

stirring<sup>9</sup> an ethereal solution of 0.20 mole of the acid chloride and the mixture refluxed for one-half hour. The reaction mixture was cooled and acidified with dilute sulfuric acid. The ether phase, with which an ether extract of the aqueous phase was combined, was washed with water and the solvent distilled.

To the crude diethyl acylmalonate was added a solution of 60 ml. of glacial acetic acid, 7.5 ml. of concentrated sulfuric acid and 40 ml. of water, and the mixture refluxed for four or five hours until the decarboxylation was complete. The reaction mixture was chilled in an ice-bath, made alkaline with 20% sodium hydroxide solution, and extracted with several portions of ether. The combined ethereal extracts were washed with water, dried with sodium sulfate followed by Drierite, and the solvent distilled. The residue containing the ketone was distilled *in vacuo* or recrystallized. The results are summarized in Table I.

(9) In certain cases a viscous mixture was formed and unless it was stirred vigorously, lower yields were obtained.

DEPARTMENT OF CHEMISTRY  
DUKE UNIVERSITY  
DURHAM, NORTH CAROLINA RECEIVED MARCH 11, 1946

### Cyclic Thioureas

By F. B. ZIENTY

A number of monoformyl-diamines were prepared and cyclized to the cyclic thioureas by reaction with sulfur.<sup>1</sup> The by-products obtained in the preparation of two *N,N'*-dialkyl-alkylene-diamines were identified.

#### Experimental<sup>2</sup>

***N,N'*-Dibutyl-ethylenediamine (I).**—In the preparation of this product, b. p. 110–111° (8 mm.),<sup>3</sup> yield, 64%, from five moles of butylamine and one mole of ethylene dichloride,<sup>4</sup> the high-boiling by-product obtained was identified as *N,N',N''*-tributyl-diethylenetriamine (II),<sup>5</sup> b. p. 163–165° (8 mm.). Upon titration in acetone solution with aqueous hydrochloric acid using brom phenol blue indicator, only two nitrogens of (II) were titrated.

(I) forms an insoluble monohydrate, m. p. 48–49°, recrystallized from hexane.<sup>6</sup>

***N,N'*-Dibutyl-trimethylenediamine (III).**—Prepared by the method under (I), this product boiled at 120–121° (14 mm.); yield, 72%. The linear amine, *N,N',N''*-tributyl-*di*-(trimethylene)-triamine, b. p. 164–165° (3 mm.), obtained as a by-product, behaves as a triatomic base on titration in acetone solution with aqueous hydrochloric acid, using brom phenol blue indicator.

(III) hydrate melts at 44–45°, after pressing on absorbent paper.

**Formylation of Ethylenediamine (IV).**—Condensation of (IV) with 85% formic acid at reflux did not produce appreciable amounts of formyl derivatives. A 30% yield of crude *N*-formyl-(IV),<sup>7</sup> b. range 90–110° (14 mm.), was obtained by the ester acylation method.<sup>8</sup>

(1) Zienty and Thielke, *THIS JOURNAL*, **67**, 1040 (1945).

(2) All melting points are corrected.

(3) Sebrell and Clifford, U. S. Patent 1,948,317 (February 20, 1934); *Chem. Zentr.*, **105**, II, 1695 (1934), reported the b. p. to be 185–187° (3 mm.), which obviously is in error.

(4) Kyrides, U. S. Patent 2,126,560 (August 9, 1938); *Chem. Zentr.*, **110**, I, 1107 (1939).

(5) Sebrell and Clifford, ref. 3, reported the formation of *N,N'*-dibutylpiperazine as the by-product when two moles of butylamine reacted with one mole of ethylene dichloride.

(6) Sebrell and Clifford, ref. 3, reported 40°.

(7) This material, heated with sulfur at 130–135°, gave ethylenethiourea, m. p. 195–196°. Ruiz and Libenson, *C. A.*, **24**, 5726 (1930), reported m. p. 195° (uncor.).

(8) Hill and Aspinall, *THIS JOURNAL*, **61**, 822 (1939).

