

We have oxidized β - and γ -tocopherol under the conditions described by Fernholz and have obtained from both the same lactone that had been obtained from α -tocopherol. We failed to obtain dimethylmaleic anhydride, but the amount of material used by us was much smaller than that employed by Fernholz so that dimethylmaleic anhydride, if formed, might have escaped our attention.

We have also pyrolyzed γ -tocopherol at 360° , and obtained trimethylhydroquinone. From these facts, it is evident that β - and γ -tocopherol differ from alpha only in the absence of one of the three methyl groups attached to the benzene ring. This had been suspected by John⁶ and Karrer, Salomon and Fritzsche.¹²

Oxidation of β -Tocopherol.—Eight hundred and nine milligrams of β -tocopherol was oxidized as described by Fernholz.¹¹ A lactone was obtained which was purified by distillation in high vacuum (yield 351 mg.). This yielded a benzylthiuronium salt which, after several recrystallizations from acetone, melted at 116 – 117° . A sample of the corresponding benzylthiuronium salt, prepared by Fernholz from α -tocopherol, melted at 116 –

(12) P. Karrer, H. Salomon, and H. Fritzsche, *Helv. Chim. Acta.*, **21**, 302 (1938).

117.5° ; mixed m. p. 116 – 117° . *Anal.* Calcd. for $C_{29}H_{52}O_2N_2S$: C, 68.45; H, 10.30; N, 5.50. Found: C, 68.22, 68.51, 68.15; H, 10.23, 10.44, 10.23; N, 5.42, 5.54.

Oxidation of γ -Tocopherol.—Three hundred and seventy four milligrams of γ -tocopherol, oxidized as above, yielded 90 mg. of lactone after purification by high vacuum distillation. This gave a benzylthiuronium salt melting at 116 – 117° which showed no depression on admixture with a sample of the corresponding benzylthiuronium salt of the same melting point from α -tocopherol. *Anal.* Calcd. for $C_{29}H_{52}O_2N_2S$: C, 68.45; H, 10.30; N, 5.50. Found: C, 68.59, 68.65; H, 10.35, 10.26; N, 5.48.

Pyrolysis of γ -Tocopherol.—Five hundred milligrams of γ -tocopherol was heated at 360° in an atmosphere of carbon dioxide. This gave 30 mg. of a crystalline sublimate, which appeared to be a mixture of trimethylhydroquinone with a little durohydroquinone. By careful recrystallization from benzene there was obtained a fraction melting at 167 – 170° which gave no depression with authentic trimethylhydroquinone. A benzoate was also obtained melting at 175 – 178° which gave no depression when mixed with an authentic sample of trimethylhydroquinone dibenzoate melting at 178 – 180° .

The trimethylhydroquinone and its dibenzoate were supplied by Professor Lee Irvin Smith to whom we wish to express our thanks.

Summary

Oxidation of β - and γ -tocopherols yielded the same $C_{21}H_{40}O_2$ lactone that had been obtained by Fernholz from α -tocopherol.

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RAHWAY, N. J.
RECEIVED MAY 11, 1938

[CONTRIBUTION NO. 180 FROM THE EXPERIMENTAL STATION OF E. I. DU PONT DE NEMOURS & COMPANY]

Carbamic Esters from Urea

BY RALPH A. JACOBSON

Esters of carbamic acid are usually prepared either by treating an alcohol with phosgene and adding ammonia to the chloroformic ester thus formed, or by treating the alcohol with cyanic acid. The reaction of urea with an alcohol has also been utilized¹ but the method has not been applied widely, probably because the lower alcohols, *e. g.*, methyl and ethyl, require pressure. Butanol, however, reacts with urea at atmospheric pressure² to give butyl carbamate in 75% yield. This suggests wider application of the

method for the preparation of carbamic esters of alcohols having boiling points higher than that of butanol. In the present paper, we have adapted this method to the synthesis of octyl carbamate, *n*-dodecyl carbamate, and several other esters of carbamic acid.

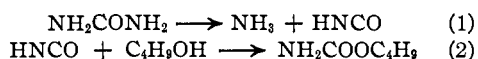
The optimum temperature range for carbamate formation appears to be 175 – 190° . At this temperature, aliphatic monohydric alcohols react smoothly with urea with the evolution of ammonia and the formation of carbamates. While the reaction is usually over within a few hours at this temperature, a reaction period of twelve to twenty-four hours or longer is required for al-

(1) Hoffmann, *Ber.*, **4**, 268 (1871); Bunte, *Ann.*, **181**, 181 (1869); Cahours, *Chem. Zentr.*, **4**, 482 (1873); *Compt. rend.*, **76**, 1387 (1873); Werner, *J. Chem. Soc.*, **118**, 626 (1918).

