ω-Methyl-ω'-nitrobiuret.—Four grams of finely powdered dry ω-methylbiuret[9] was added gradually and with stirring to a mixture, below −15°, of 12 cc. of concd. sulfuric acid (1.84) and 3 cc. of nitric acid (1.42). On drowning the clear liquid in 25 cc. of ice-water, the ω-methyl-ω'-nitrobiuret precipitated as an almost impalpable powder. Washed with ice-water and dried in vacuum, this yielded without recrystallization 2.9 g. (52%) of product which did not melt but decomposed at 99–100°.

Anal. Calcd. for $C_3H_6O_4N_4$: N, 34.5. Found: N, 34.5, 34.6.

ω-Methyl-ω'-nitrobiuret did not yield a chloroform soluble copper pyridine complex. Warmed with ammonia water, it yielded ω-methylbiuret, identified by mixed melting point with a known sample.

ω,ω-Dimethyl-ω'-nitrobiuret.—Ten grams of ω,ω-dimethylbiuret, nitrated with a mixture of 18.5 cc. of concd. sulfuric acid (1.84) and 4.5 cc. of nitric acid (1.42) and drowned in 100 cc. of ice-water, gave 9.8 g. (73%) of ω,ω-dimethyl-ω'-nitrobiuret, m. p. 114–115°, with decomposition.

Anal. Calcd. for $C_4H_8O_4N_4$: N, 31.8. Found: N, 31.7, 31.4.

ω,ω-Dimethyl-ω'-nitrobiuret, warmed with ammonia water, yielded ω,ω-dimethylbiuret, identified by mixed melting point with a known sample. It did not form a chloroform soluble copper pyridine complex.

ω,ω-Dimethyl-ω'-phenylbiuret.—Two grams of ω,ω-dimethyl-ω'-nitrobiuret was treated with a slight excess of aniline in aqueous solution. Gassing set in at once. The material was warmed until gassing ceased and evaporated to dryness on the water-bath. The product was purified by recrystallization from methyl alcohol and by sublimation in vacuum. At ordinary pressure it sublimed without melting at about 225°.

Anal. Calcd. for $C_{10}H_{18}O_2N_3$: N, 20.3. Found: N, 20.6.

(9) Prepared according to the method of Davis and Blanchard, seventh paper of this series.

ω,ω,ω'-Trimethylbiuret, prepared in similar manner from ω,ω-dimethyl-ω'-nitrobiuret and methylamine, melted at 154°, small crystals from chloroform.

Anal. Calcd. for $C_5H_{11}O_2N_3$: N, 29.0. Found: N, 29.2, 29.3.

ω,ω-Dimethyl-ω'-*n*-amylbiuret, prepared in similar manner from ω,ω-dimethyl-ω'-nitrobiuret and *n*-amylamine, melted at 149°, small crystals from chloroform.

Anal. Calcd. for $C_9H_{19}O_2N_3$: N, 20.9. Found: N, 21.1.

Very few substituted biurets containing substituents in both the ω- and the ω'-positions are described in the literature. Experimentation along this line is being continued.

Summary

The nitration of alkylureas has been studied by the method of treating the urea nitrates with concentrated sulfuric acid.

Ethyl-, *n*-propyl- and *n*-butylurea, like the corresponding guanidines, nitrate in the non-alkylated amino group.

Methylurea, unlike methylguanidine, nitrates on the nitrogen atom which is attached to the methyl.

Dialkylureas in which the two alkyl groups are attached to the same nitrogen atom yield dialkylnitramines.

Dialkylureas in which the two alkyl groups are attached to different nitrogen atoms could not be nitrated.

ω-Methyl- and ω,ω-dimethylbiuret with mixed acid take on a nitro group in the non-alkylated amino group at the remote end of the molecule.

Three ω,ω,ω'-trisubstituted biurets are described.