TABLE I

Derivative	Formula	Nitrogen, % Calcd. Found	
<i>N,N'</i> -Dibutyl-ethylenediamine (I)	C <sub>10</sub> H <sub>24</sub> N <sub>2</sub>	16.3	16.1
Hydrate of I	C <sub>10</sub> H <sub>26</sub> N <sub>2</sub> O	14.7	14.5
<i>N,N',N''</i> -Tributyl-diethylenetriamine (II)	C <sub>16</sub> H <sub>37</sub> N <sub>3</sub>	15.5	15.3
<i>N</i> -Formyl-(I)	C <sub>11</sub> H <sub>24</sub> N <sub>2</sub> O	14.0	13.7
<i>N,N'</i> -Diformyl-(I)	C <sub>12</sub> H <sub>24</sub> N <sub>2</sub> O <sub>2</sub>	12.3	12.6
(I)-Dithiocarbamate <sup>a</sup>	C <sub>11</sub> H <sub>24</sub> N <sub>2</sub> S <sub>2</sub>	11.3	11.2
1,3-Dibutyl-ethylenethiourea (VI)	C <sub>11</sub> H <sub>22</sub> N <sub>2</sub> S	13.1	13.1 <sup>b</sup>
<i>N,N'</i> -Dibutyl-trimethylenediamine (III)	C <sub>11</sub> H <sub>26</sub> N <sub>2</sub>	15.0	14.9
Hydrate of III	C <sub>11</sub> H <sub>28</sub> N <sub>2</sub> O	13.7	13.7
<i>N,N',N''</i> -Tributyl-di-(trimethylene)-triamine	C <sub>18</sub> H <sub>41</sub> N <sub>3</sub>	14.0	13.9
<i>N</i> -Formyl-(III)	C <sub>12</sub> H <sub>26</sub> N <sub>2</sub> O	13.1	13.1
<i>N,N'</i> -Diformyl-(III)	C <sub>13</sub> H <sub>26</sub> N <sub>2</sub> O <sub>2</sub>	11.6	11.9
1,3-Dibutyl-trimethylenethiourea (VII)	C <sub>12</sub> H <sub>24</sub> N <sub>2</sub> S	12.3	12.3
<i>N</i> -Formyl-(V)	C <sub>15</sub> H <sub>16</sub> N <sub>2</sub> O	11.7	11.9
<i>N,N'</i> -Diformyl-(V)	C <sub>16</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub>	10.4	10.2
1,3-Diphenyl-ethylenethiourea <sup>c</sup>	C <sub>15</sub> H <sub>14</sub> N <sub>2</sub> S	11.0	10.9

<sup>a</sup> M. p. 135–136° with effervescence. Sebrell and Clifford, ref. 3, reported 134–136°. <sup>b</sup> Calcd.: S, 15.0. Found: S, 14.8. <sup>c</sup> Recrystallized from methanol, m. p. 189–190°.

**Formylation of *N,N'*-Dibutyl-ethylenediamine (I).**—Technical 85% formic acid (108 g. or 2 moles) and 86 g. (0.5 mole) of (I) reacted by the procedure described.<sup>1</sup> The mixture was quenched with water, alkalized strongly, and the water-insoluble product was separated with the aid of benzene and distilled. *N*-Formyl-(I), 47 g., was obtained at 153–165° (7 mm.); on redistillation, the fraction boiling at 134–135° (4 mm.) was collected. *N,N'*-Diformyl-(I), 40 g., was recovered at 197–199° (7 mm.).

**Formylation of *N,N'*-Dibutyl-trimethylenediamine (III).**—From the reaction of 108 g. of 85% formic acid and 93 g. (0.5 mole) of (III), *N*-formyl-(III) was collected at 146–155° (4 mm.), and on redistillation yielded 41.6 g. (39%) of product at 148–149° (4 mm.). *N,N'*-Diformyl-(III), 41.3 g. (34%), was obtained at 200–201° (4 mm.).

**Formylation of *N,N'*-Diphenyl-ethylenediamine<sup>9</sup> (V).**—The reaction mixture from 108 g. of 85% formic acid and 106 g. (0.5 mole) of (V) was poured into 500 cc. of water, precipitating a thick oil which hardened to a semi-solid mass on standing. The supernatant liquid was decanted, the semi-solid was air-dried for 24 hours and then treated with 150 cc. of methanol at 25°. The crystals were filtered from the methanol mother liquor, washed with 50 cc. of methanol and air-dried; yield, 54 g. (45%) of *N,N'*-diformyl-(V), which, after crystallization from methanol, melted at 121–122°.

The aqueous supernatant liquid obtained above was filtered, alkalized with 80 g. of 50% sodium hydroxide solution, and cooled to 25°. The solid *N*-formyl-(V) precipitated was filtered off, washed with water and air-dried; yield, 19 g. (14%); m. p. 65–66°, recrystallized from methanol. The monoformyl derivative is somewhat soluble in hot water and in aqueous acids.<sup>10</sup>

**1,3-Dibutyl-ethylenethiourea (VI).**—(1) A mixture of 20 g. (0.1 mole) of *N*-formyl-(I) and 4.0 g. of sulfur heated

(9) Prepared by the method of Bennett, *J. Chem. Soc.*, **115**, 577 (1919).

(10) These properties are similar to those of *N*-acetyl-*N,N'*-diphenyl-ethylenediamine described by Bischoff and Nastvogel, *Ber.*, **22**, 1784 (1889).

at 135–140° for two hours produced 17.3 g. (80.8%) of (VI), a yellow liquid, at 183–185° (8 mm.).

(2) Twenty-nine grams of *N,N'*-dibutyl-ethylenediamine dithiocarbamate heated at 130–135° for about two hours gave 21.5 g. (85%) of (VI) at 183–184° (8 mm.).

**1,3-Dibutyl-trimethylenethiourea (VII).**<sup>11</sup>—(1) Starting with 21.4 g. (0.1 mole) of *N*-formyl-(III) and 4.0 g. of sulfur and heating at 145–150° for two hours and at 175° for one-half hour, 9.2 g. of unconverted *N*-formyl-(III) was recovered, and 5.8 g. (25%) of (VII) was obtained as a yellow liquid, b. p. 177–178° (3 mm.).

