

*Analysis.* Subs., 0.1041: AgBr, 0.1199. Calc. for  $C_{14}H_{11}O_2NBr_2$ : Br, 41.51. Found: 41.01.

To prepare directly the diacyl derivative having benzoyl on nitrogen and acetyl on oxygen the monobenzoyl derivative specified above was acetylated; 1 g. of this substance mixed with an equal weight of dry sodium acetate was treated with 0.4 g. of acetic anhydride, the mixture warmed gently on the water-bath for 5 minutes, and allowed to cool to a hard mass. Sodium salt was removed by extraction with water, and the insoluble residue collected on a filter and dried. Crystallization from alcohol gave a brownish-white powder that melted at 194–195°, which is in agreement with the properties of the product obtained by benzoylating the mono-acetyl compound and described above. A mixture of the 2 products melted at the same temperature as either of them separately which indicates identity, and from which it follows that in the benzoylation of 2-acetyl-amino-4,6-dibromo-5-methylphenol, the acetyl radical migrates from nitrogen to oxygen, while benzoyl attaches to nitrogen.

### Summary

1. Additional evidence has been obtained to indicate that the migration of acetyl from nitrogen to oxygen, when an *o*-acetylaminophenol is benzoylated in accordance with the Schotten-Baumann method, is probably general.

2. It has been shown that under the same conditions benzoylation of a *p*-acetylaminophenol does not cause migration of the acetyl radical.

3. These differences furnish additional criteria for distinguishing *o*-, *p*-aminophenols.

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## URETHANES FROM CHLORINE-SUBSTITUTED SECONDARY AND TERTIARY ALCOHOLS<sup>1</sup>

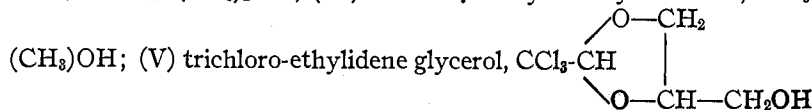
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Alkyl carbamates of the type represented by urethane,  $C_2H_5OCONH_2$ , are mild hypnotics with little or no injurious effect. The carbamic esters of secondary and tertiary alcohols are considered stronger hypnotics. Where chlorine atoms are substituted on the  $\beta$ -carbons of a secondary alkyl carbamate, as in Aleudrin,  $(CH_2Cl)_2CHOCONH_2$ , the hypnotic action is claimed to be still more marked. The action of the carbamate is considerably stronger than that of the alcohol itself unless the latter is too insoluble in water. It was considered of interest, therefore, to prepare the carbamates of the following chlorine-substituted alcohols: (I) trichloromethyl dimethyl carbinol or Chloretone,  $CCl_3C(CH_3)_2OH$ ; (II) trichloromethyl

<sup>1</sup> Read at the Fall Meeting of the American Chemical Society, Pittsburgh, Pa., Sept. 1922.

phenyl carbinol,  $\text{CCl}_3\text{CH}(\text{C}_6\text{H}_5)\text{OH}$ ; (III) dichloromethyl-dimethyl carbinol,  $\text{CHCl}_2\text{C}(\text{CH}_3)_2\text{OH}$ ; (IV) trichloromethyl-methyl carbinol,  $\text{CCl}_3\text{CH}(\text{CH}_3)\text{OH}$ ; (V) trichloro-ethylidene glycerol,  $\text{CCl}_3\text{-CH}$



Of these alcohols, Chloretone (I) and Isopral (IV) are in use as hypnotics. Chloretone and trichloromethyl-phenyl carbinol are prepared from the corresponding ketone and aldehyde, respectively, by addition of chloroform in the presence of alkali. Isopral and dichloromethyl-dimethyl carbinol are obtained in good yields from chloral and methyl dichloroacetate, respectively, through the Grignard reaction.