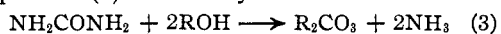
(2) Davis and Lane, *Org. Syntheses*, **9**, 24 (1920).

cohols having boiling points considerably lower than the optimum temperature. In such cases the reaction is usually very slow initially, but as the concentration of carbamate in the mixture increases and the boiling point of the mixture approaches the optimum temperature, the reaction rate increases markedly. The products are isolated by filtering the mixture to remove the small amount of cyanuric acid usually formed, and distilling the filtrate. After removal of the alcohol, the less volatile carbamates are purified by distillation or by crystallization.

The formation of butyl carbamate from urea and *n*-butanol is expressed by Davis and Lane as follows



If these reactions correctly express the mechanism, the formation of carbonates by the reaction of urea with two molecules of the alcohol as shown in equation (3) is unlikely.



Since phosgene, however, reacts with two molecules of an alcohol to yield the carbonate, it seems at least theoretically possible that urea—the diamide from phosgene—could react similarly. In other words, the reaction expressed by equation (3) might take place in either direction depending upon the conditions. Indeed the reaction from right to left does go readily in the case of diphenyl carbonate which can be converted into urea and phenol in 70% yields by treatment with aqueous ammonia³



Our attempts to force the reaction (3) from left to right, however, were unsuccessful since none of the experiments yielded carbonates. In one instance, sulfuric acid was added to a mixture of urea and *n*-dodecyl alcohol to remove the ammonia immediately upon formation, but quantitative dehydration of the *n*-dodecyl alcohol to *n*-dodecyl ether resulted.

The reaction of urea with polyhydric alcohols also was examined briefly. Ethylene glycol, sorbitol, and triethylene glycol reacted readily with urea to give viscous water-soluble sirups. Upon standing, the sirup from triethylene glycol deposited crystals of the diurethan (m. p. 108°). In general, however, the reaction of urea with polyhydric alcohols appears unpromising for

(3) Kirkhof and Astrova, *Khim. Farm. Prom.*, 281 (1933); *C. A.*, 28, 3718 (1934).

the preparation of pure carbamates of polyhydric alcohols.

Experimental Part

***n*-Dodecyl Carbamate.**—A mixture of 120 g. of urea, 372 g. of *n*-dodecyl alcohol, and 12 g. of glycerol was heated at 170° for two hours and finally at 190° for three hours. The reaction mixture was distilled in a vacuum and 150 g. of *n*-dodecyl alcohol boiling at 135° under 12 mm. was recovered. The liquid in the distilling flask solidified on cooling. The crystalline product was washed with petroleum ether and melted at 81–82°; yield 138 g. (60%). The product was soluble upon heating in toluene, alcohol, ethyl acetate, ether, carbon tetrachloride, and acetic acid.

Anal. Calcd. for $\text{C}_{18}\text{H}_{37}\text{O}_2\text{N}$: C, 68.12; H, 11.79. Found: C, 67.68; H, 11.14.

***n*-Octyl Carbamate.**—This compound was prepared as above except that purification was effected by distillation, followed by crystallization from benzene. The compound boiled at 136° under 4 mm. pressure and melted at 67°. The yield was 55% of the theoretical.

Isobutyl Carbamate.—A mixture of 270 g. of urea, and 1813 g. of isobutanol was refluxed for seventy-two hours. The excess isobutanol was distilled and the residue extracted three times with ligroin, b. p. 90–100°. Urea amounting to 101 g. was recovered. After removal of the ligroin the isobutyl carbamate was collected at 117° under 25 mm. pressure, the product m. p. 65–66° weighing 225 g. (42.8% conversion or 65% based on the urea consumed).

An attempt was made to reduce the time of reaction by utilizing isobutyl phthalate to increase the initial boiling point of the mixture. Under these conditions isobutyl allophanate was obtained as a by-product.

A mixture of 120 g. of urea, 148 g. of isobutanol, 250 g. of isobutyl phthalate, and 12 g. of glycerol was heated on the hot-plate for nineteen hours. During the first twelve hours, the boiling point of the mixture increased from 123 to 137° and during the next seven hours from 137 to 170°. The solution upon cooling deposited crystals (15 g.) of isobutyl allophanate which on purification from acetone melted at 174°. The liquid portion was distilled and the fraction boiling at 95–110° under 12 mm. was collected. Upon cooling, the liquid solidified to a white crystalline solid which, after being washed with petroleum ether, melted at 65–66°.

Anal. of isobutyl allophanate m. p. 174°. Calcd. for $\text{C}_8\text{H}_{12}\text{O}_3\text{N}_2$: C, 45.00; H, 7.50; N, 17.50. Found: C, 44.92; H, 7.10; N, 17.32.

Anal. of isobutyl carbamate m. p. 65–66°. Calcd. for $\text{C}_8\text{H}_{11}\text{O}_2\text{N}$: C, 51.28; H, 9.40. Found: C, 51.77; H, 8.96.

Mixed Carbamates from the Higher Alcohol Mixture Obtained in the Synthetic Methanol Process.—A mixture of 90 g. of urea, 9 g. of glycerol, and 308 g. of the fraction

(4) Béhal, *Bull. soc. chim.*, 25, 480 (1919), prepared dodecyl carbamate by passing cyanic acid into the alcohol but gave 77° as the melting point.

