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Reactions of Long-chain Amines. II. Reactions with Urea¹

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When heated with urea, primary long-chain amines yield alkylureas, 1,3-dialkylureas, 1-alkylbiurets, 1,3-dialkylbiurets and 1,5-dialkylbiurets. When alcohols are present, urethans may be formed. Secondary long-chain amines form 1,1-dialkylureas.

It has been known for many years that amines will react with urea to form substituted ureas. Davis and colleagues² have pointed out that this reaction involves a "dearrangement" of urea, whereby isocyanic acid is formed and then reacts with an amine to form a monosubstituted urea. The monosubstituted urea may itself dearrange to an isocyanate; this, upon reaction with more amine, forms a disubstituted urea.

Olin³ has described the reaction of dodecylamine with urea to form dodecylurea. We have found that this type of reaction may go farther yet with primary long-chain amines, leading to alkylbiurets and dialkylbiurets. To form these compounds isocyanic acid or alkyl isocyanates react with alkylureas or dialkylureas. If the heating is carried out in the presence of an alcohol a urethan may be formed. Schweitzer⁴ has described urethan formation with mixtures of other amines, urea and alcohol. With secondary amines, the reaction with urea stops at the 1,1-dialkylurea stage.

The reaction of a primary amine with urea may lead to the formation of many compounds through a series of reversible reactions. By controlling such reaction conditions as molar ratio of reagents and temperature and time of heating, one may direct the reaction so as to favor one type or another of the products. A hot equimolar mixture of primary amine and urea evolves ammonia rapidly at first. It is during this stage that alkylureas, RNHCONH₂, are formed. On further heating, the evolution of ammonia continues, although at a reduced rate. During this period 1,5-dialkylbiurets, RNHCONHCONHR, are produced, together with 1,3-dialkylureas, RNHCONHR. If the mixture of primary amine and urea is heated for a long time at 200°, the 1,5-dialkylbiuret disappears, the amount of 1,3-dialkylurea increases and 1,3-dialkylbiuret, RNHCON(R)CONH₂, is formed.

By using an excess of urea over primary amine, one increases the amount of 1-alkylbiuret, RNHCONHCONH₂, produced. When an excess of amine is used, the 1,3-dialkylurea is increased, practically to the exclusion of all other products. In the presence of an alcohol, a urethan, RNHCOOR, may be formed but this is not necessarily the case. A mixture of octadecylamine, urea and ethylene glycol, heated at 130°, yields 1,5-dioctadecylbiuret

but no urethan. A refluxing mixture of dodecylamine, urea and butyl alcohol, however, yields butyl dodecylcarbamate, together with 1,3-didodecylurea.

One might expect 1,1-dialkylureas, R₂NCONH₂, to react further, forming 1,1-dialkylbiurets, R₂NCONHCONH₂, or similar compounds. If these reactions occur, they are insignificant in extent. Probably the dearrangement of 1,1-dialkylurea to secondary amine is much more important.

Buck, Hjort, Ide and deBeer⁵ have pointed out the remarkable constancy in melting point in the series of monoalkyl ureas. From methylurea to docosylurea, only two compounds (ethylurea, m.p. 96°, and butylurea, m.p. 92°) have melting points falling outside the range 100–115°. We have observed that the melting points of the long chain 1,3-dialkylureas, 1,3-dialkylbiurets and 1,5-dialkylbiurets (but not the 1,1-dialkylureas or 1-alkylbiurets) tend to fall in this same range. For this reason, analyses may be more useful than melting points in identifying these compounds. One of the two dioctadecylbiurets isolated melts several degrees lower than the other and was therefore assigned the 1,3-dialkylbiuret structure. The higher melting compound is believed to be the symmetric 1,5-dialkylbiuret. 1,3-Dioctadecylbiuret resembles 1,3-dioctadecylurea not only in structure but also in an annoying tendency to develop electrostatic charges.

Preliminary studies of the infrared absorption spectra of the 1,3- and 1,5-dioctadecylbiurets by Mr. Wesley E. Tolberg confirm these assignments of structure. He will publish more information on this later.

Acknowledgment.—Analyses were performed by James Kerns and Mrs. Olive W. Schmidt.

Experimental⁶

Dodecylurea.—A mixture of dodecylamine (18.5 g., 0.10 mole), urea (6.6 g., 0.11 mole) and pyridine (200 ml.) was refluxed for 4.5 hours. The product crystallized upon cooling; it was filtered off and washed with water; wt. 11.1 g. (49%), m.p. 97–100.5°. Recrystallization from chloroform raised the m.p. to 106.8–107.5°. The literature⁵ gives 107°.