Alcohol V, the condensation product of chloral and glycerol has not been described previously. Harnitsky and Manchutkin,<sup>2</sup> Schulz and Tollens,<sup>3</sup> Fischer<sup>4</sup> and Nef<sup>5</sup> have prepared a large number of condensation products of this type from aldehydes and ketones with glycerol by the action of heat or by the use of dehydrating agents. In cases where it has not been established that isomers are formed, one a primary alcohol on a 5-membered ring, the other a secondary alcohol with a 6-membered ring, it is a question which isomer is obtained. We prefer to give Alcohol V the structure of a primary alcohol with a 5-membered ring, because it reacts quite readily with carbonyl chloride evolving hydrochloric acid, whereas it is known that secondary alcohols, particularly those containing halogen, either do not react, or react with great difficulty. Irvine, Macdonald and Soutar<sup>6</sup> and, more recently, Fischer and Pfahler<sup>7</sup> studied the condensation of acetone and of benzaldehyde with glycerol and found that only the isomer with the structure of a dioxolane and primary alcohol is formed in each case. In the preparation of this alcohol, the presence of an isomer was not evident.

A number of methods for the preparation of carbamates from alcohols have been proposed. They are briefly: (1) heating the alcohol with urea,<sup>8</sup> (2) heating the alcohol with urea nitrate,<sup>9</sup> (3) addition of carbonyl chloride to the alcohol and subsequent treatment of the acid chloride with ammonia,<sup>10</sup> (4) addition of chloroformamide to the alcohol;<sup>11</sup> (5) addition of cyanic acid to the benzene solution of the alcohol; (6) addition of cyanogen chlor-

<sup>2</sup> Harnitsky and Manchutkin, *Ann.*, **136**, 126 (1865).

<sup>3</sup> Schulz and Tollens, *ibid.*, **289**, 29 (1896).

<sup>4</sup> Fischer, *Ber.*, **27**, 1524 (1894).

<sup>5</sup> Nef, *Ann.*, **335**, 215 (1904).

<sup>6</sup> Irvine, Macdonald and Soutar, *J. Chem. Soc.*, **107**, 337 (1915).

<sup>7</sup> Fischer and Pfahler, *Ber.*, **53**, 1606 (1920).

<sup>8</sup> Cahours, *Compt. rend.*, **76**, 1387 (1873).

<sup>9</sup> Ger. pat. 114,396, 1900.

<sup>10</sup> Ger. pat., 251,805, 1912.

<sup>11</sup> U. S. pat., 1,108,676, 1914.

ide to the moist alcohol;<sup>12</sup> and (7) treatment of a solution of carbonyl chloride in the alcohol with a tertiary amine or sodium carbonate.<sup>13</sup>

These methods were not applicable to the preparation of carbamates from the secondary and tertiary alcohols mentioned above. When any reaction was evident, other products were formed containing a much higher percentage of nitrogen than that of the carbamate. This is in agreement with the result reported by Wolfenstein, Loewy and Bachstesz;<sup>14</sup> they treated trichloromethyl-dimethyl carbinol with chloroformamide and obtained the allophanic ester instead of the carbamic ester.

Trichloromethyl-dimethyl carbinol (I) and trichloromethyl-phenyl carbinol (II) combine with sodium in benzene or ether to form the sodium salts of the alcohols which are stable when enough solvent is used to keep the sodium derivative in solution. In case too little solvent is used, evolution of hydrogen ceases long before the equivalent of sodium has dissolved, the solution becomes cloudy, heat develops and the mixture darkens. The solution of the sodium derivative reacts with carbonyl chloride thus:  $\text{RONa} + \text{ClCOCl} = \text{ROCOC} + \text{NaCl}$ . Addition of ammonia to the mixture then gives the carbamates.

The products of the reaction of magnesium alkyl halides with aldehydes, ketones and esters should also react readily with carbonyl chloride, thus:  $\text{ROMgX} + \text{ClCOCl} = \text{ROCOC} + \text{MgXCl}$ . Treatment of the acid chloride with ammonia should then give the carbamate. This was found to be a short and practical synthesis of the carbamate derived from trichloromethyl-methyl carbinol.

A recent German patent<sup>15</sup> describes the following synthesis of carbamates of tertiary alcohols. The carbamate of dimethylethyl carbinol was prepared by the addition of chloroformamide either to a solution of sodium in dimethylethyl carbinol or to the sodium derivative in benzene. The carbamate of diethylmethyl carbinol was prepared by treating the reaction product formed by the interaction of magnesium ethyl chloride and ethyl methyl ketone with chloroformamide.

The synthesis of carbamates of chlorine-substituted secondary and tertiary alcohols described in this paper differs from the above in that the chlorocarbonic ester of the carbinol is first made by the addition of the sodium or magnesium halogen derivative to a solution of carbonyl chloride and by the subsequent treatment of the chlorocarbonic ester with ammonia.