(5) Béhal⁴ reported 67° as the melting point.

(6) Béhal⁴ gives 180.5° for the allophanate and 59.5° for the carbamate.

of higher alcohols boiling at 135–150° obtained from the synthetic methanol process,⁷ was refluxed for twelve hours. The liquid was decanted from a small amount of solid material (4.5 g.) and distilled. After removal of the excess alcohols, the carbamate was obtained at 110–125° under 4 mm. pressure. The product was slightly yellow and remained liquid at room temperature. The yield was 137 g. or about 60% of the theoretical.

Ethylene Glycol and Urea.—A mixture of 240 g. of urea, 124 g. of ethylene glycol, and 12 g. of glycerol yielded a transparent water-soluble sirup after a heating period of six hours at 160–165° and four hours at 170–175°.

Triethylene Glycol and Urea.—A mixture of 60 g. of urea, 6 g. of glycerol, and 150 g. of triethylene glycol was heated at 140–150° for one and one-half hours and slowly increased during eight hours to 175°. The excess triethylene glycol was removed by distillation and 115 g. (57.8%) of a non-volatile water soluble sirup obtained. Upon standing for two weeks, a small amount of crystalline material separated which, upon crystallization from acetone, melted at 108° and proved to be the diurethan.

(7) The following compounds have been identified in this fraction by Graves, *Ind. Eng. Chem.*, **23**, 1381 (1931): 2-methyl-1-pentanol, 2,4-dimethyl-3-pentanol and 2,4-dimethyl-1-pentanol.

Anal. Calcd. for $C_8H_{16}O_6N_2$: C, 40.67; H, 6.77; N, 11.86. Found: C, 40.87; H, 6.65; N, 11.32.

Sorbitol and Urea.—Resins of varying viscosity were obtained depending upon the ratio of urea to sorbitol. Pure compounds could not be isolated.

Summary

n-Dodecyl carbamate, octyl carbamate, isobutyl carbamate, and the mixed carbamates from one fraction (b. p. 135–150°) of the higher alcohols obtained in the methanol synthesis have been prepared by the reaction of urea with the corresponding alcohols at atmospheric pressure. Attempts to obtain alkyl carbonates by the same procedure were unsuccessful.

Polyhydric alcohols reacted with urea under the same conditions to yield sirups from which pure compounds could not be isolated except in the case of triethylene glycol. The latter yielded a sirup from which a small amount of the diurethan of m. p. 108° was obtained.

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RECEIVED MAY 19, 1938

[CONTRIBUTION FROM THE LABORATORY OF BIOLOGICAL CHEMISTRY, SCHOOL OF MEDICINE, UNIVERSITY OF BUFFALO]

A Critical Examination of the Reaction of Iodine Monobromide with Cholestenone and β -Cholestanone

BY J. O. RALLS

In a previous study,¹ it was shown that cholestenone was one of the products of the reaction of iodine monobromide with cholesterol. It was also shown that cholestenone behaved toward halogen in a manner that was then considered "abnormal." In addition, Copping² had stated that cholestenone did not yield analytically correct iodine numbers when Dam's³ suggested application of the Rosenmund and Kuhnemann⁴ method was used. We were interested, therefore, in attempting to ascertain the causes of this peculiarity.

Inasmuch as $\Delta^{4,5}$ -cholestenone, commonly called cholestenone (suggested name, coprostenone),⁵ contains a double bond and a ketone group (in a conjugated system), the problem was one of attempting to evaluate the role of each in the reaction of cholestenone with iodine monobro-

mid. Cholestanone, which contains no double bond, and cholestanoxime, which contains neither the double bond nor the ketone group, served to evaluate the effect of the carbonyl group; while cholestenoxime, which does not contain the ketone group but still possesses the double bond, was used in attempting to evaluate the role of the latter group.

In the course of the experimentation, hydrogen bromide catalysis of halogenation was investigated, as was, also, the effect of the oximino hydroxyl upon the halogenation of the ethylene group in cholestenoxime. In the latter work, the factors of solvent nature, of air (oxygen) inhibition, and of the configuration of the oxime were considered. In these studies, *syn*-styrylphenylketoxime, 3,5-diphenylisoxazol, and 3,5-diphenylisoxazoline were also used.

Discussion and Results

The peculiarities of the reaction of cholestenone with iodine monobromide (Curves 1, Fig. 1) are especially evident in the graph of the organic

(1) Ralls, *THIS JOURNAL*, **55**, 2083 (1933).

(2) Copping, *Biochem. J.*, **22**, 1142 (1928).

(3) Dam, *Biochem. Z.*, **152**, 101 (1924).

(4) K. W. Rosenmund and W. Kuhnemann, *Z. Unters. Nahr. u. Genussm.*, **46**, 154–9 (1923).

(5) O. Rosenheim and H. King, *Ann. Rev. Biochem.*, **3**, 90 (1934).