[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

Studies in the Thiamorpholine Series. III. Derivatives of Thiamorpholine-3,5-dicarboxylic Acid

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A study of thiamorpholine-3,5-dicarboxylic acid with the view to the preparation of possibly pharmacologically active products has been in progress since the original synthesis of the parent substance, described in the first paper of this series.[3]

The thiamorpholine nucleus with acid groups in the 3,5-positions seems to be reasonably stable to ordinary reactions. The sulfur atom has been oxidized by peroxide to sulfoxide and the carboxyl groups themselves can be esterified readily. The NH group, being alpha to both carboxyls, is apparently somewhat sterically hindered, as the hydrogen is replaced with comparative slowness by such reagents as carbobenzoxy chloride and ethyl chlorocarbonate.

The action of acetic anhydride on the acid leads to a compound which seems to be the anhydride of the acetyl derivative. This would seem to indicate, but not necessarily prove, that the thiamorpholine-3,5-dicarboxylic acid previously described had the meso (*cis*) structure, rather than the racemic (*trans*).

A description of the derivatives prepared is given.

Experimental

All melting points are corrected.

1-Oxothiamorpholine-3,5-dicarboxylic Acid.—One gram of thiamorpholine-3,5-dicarboxylic acid, 20 cc. of acetic acid and 5 cc. of acetic anhydride were mixed in a round-bottomed flask and cooled in an ice–salt-bath. One gram of 30% hydrogen peroxide was then added slowly during vigorous stirring. The reaction was now allowed to stand at room temperature for five days, during which time crystals separated. These were filtered off, washed with water and recrystallized from water; m. p. 242° (dec.). The yield was 0.69 g. (64%).

Anal. Calcd. for $C_6H_9O_5NS$: C, 34.8; H, 4.4; N, 7.8; S, 15.5. Found: C, 34.8; H, 4.6; N, 6.1; S, 15.6.

N-Acetylthiamorpholine-3,5-dicarboxylic Acid Anhydride.—This compound was obtained by adding thiamorpholine-3,5-dicarboxylic acid to boiling acetic anhydride; m. p. 143° (dec.).

Anal. Calcd. for $C_8H_9O_4NS$: C, 44.6; H, 4.2. Found: C, 44.4; H, 4.5.

N - Carbobenzoxythiamorpholine - 3,5 - dicarboxylic Acid.—A mixture of 2 g. of thiamorpholine-3,5-dicarboxylic acid and 5 g. of sodium bicarbonate was dissolved in about 20 cc. of water. The solution was treated with 6 cc. of carbobenzoxy chloride, added in four portions over a period of two hours. Between additions the mixture was shaken in the shaking machine and shaking was continued overnight (fifteen hours) to complete the reaction. The solution was then extracted three times with ether to remove benzyl alcohol and any unchanged carbobenzoxy chloride, treated with Norite for an hour at room temperature, and filtered. Upon acidification of the filtrate with hydrochloric acid, the product separated as an oil, which after standing overnight in an oven at about 40° became crystalline; yield, 2 g. (59%). Upon slow evaporation of a water solution of this material, colorless rectangular prisms were obtained which melted at 149.5–150°.

Anal. Calcd. for $C_{14}H_{15}O_6NS$: C, 51.7; H, 4.6; S, 9.9. Found: C, 51.6; H, 4.6; S, 10.2.

Diethyl Ester of Thiamorpholine-3,5-dicarboxylic Acid.—A mixture of 10 g. of finely-powdered thiamorpholine-3,5-dicarboxylic acid, 200 cc. of absolute alcohol, and 5 cc. of concentrated sulfuric acid was refluxed for twenty-four hours in a 500-cc. 2-necked flask fitted with a dropping funnel and an efficient fractionating column equipped with a total-condensation variable take-off stillhead. Ten cc. of dry benzene was added through the dropping funnel and distilled from the flask, first as the ternary mixture with alcohol and water boiling at 64°, and later as the binary mixture with alcohol boiling at 68°, until the distillation temperature had risen to the boiling point of pure alcohol. This procedure was repeated after the eighth hour of refluxing. Little or none of the distillate came over below 68°. After four hours of refluxing, the sulfuric acid was neutralized by the cautious addition of 10 g. of calcium carbonate, after which the mixture was filtered and the precipitate washed by trituration with a small amount of 95% alcohol. The alcohol was distilled from the combined filtrate and washings under reduced pressure and the residual sirup taken up in 25–30 cc. of water. The solution was made basic with sodium bicarbonate and extracted four times with 20-cc. portions of ether. After drying of the extract and removal of the ether the product was distilled *in vacuo*. A light yellow oil boiling at 154–156° at 3 mm. was obtained; yield, 8.3 g. (64%); $n^{20}D$ 1.4924.

Anal. Calcd. for $C_{10}H_{17}O_4NS$: S, 12.96. Found: S, 12.90. The ester formed a hydrochloride, m. p. 148°.