The urethanes thus obtained are very slightly soluble in water, very soluble in alcohol, benzene or ether, and sparingly soluble in ligroin; they

<sup>12</sup> Ger. pat., 120,864, 1901.

<sup>13</sup> Ger. pat., 246,298, 1912.

<sup>14</sup> Wolfenstein, Loewy and Bachstesz, *Ber.*, **48**, 2035 (1915).

<sup>15</sup> Ger. pat., 245,491, 1912. *Chem. Centr.*, 1912, I, 1407.

are quite stable in boiling water, but are decomposed by strong acid or alkali. They melt above  $100^{\circ}$  but below  $130^{\circ}$ .

### Physiological Properties

The new trichloromethyl alkyl carbamates are tasteless and odorless. Trichloromethyl-dimethyl and trichloromethyl-methyl carbinol esters of carbamic acid have quite strong hypnotic action. The new alcohol, trichloro-ethylidine glycerol, has a pleasant odor and a sweet, slightly burning taste. It has a marked and fleeting hypnotic effect, whereas the urethane prepared from it has practically no hypnotic effect.

### Experimental Part

**Trichloromethyl-dimethyl Carbinol Ester of Carbamic Acid.**—Two and one-half g. of finely divided sodium was added to 18 g. of anhydrous chloretone dissolved in 350 cc. of benzene and the mixture, stirred occasionally, was allowed to stand at  $20^{\circ}$  to  $25^{\circ}$ . After 4 hours, all but about 0.3 g. had passed into solution. The solution was poured from this residue into a slight excess of carbonyl chloride, a 20% solution in toluene. Sodium chloride separated at once and, after an hour, ammonia in excess was passed into the mixture. The sodium and ammonium chlorides were removed and, on evaporation of the filtrate to a small volume and addition of ligroin, 12 g. of the carbamate separated, a 55% yield. Pearly plates crystallized from benzene which were soluble in alcohol or ether, and rather insoluble in water; m. p.,  $102^{\circ}$ .

*Analyses.* Subs., 0.2, 0.2: 9.2, 9.1 cc. of 0.1 *N*  $\text{NH}_3$ . Calc. for  $\text{C}_6\text{H}_8\text{O}_2\text{NCl}_3$ : N, 6.36. Found: 6.44, 6.37.

**Trichloromethyl-phenyl Carbinol Ester of Carbamic Acid.**—The same general procedure as that employed in the preceding preparation was followed. 2.5 g. of finely divided sodium was added to 22.5 g. of the carbinol dissolved in 300 cc. of benzene. The sodium disappeared very rapidly in the solution which was cooled in ice water. After the addition to a slight excess of carbonyl chloride solution, the mixture was shaken while aqueous ammonia was added. After separation and evaporation of the oily layer, 10 g. of the carbamate was obtained; this represented a yield of 37%. The substance crystallized as needles from benzene, was insoluble in water, and soluble in alcohol or ether; m. p.,  $127^{\circ}$ .

*Analyses.* Subs., 0.2, 0.2: 7.6, 7.5 cc. of 0.1 *N*  $\text{NH}_3$ . Calc. for  $\text{C}_9\text{H}_9\text{O}_2\text{NCl}_3$ : N, 5.22. Found: 5.32, 5.24.

**Trichloromethyl-dimethyl Carbinol Ester of Carbanilic Acid.**—The same procedure as that used in the preceding preparations was followed, except that aniline instead of ammonia was added to the acid chloride. A much poorer yield was obtained in this case; the substance formed needles from benzene, was insoluble in water, but soluble in alcohol or ether; m. p.,  $118^{\circ}$ .

*Analyses.* Subs., 0.2, 0.2: 7.1, 7.0 cc. of 0.1 *N*  $\text{NH}_3$ . Calc. for  $\text{C}_{11}\text{H}_{12}\text{O}_2\text{NCl}_3$ : N, 4.73. Found: 4.97, 4.90.