Octadecylurea.—A mixture of octadecylamine (269 g., 1.0 mole) and urea (120 g., 2.0 moles) was stirred and heated at 160° for 3 hours. The cooled reaction product was crushed and heated with water to extract unreacted urea. Recrystallization from chloroform yielded 168.0 g., m.p. 100–104°; m.p., after further recrystallization from chloroform, 107.8–109°. The literature gives 111⁹⁷ and 111.5⁹⁸.

Anal. Calcd. for C₁₉H₄₀N₂O: C, 73.1; H, 12.90; N, 8.97. Found: C, 73.52; H, 12.25; N, 8.63.

Hexadecylurea and 1,3-Dihexadecylurea.—A mixture of hexadecylamine (50.2 g., 0.20 mole) and urea (24.0 g., 0.40

(1) Paper No. 163, Journal Series, Research Laboratories, General Mills, Inc.

(2) T. L. Davis and H. W. Underwood, *THIS JOURNAL*, **44**, 2595 (1922); T. L. Davis and K. C. Blanchard, *ibid.*, **45**, 1816 (1923); **51**, 1790, 1801 (1929); T. L. Davis, *Proc. Natl. Acad. Sci.*, **11**, 68 (1925); T. L. Davis and A. J. J. Abrams, *Proc. Am. Acad. Arts Sci.*, **61**, 437 (1926); T. L. Davis and S. B. Luce, *THIS JOURNAL*, **49**, 2303 (1927).

(3) J. F. Olin, U. S. Patent 2,257,717 (September 30, 1941).

(4) C. E. Schweitzer, U. S. Patent 2,409,712 (Oct. 22, 1946).

(5) J. S. Buck, A. M. Hjort, W. S. Ide and E. J. deBeer, *THIS JOURNAL*, **60**, 461 (1938).

(6) M.p.'s are corrected.

(7) N. K. Adam, *Proc. Roy. Soc. (London)*, **A101**, 452 (1922).

mole) was stirred and heated at 175–210° for one hour. It was poured into water, filtered and dried; wt. 66.8 g. A portion of this crude product was extracted with hot acetone. Recrystallization of the acetone-soluble portion from chloroform showed the crude product to be 36% hexadecylurea, m.p. 105.7–107.0°. The literature gives 106–107°⁸ and 108.5°.⁵

Anal. Calcd. for C₁₇H₃₆N₂O: C, 71.75; H, 12.75; N, 9.85. Found: C, 72.17; H, 12.36; N, 10.30.

Recrystallization of another portion of crude reaction mixture from chloroform showed it to be 42% 1,3-dihexadecylurea, m.p. 110.7–112.2°.

Anal. Calcd. for C₂₃H₄₆N₂O: C, 77.90; H, 13.47; N, 5.31. Found: C, 78.40; H, 13.25; N, 5.93.

1,3-Dioctadecylurea.—A mixture of octadecylamine (59.2 g., 0.22 mole) and urea (6.0 g., 0.10 mole) was stirred and heated for 3 hours at 160–165°. It became homogeneous within an hour and noticeable evolution of ammonia had ceased after 2 hours. The product was recrystallized several times from chloroform to yield 1,3-dioctadecylurea as white flakes, m.p. 113.8–114.7°, having an annoying tendency to develop electrostatic charges. The literature⁹ gives the m.p. 112.0–112.5°. The yield of once-recrystallized product was 67%.

Anal. Calcd. for C₂₇H₅₄N₂O: C, 78.65; H, 13.56; N, 4.96. Found: C, 79.00; H, 12.61; N, 5.21.

1,3-Didodecylurea and Butyl Dodecylcarbamate.—A mixture of dodecylamine (37.0 g., 0.20 mole), urea (24.0 g., 0.40 mole) and *n*-butyl alcohol (44.4 g., 0.60 mole) was refluxed for 31.5 hours, the temperature rising to 154°. Recrystallization from acetone gave 29.2 g. (74%) of 1,3-didodecylurea, m.p. 100.3–102.5°; m.p., after further recrystallization, 103.3–105.5°.

Anal. Calcd. for C₂₅H₅₂N₂O: C, 75.69; H, 13.21; N, 7.06; mol. wt., 397. Found: C, 75.91; H, 13.00; N, 7.32; mol. wt. (benzene b.p.), 412.

The acetone filtrate contained butyl dodecylcarbamate, m.p. 35.2–36.2°. In a subsequent experiment, where equimolar amounts of amine, urea and alcohol were heated at 200°, this compound was obtained in 84% yield.

Anal. Calcd. for C₁₇H₃₅NO₂: C, 71.52; H, 12.36; N, 4.91; mol. wt., 285. Found: C, 71.67; H, 12.30; N, 5.37; mol. wt. (benzene b.p.), 292.

(8) S. P. Massie, *Iowa State Coll. J. Sci.*, **21**, 41 (1946).

(9) W. I. Harber, *ibid.*, **15**, 13 (1940).