(2) A stirred solution of 37.2 g. (0.2 mole) of (III) in 50 cc. of methanol was treated with a solution of 15.2 g. (0.2 mole) of carbon disulfide in 40 cc. of methanol in the course of fifteen minutes. The solvent was evaporated from the resulting solution and the remaining thick liquid, the dithi-

(11) *N*-Monosubstituted-trimethylenethioureas have been made by pyrolysis of the dithiocarbamates of the corresponding *N*-substituted-trimethylenediamines; Goldenring, *Ber.*, **23**, 1171 (1890); Fränkel, *ibid.*, **30**, 2501 (1897).

ocarbamate, was heated at 150–155° until the evolution of gas ceased (about two hours). The reaction mixture then was distilled, yielding 12.4 g. of recovered (III), b. p. 107° (7 mm.), and 14.6 g. (31%) of (VII), b. p. 177–178° (3 mm.).

**1,3-Diphenyl-ethylenethiourea.**—This product was prepared in 71% yield by heating *N*-formyl-(V) with sulfur, but in this case little reaction was observed below 195°. (V) did not form a dithiocarbamate on treatment with carbon disulfide and water under reflux at atmospheric pressure for twenty hours.

**Acknowledgments.**—The author is indebted to Mrs. J. D. Nevins and Mrs. R. C. Schropp of the Monsanto Analytical Laboratory for the analyses reported.

RESEARCH LABORATORIES  
MONSANTO CHEMICAL CO.  
ST. LOUIS 4, MISSOURI

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## COMMUNICATIONS TO THE EDITOR

### CRYSTALLINE VITAMIN A METHYL ETHER

Sir:

In recent years much interest has been shown in the synthesis of vitamin A ethers. However, since no data are available concerning the biological activity of these ethers, we have undertaken the preparation of vitamin A methyl ether from the natural vitamin.

The methyl ether was prepared by the action of dimethyl sulfate on the lithium derivative of the vitamin, which was formed by the reaction of *n*-butyl lithium<sup>1</sup> and crystalline vitamin A alcohol.<sup>2</sup> It was purified by chromatography on activated alumina<sup>3</sup> and was obtained as an orange oil, which crystallized from methanol after several months at –70°, m. p. 31–33°. After three recrystallizations from methanol and two from a 65–70° hydrocarbon fraction [Purified Skelly Solve B],<sup>4</sup> vitamin A methyl ether was obtained as light yellow crystals melting at 33–34°. *Anal.* Calcd. for C<sub>21</sub>H<sub>32</sub>O: C, 83.95; H, 10.74; OCH<sub>3</sub>, 10.34. Found: C, 83.76; H, 11.07; OCH<sub>3</sub>, 9.94.

The spectrophotometric curve for crystalline vitamin A methyl ether is identical in all respects with that of vitamin A alcohol, both having absorption maxima at 326 m $\mu$  on the Beckman spectrophotometer. The extinction coefficient ( $E_{1\text{cm.}}^{1\%}$ ) in isopropanol at 326 m $\mu$  is 1660. This corresponds to an equivalent extinction coefficient of 1742 for vitamin A alcohol.

Vitamin A methyl ether possesses a biological potency greater than 3,000,000 U. S. P. XII units

(1) Gilman, Langham and Moore, *THIS JOURNAL*, **62**, 2327 (1940).

(2) Distillation Products, Inc., Rochester, N. Y.

(3) Aluminum Ore Co., East St. Louis, Illinois.

(4) Purified by treatment with concentrated sulfuric acid and distillation.

per gram and is of the same order of activity as crystalline vitamin A alcohol.

The experimental details and complete biological data will appear in a forthcoming paper.

THE UPJOHN COMPANY  
NUTRITION DIVISION  
KALAMAZOO, MICHIGAN

A. R. HANZE  
T. W. CONGER  
E. C. WISE  
D. I. WEISBLAT

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### AMINOMETHYLATION OF THIOPHENE

Sir:

During the course of formylation studies with thiophene it was noted that in the presence of ammonium chloride and formaldehyde thiophene appeared to undergo a reaction to give water-soluble amine hydrochlorides. From the reaction mixture was isolated 2-thenylamine (2-aminomethylthiophene) (I), b. 58° (5 mm.),  $n_{\text{D}}^{20}$  1.5589; secondary di-(2-thenyl)-amine, b. p. 150–152° (10 mm.),  $n_{\text{D}}^{20}$  1.5914; and a third amine (III). Amine III is polymeric in nature and is believed to contain methylol groups. The hydroxyl number of III produced by the reaction of one mole of thiophene with four moles of 37% formaldehyde and one mole of ammonium chloride at the reflux was 475, indicating that methylol groups may be substituted around the thiophene in all remaining positions. Other analysis obtained on the product were as follows: 20.6% sulfur and 7.3% nitrogen. With the use of aqueous 37% formaldehyde in excess III is obtained exclusively and molecular weights of 600–750 are the usual order. The use of trioxymethylene with a few per cent. by weight acetic acid (to promote depolymerization at lower temperatures) gave