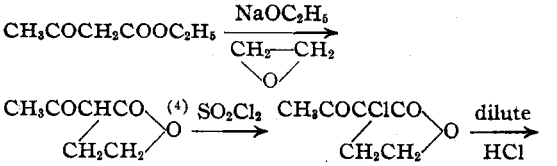
CAMBRIDGE, MASS. RECEIVED JULY 1, 1936

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

Studies of Crystalline Vitamin B_1. XIV. Sulfite Cleavage. IV. The Thiazole Half

BY EDWIN R. BUCHMAN

The vitamin B_1 molecule is split by sulfite[1] yielding 4-methyl 5-(β-hydroxyethyl) thiazole[2] as basic cleavage product. The synthesis of this substance from brominated acetopropyl alcohol and thioformamide was announced[3] over a year ago. Subsequently H. T. Clarke and S. Gurin prepared[2] the compound in connection with their establishment of the presence of the thiazole nucleus in the vitamin. Recently the following improved method has been developed.

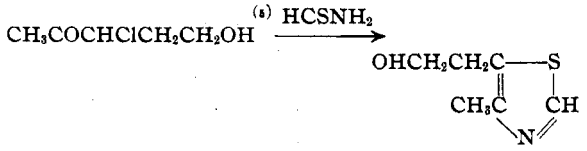


(1) R. R. Williams, R. E. Waterman, J. C. Keresztesy and E. R. Buchman, THIS JOURNAL, **57**, 536 (1935).

(2) H. T. Clarke and S. Gurin, *ibid.*, **57**, 1876 (1935).

(3) E. R. Buchman and R. R. Williams, Paper read before the Organic Division of the American Chemical Society at the New York meeting, April, 1935.

(4) I. L. Knunyantz, G. V. Chelintzev and E. D. Osetrova, *Compt. rend. acad. sci.* (U. R. S. S.), [N. S.], **1**, 312 (1934); *C. A.*, **28**, 4382 (1934).



The yield of thiazole varies from 8 to 12 g. per 100 g. of ethyl acetoacetate used as starting material.

The similarity between the vitamin and the methiodide of the basic cleavage product has been pointed out.[6] Although the resemblance does not extend to the sulfite cleavage,[1] it was found that the characteristic color test which the vitamin gives with diazotized sulfanilic acid is a property of quaternary salts of the hydroxy thiazole.

Experimental

Brominated Acetopropyl Alcohol and Thioformamide.[7]—Thirty-one grams of γ-acetopropyl alcohol[4] was dissolved in 150 cc. of water and stirred while 48 g. of bromine was added slowly at room temperature over a period of two hours. The aqueous layer was decanted from a small amount of oil, extracted with ether and the ethereal solution dried over sodium sulfate. After removal of the solvent *in vacuo*, the crude bromo compound (unstable even at room temperature), weighing 30 g., was added directly to 13 g. of crude thioformamide[8] dissolved in 10 cc. of ethanol. A spontaneous reaction took place during which the temperature was kept below 60° by external cooling. The reaction mixture, after standing overnight at room temperature, was heated for one hour on the steam-bath, taken up in water and washed with ether. Excess alkali was added and the liberated thiazole extracted with ether, dried over sodium sulfate and fractionated. The yield was 7.1 g.; b. p. 110–112° (3 mm.).

Anal.[9] Calcd. for C_6H_9NSO: C, 50.30; H, 6.34. Found: C, 49.96; H, 6.29.

The presence in the product of a small amount of the isomer, 4-(γ-hydroxypropyl) thiazole, may be inferred from the unsharp melting points of crude derivatives. These, on recrystallization, were found to be identical with corresponding material[6a] from the vitamin: picrolonate, m. p. 184° d.; picrate, from ethanol, m. p. 163°; *p*-nitrobenzoate, from methanol, m. p. and mixed m. p. 124°.[10]

α-Chloro-α-acetobutyrolactone.—Sixty-four grams of α-acetobutyrolactone[4] was placed in a flask equipped with a mechanical stirrer and 68 g. of sulfuryl chloride added over a period of one and one-half hours. The reaction was accompanied by spontaneous warming and a steady evolution of hydrogen chloride and sulfur dioxide. The product was washed with water, taken up in ether and dried over calcium chloride. Fractionation yielded 67.5 g. (83% of the theoretical); b. p. 84–86° at 3 mm.; d^{24}_4 1.325.

