles) of 1,6-diaminohexane, 204 g. (2.26 moles) of 1,4-butanediol, 1000 ml. of anhydrous toluene and 50 g. of Raney nickel (washed with toluene) was stirred and refluxed 23 hr. under a condenser fitted with a Dean-Stark water trap. During this time a large amount of ammonia was evolved. Filtration of the mixture and fractionation of the filtrate yielded 109.6 g. of slightly amber

colored, crude *N*-(4-hydroxybutyl)hexahydroazepine (I), b.p. 106–143° (4.5 mm.),  $n_D^{25}$  1.4806, and 213 g. of a dark, viscous oil which decomposed during attempts at distillation under reduced pressure. Two further distillations of the crude I gave 25.75 g. (15% yield) of colorless I, b.p. 111–115° (2.8 mm.),  $n_D^{25}$  1.4831,  $d_4^{20}$  0.9487.

*Anal.* Calcd. for  $C_{10}H_{21}NO$ : C, 70.12; H, 12.36; N, 8.18. Found: C, 69.46, 69.49; H, 12.62, 12.67; N, 8.20, 8.31.

The results of the carbon and hydrogen analyses indicated that the product was still impure even after the third distillation. The methiodide melted at 147.5–148.5° when recrystallized from absolute ethanol; the benzoate boiled at 168–170° (2.8 mm.),  $n_D^{25}$  1.5132.

The molecular weight as determined by acidification of a sample of I with standard hydrochloric acid followed by titration of the excess acid with standard base using phenolphthalein indicator was 171.3; the Rast method using camphor gave a value of 161.4. The calculated molecular weight of I is 171.28.

The molar refraction determined from the density and refractive index data is 51.56 ml.; the value calculated from the data of Vogel<sup>14</sup> is 51.41 ml. In this calculation the increment due to the steric effect of the hexahydroazepine ring was assumed to be the same as that of cycloheptane.

*Independent synthesis of I.* The procedure of Moffett<sup>6</sup> was followed using 4-aminobutanol-1 and 1,6-dibromohexane, except that the nitrous acid treatment of the crude product was omitted. From 7.0 g. (0.0785 mole) of 4-aminobutanol-1 and 19.16 g. (0.0785 mole) of redistilled 1,6-dibromohexane there was obtained 0.43 g. (3.2% yield) of *N*-(4-hydroxybutyl)hexahydroazepine (I), b.p. 92.5–93.5° (0.02 mm.),  $n_D^{25}$  1.4813. The infrared spectrum in the range 2–15 $\mu$  was identical with that of the sample of I obtained from the diamine-diol reaction. The methiodide melted at 147.5–148.5°, after recrystallization from absolute ethanol.

*N*-(6-Hydroxyhexyl)pyrrolidine (II). *N*-( $\omega$ -bromohexyl)-phthalimide was prepared in 92% yield by the method of Kremer.<sup>15</sup> Hydrolysis of this compound with 20% KOH<sup>15</sup> gave a 36% yield of crude 6-aminohexanol-1. When this aminoalcohol was treated with redistilled 1,4-dibromobutane, according to the procedure of Moffett,<sup>6</sup> a 28% yield of II was obtained, b.p. 132–134° (9 mm.),  $n_D^{25}$  1.4739.

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(15) C. B. Kremer, *J. Am. Chem. Soc.*, **61**, 1322 (1939).