**Dichloromethyl-dimethyl Carbinol Ester of Carbamic Acid.**—The magnesium bromide salt of the carbinol was prepared from 28.5 g. of methyl dichloro-acetate according to the method employed by Henry<sup>16</sup> to prepare the carbinol. The reaction mixture in ether was added to a slight excess of 20% carbonyl chloride solution. After this mixture stood for a week, the sodium chloride was removed by filtration, and the filtrate, evaporated to a small volume, was shaken with ammonia water. The carba-

<sup>16</sup> Henry, *Bull. soc. chim. Belg.*, **20**, 156 (1906); *Chem. Centr.*, **1906**, II, 1178.

mate was obtained in a 7 g. yield in the usual manner. It resembled the carbamic ester of chlorotone in solubility and in the character of its crystals. It melted at 122°.

*Analyses.* Subs., 0.2, 0.2: 10.8, 11.0 cc. of 0.1 *N* NH<sub>3</sub>. Calc. for C<sub>6</sub>H<sub>9</sub>O<sub>2</sub>NCl<sub>2</sub>: N, 7.87. Found: 7.56, 7.70.

**Trichloromethyl-methyl Carbinol Ester of Carbamic Acid.**—The magnesium bromide derivative of the carbinol was obtained from 50 g. of chloral according to the method of Vitoria<sup>17</sup> described in a German patent<sup>18</sup> for the production of "Isopral." The magnesium bromide salt of the carbinol mixed with ether and stirred was treated with a slight excess of carbonyl chloride dissolved in toluene, and then allowed to stand overnight. Ammonia in excess was added to the mixture and after washing the oily layer with water and drying, it was evaporated; 25 g. of the carbamate crystallized from the residue, representing a 35% yield. It forms flat crystals from benzene, is very soluble in benzene, alcohol or in ether and is rather insoluble in water; m. p., 125°.

*Analyses.* Subs., 0.2, 0.2: 9.85, 9.75 cc. of 0.1 *N* NH<sub>3</sub>. Calc. for C<sub>4</sub>H<sub>9</sub>O<sub>2</sub>NCl<sub>3</sub>: N, 6.79. Found: 6.89, 6.82.

**2-Trichloromethyl-1,3-dioxolane-4-carbinol.**—To 30 g. of glycerol and 50 g. of chloral hydrate, heated to 80°, 25 g. of fused zinc chloride was added in portions and the mixture stirred until the salt dissolved. The solution was then heated under pressure at 130° for 8 hours. The resulting sirup was thoroughly washed with water, dried and distilled under diminished pressure. A yield of 35%, 24 g., boiling at 125° to 128° at 10 mm. pressure, was obtained. The substance is slightly soluble in water, very soluble in benzene, alcohol or ether. The alcohol is quite stable in boiling water or dil. acids.

*Analyses.* Subs., 0.1496, 0.1540: (Carius) AgCl, 0.2789, 0.2871. Calc. for C<sub>5</sub>H<sub>7</sub>O<sub>3</sub>Cl<sub>3</sub>: Cl, 48.0. Found: 46.12, 46.12.

**2-Trichloromethyl-1,3-dioxolane-4-carbinol Ester of Carbamic Acid.**—Eleven g. of the alcohol was dissolved in 30 g. of 20% solution of carbonyl chloride in toluene. After 12 hours, the mixture was warmed on the steam-bath for 1 hour. An excess of ammonia water was shaken with the cooled solution. The oily layer was then washed, dried and evaporated. From the residue 8 g. of the carbamate, was obtained a 60% yield. Flat, boat-shaped crystals were formed from benzene solution. It is very soluble in alcohol or in ether and slightly soluble in water; m. p., 114°.

*Analyses.* Subs., 0.2, 0.2: 7.75, 7.65 cc. of 0.1 *N* NH<sub>3</sub>. Calc. for C<sub>6</sub>H<sub>9</sub>O<sub>4</sub>NCl<sub>3</sub>: N, 5.30. Found: 5.42, 5.35.

### Summary

Carbamates of chlorine-substituted secondary and tertiary alcohols containing a trichloromethyl group were prepared by treating the sodium or the magnesium bromide salt in benzene or ether solution with phosgene and then adding ammonia to the acid chloride thus formed.

Chloral condenses with glycerol to form a substituted 1,3-dioxolane, of which the alcohol group likewise reacts with phosgene and ammonia.

This dioxolane and some of these chlorine substituted urethanes are hypnotics.

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<sup>17</sup> Vitoria, *Bull. acad. roy. Belg.*, 1904, 1087; *Chem. Centr.*, 1905, I, 344.

<sup>18</sup> Ger. pat., 151,545, 1904; Bayer and Co., *ibid.*, 1904, I, 1586.