Anal. Calcd. for $C_6H_7O_2Cl$: C, 44.30; H, 4.35. Found: C, 44.19; H, 4.39.

γ-Chloro-γ-acetopropyl Alcohol.—Eighty-one grams of the chloro lactone, 80 cc. of water and 15 cc. of concentrated hydrochloric acid were mixed and heated under reflux at 100° for seventy-five minutes. During this time carbon dioxide was evolved and complete solution took place. The reaction mixture was extracted several times with small portions of ether and the ethereal solution dried over sodium sulfate and distilled. The portion boiling at 85–110° at 3 mm. was collected; yield 50 g. or 73%; d^{25}_4 1.221.

Anal. Calcd. for $C_5H_9O_2Cl$: Cl, 25.97. Found: Cl, 27.26.

The stability of the chloro alcohol is in marked contrast to the behavior of the corresponding bromo compound.

4-Methyl 5-(β-Hydroxyethyl) Thiazole.—Nine and one-half grams of chloroacetopropyl alcohol, 6.7 g. of crude thioformamide and 3 cc. of ethanol were mixed and allowed to stand in a stoppered vessel for three days at room temperature. During this time an additional 3.0 g. of thioformamide was added. The product was isolated as described above. On distillation at 2 mm. there was obtained a 4.9-g. fraction (corresponding to a 50% yield) boiling at 93–95°; d^{24}_4 1.196.

Anal. Calcd. for C_6H_9NSO: C, 50.30; H, 6.34; N, 9.79. Found: C, 50.27; H, 6.31; N, 9.52.

The sharp melting points of even crude derivatives attest the high purity of the product.

The thiazole was also prepared by brominating the acetobutyrolactone in aqueous suspension, hydrolyzing the bromo lactone with 10% hydrobromic acid and condensing the resulting γ-bromo-γ-acetopropyl alcohol with thioformamide as before. The yields however are only about one-half of those obtained through the chloro lactone.

The thiazole methiodide,[6a] m. p. 89°, when treated with sulfite[1] did not cleave appreciably but with alkali and diazotized sulfanilic acid[11] gave the red color characteristic of the vitamin under these conditions. The azo test is not given by the hydroxythiazole itself nor is it a general reaction of quaternary thiazolium salts. Acetopropyl alcohol gave a strong positive test.

4-Methyl 5-(β-Chloroethyl) Thiazole.[6a]—Two grams of the hydroxythiazole was heated with 25 cc. of concentrated hydrochloric acid for three hours in a sealed tube at 145°. After evaporation of excess acid, the free base was liberated with alkali and isolated by distillation; yield 1.5 g. The compound has a characteristic odor and is stable[12] at room temperature: b. p. 74–75° (3 mm.) d^{25}_4 1.233. *Anal.* Calcd. for C_6H_8NSCl: C, 44.56; H, 4.99; N, 8.67. Found: C, 44.40; H, 5.06; N, 8.60. Picrate[2] m. p. 139–140°; chloroplatinate m. p. 215–218° d.; methiodide m. p. 165°.

The author wishes to acknowledge the kind cooperation of Drs. R. R. Williams and E. E. Reid.

(5) Acetopropyl alcohol and its simple derivatives exist largely in the cyclic oxide form.

(6) (a) E. R. Buchman, R. R. Williams and J. C. Keresztesy, THIS JOURNAL, **57**, 1849 (1935); see also (b) R. R. Williams and A. E. Ruehle, *ibid.*, **57**, 1856 (1935), and ref. 2.

(7) This experiment was carried out at Teachers College, Columbia University, Department of Physiological Chemistry.