1,1-Dioctadecylurea.—A mixture of dioctadecylamine (52.1 g., 0.10 mole) and urea (12.0 g., 0.20 mole) was stirred and heated at 160–165° for 5 hours. The molten, two-phase mixture was poured onto ice, filtered, washed with water, and dried; wt. 58.2 g., m.p. 57–64.5°. The literature⁹ gives the m.p. 65.0–65.5°. Attempts to shorten the m.p. range by recrystallization from various solvents were not successful. Nevertheless, according to analysis, it was relatively pure.

Anal. Calcd. for C₃₇H₇₆N₂O: C, 78.65; H, 13.56; N, 4.96. Found: C, 78.50; H, 13.97; N, 5.38.

1-Dodecylbiuret.—A mixture of dodecylamine (37.0 g., 0.20 mole) and urea (24.0 g., 0.40 mole) was stirred and heated at 170–175° for 4 hours; wt. of crude product 54.5 g. Recrystallization from chloroform showed that this consisted largely of dodecylurea. By recrystallization from ethyl acetate, 1.6 g. of crude 1-dodecylbiuret, m.p. 111.5–120°, was isolated. Further recrystallization from Skelly B-chloroform raised the m.p. to 129–130.5°.

Anal. Calcd. for C₁₄H₂₆N₃O₂: C, 61.96; H, 10.77; N, 15.49. Found: C, 61.82; H, 10.79; N, 15.24.

1,3-Dioctadecylbiuret.—A mixture of octadecylamine (53.8 g., 0.20 mole) and urea (12.0 g., 0.20 mole) was heated at 150–160° for 4 hours. Then, over a period of 2 hours, the temperature was raised to 195–200°. The mixture was heated at 195–200° for 6 hours; at the end of this time the evolution of ammonia had ceased. The weight of crude product was 59.2 g., consisting mostly of 1,3-dioctadecylurea. However, recrystallization from chloroform yielded 16.1 g. of crude 1,3-dioctadecylbiuret, m.p. 90–94°. Further recrystallization from Skelly B and pyridine-acetonitrile raised the m.p. to 96.5–98.5°. The material shows a strong tendency to develop electrostatic charges.

Anal. Calcd. for C₂₈H₅₇N₃O₂: C, 75.06; H, 12.77; N, 6.91. Found: C, 75.07; H, 12.29; N, 6.80.

1,5-Dioctadecylbiuret.—A mixture of octadecylamine (53.8 g., 0.20 mole), urea (12.0 g., 0.20 mole) and ethylene glycol (6.5 g., 0.105 mole) was stirred and heated at 120–130° for 6 hours. It was homogeneous after the first 2 hours. Recrystallization from chloroform-acetone gave 47.3 g. of crude product, m.p. 98–101°. Further recrystallization from chloroform raised the m.p. to 104.5–105.5°.

Anal. Calcd. for C₃₈H₇₇N₃O₂: C, 75.06; H, 12.77; N, 6.91. Found: C, 75.05; H, 12.61; N, 7.35.

This compound was also obtained in good yield by heating octadecylamine and urea for 3 hours at 162–172°.

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[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

The Conversion of Formamides into Formamidines¹

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N,N'-Diarylformamidines have been prepared by the interaction of substituted formamides with anilines in the presence of phosphorus pentachloride, in chloroform medium. The homodisubstituted amidines were obtained in yields up to 70%. Heterosubstituted amidines could be prepared by two different routes but usually were contaminated with the corresponding homodisubstituted compounds. Ethoxy-, carbethoxy-, amino- and nitro derivatives of diphenylformamide were prepared. The nitroamidines could be reduced to the corresponding amino compounds. Trisubstituted formamidines were synthesized by different routes and alkyl-aryl amidines were obtained. Neither dialkyl nor alkyl-aryl disubstituted formamidines could be prepared.

The structural relationship of formamidines to the imidazole ring, which forms a portion of the histamine molecule, suggested that these compounds might possess antihistaminic or other biological activity. The synthesis of a number of substituted derivatives of these compounds was therefore investigated.

(1) From the dissertation presented by H. George Mandel in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Yale University, 1949.

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The application of the phosphorus halide method for the synthesis of amidines from amines and amidines has been previously reported by Hill and Rabinowitz.³ In their study of homologs of phenacaine, $\text{CH}_3\text{C} \begin{matrix} \diagup \text{NC}_6\text{H}_4\text{OC}_2\text{H}_5 \\ \diagdown \text{NHC}_6\text{H}_4\text{OC}_2\text{H}_5 \end{matrix}$, these investigators prepared several amidines in which the methyl group had been replaced with other alkyl radicals. The method was extended by Hill and Cox⁴ to hetero-

(3) A. J. Hill and I. Rabinowitz, *THIS JOURNAL*, **48**, 732 (1926).

(4) A. J. Hill and M. V. Cox, *ibid.*, **48**, 3214 (1926).