(8) S. Gabriel, *Ber.*, **43**, 1115 (1916).

(9) Microanalyses by Dr.-Ing. A. Schoeller, Berlin.

(10) The previously recorded[6a] m. p. (131°) is in error.

(11) Spot plate technique of T. B. Johnson and S. H. Clapp, *J. Biol. Chem.*, **5**, 163 (1908).

(12) Compare F. E. Hooper and T. B. Johnson, THIS JOURNAL, **56**, 470 (1934).

Summary

There has been described a practical method of synthesis of the thiazole half of vitamin B_1.

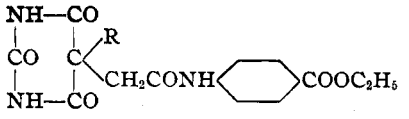
BALTIMORE, MARYLAND RECEIVED JULY 20, 1936

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Alkylacetanilidobarbituric Acids. II. *p*-Carbethoxy Derivatives

BY JOHN A. TIMM AND JOHN B. HOWARD[1]

In many instances the simultaneous administration of either mixtures or addition products of hypnotic and antipyretic substances produces an analgesic effect.[2] Further, compounds have been synthesized in which groups tending to exhibit hypnotic properties and others, antipyretic properties are present within the same molecules. Hepner and Frenkenberg[2] have prepared 5,5-dialkyl derivatives of 1-phenyl-3-methylbarbituric acid. Dox and Yoder[3] have synthesized derivatives of two dialkylbarbituric acids (5-ethyl-5-propyl- and 5-isoamyl-5-propylbarbituric acids) with diethylamine, ethylaniline, acetanilide, and phenacetin, respectively, attached to the γ-carbon atom of the propyl group. Timm[4] prepared a series of 5-alkyl-5-acetanilidobarbituric acids. This work has now been extended to include a series of 5-alkyl-5-*p*-carbethoxyacetanilidobarbituric acids of the type



These compounds may be considered as derivatives of ethyl *p*-aminobenzoate, the local anesthetic.

(1) From the essay presented by John B. Howard to the Faculty of the Sheffield Scientific School of Yale University in partial fulfilment of the requirements for the degree of Bachelor of Science with Honors, June, 1936.

(2) For a review of the literature in this field see Hepner and Frenkenberg, *Ber.*, **65B**, 123 (1932).

(3) Dox and Yoder, THIS JOURNAL, **45**, 1757 (1923).

(4) Timm, *ibid.*, **57**, 1943 (1935).

Experimental Part

Barbituric Acids Containing the *p*-Carbethoxyacetanilido Group.—The method used in the synthesis of these compounds was identical with that used for the corresponding acetanilido derivatives[4] except that ethyl *p*-chloroacetaminobenzoate[5] was substituted for chloroacetanilide. The products were recrystallized from 90% ethyl alcohol except in the cases of the allyl and the isopropyl derivatives in which cases absolute alcohol was used to avoid the formation of hydrates. All melt with decomposition at temperatures above 225°.

TABLE I

Barbituric acid, 5-*p*-carbethoxyacetanilido-	Yield, %	N Analysis, % Calcd.	Found	
5-Ethyl-	40	11.63	11.54	11.60
5-Isopropyl-	9	11.20	11.22	11.24
5-*n*-Butyl-	13	10.79	10.78	10.81
5-Isobutyl-	25	10.79	10.73	10.77
5-Isoamyl-	43	10.42	10.41	10.43
5-Allyl-	20	11.25	11.18	11.22

Summary

The following 5-*p*-carbethoxyacetanilidobarbituric acids have been prepared: 5-ethyl-, 5-isopropyl-, 5-*n*-butyl-, 5-isobutyl-, 5-isoamyl- and 5-allyl-.

NEW HAVEN, CONN. RECEIVED JULY 2, 1936

(5) This compound has been prepared in this Laboratory by Ruth Watts. Its preparation and properties will be reported shortly.