Anal. Calcd. for $C_{10}H_{18}O_4NSCl$: Cl, 12.49. Found: Cl, 12.45.

β-Diethylaminoethyl Ester of Thiamorpholine-3,5-dicarboxylic Acid (Trihydrochloride).—To 3.3 g. of the diethyl ester of thiamorpholine-3,5-dicarboxylic acid were added 50 cc. of freshly distilled β-diethylaminoethanol and 0.2 g. of sodium. The mixture was then refluxed for one and one-half hours in a flask fitted with an efficient frac-

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[1] This paper is constructed from the Dissertations of Helen I. Miner and Edwin O. Hook which were submitted in candidacy for the degree of Doctor of Philosophy at Yale University, June, 1939.

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[3] R. D. Coghill, THIS JOURNAL, **59**, 801 (1937).

tionating column equipped with a total-condensation variable take-off stillhead. The ethyl alcohol formed in the alcoholysis was fractionated from the mixture at frequent intervals. About 1.5 cc. of material boiling below 150° was separated during the course of the reaction. The excess β-diethylaminoethanol was removed from the reaction mixture by distillation on the steam-bath under reduced pressure, and the residue was dissolved in a small amount of ice-water. The solution was extracted three times with ether and the extracts washed three times with ice-water and dried. On passing hydrogen chloride into the ether solution the product separated as a dark tar which was recrystallized from *n*-butyl alcohol; m. p. 208°, (dec.); yield, 1.3 g. (17%).

Anal. Calcd. for $C_{18}H_{38}O_4N_3SCl_3$: C, 43.3; H, 7.7; N, 8.4; S, 6.4; Cl, 21.3. Found: C, 43.9; H, 7.8; N, 8.5; S, 6.2; Cl, 20.3.

γ-Diethylaminopropyl Ester of Thiamorpholine-3,5-dicarboxylic Acid (Trihydrochloride).—This substance was prepared in the same general fashion as just described for the β-diethylaminoethyl ester; m. p. 215° (dec.).

Anal. Calcd. for $C_{20}H_{42}O_4N_3SCl_3$: N, 7.97. Found: N, 7.98, 7.71.

Thiamorpholine-3,5-di-(β-diethylaminoethyl)-carboxamide.—A mixture of 1 g. of the diethyl ester of thiamorpholine-3,5-dicarboxylic acid and 1.5 g. of β-diethylaminoethylamine was heated to 160–170° for twelve hours in an open test-tube supported in a Wood's metal bath. Excess amine was removed from the reaction mixture by distillation on the steam-bath under reduced pressure. The residue was dissolved in 50 cc. of dry ether and the product precipitated as the hydrochloride by adding an ethereal solution of hydrogen chloride. The material so obtained was a tan-colored, very hygroscopic, crystalline solid. It was purified by dissolving in hot absolute alcohol, adding ether to the point of turbidity, and allowing to cool. After four such recrystallizations a pure white, practically non-hygroscopic product was obtained which decomposed in the neighborhood of 245°, depending on the rate of heating; yield, 1.1 g. (55%).

Anal. Calcd. for $C_{18}H_{40}O_2N_5SCl$: C, 43.5; H, 8.1. Found: C, 43.0; H, 8.3.

We gratefully acknowledge a grant from Sharp and Dohme which made possible a part of this work.

Summary

Some new derivatives of thiamorpholine-3,5-dicarboxylic acid have been prepared, several of them having interesting pharmacological potentialities.

NEW HAVEN, CONN. RECEIVED APRIL 24, 1940

[CONTRIBUTION FROM THE HOSPITAL OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

The Structure of Trimethyl Glucurone

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Pryde and Williams[2] have prepared from glucurone a crystalline trimethyl derivative which they regard to be 1,2,4-trimethylglucurone (I). Although no evidence substantiating this structure has been presented, Marrack and Carpenter[3] also refer to the trimethylglucurone as having this structure. Such a substance on hydrolysis and oxidation might be expected to yield 2,4-dimethylsaccharic acid, which is wanted as a reference compound in this Laboratory.

When the trimethylglucurone, m. p. 129–130°, was prepared, its properties were found to resemble those of a methylfuranoside more than the methylpyranoside called for by structural formula I. On acid hydrolysis reducing sugar was liberated at the rapid rate characteristic of methylfuranosides.[4] Pryde and Williams have noted the rapid fall in rotation when trimethylglucurone is dissolved in methanol containing hydrogen chloride. It is now shown that this fall in rotation is accompanied by the formation of an isomeric trimethylglucurone, m. p. 90–91°, having a low rotation. This suggests the rapid mutarotation which Levene and Meyer[5] have observed for α- and β-methylfuranosides under similar conditions.

The high melting trimethylglucurone was hydrolyzed and oxidized to a dimethylsaccharic acid which was characterized as the crystalline diamide. When the crude dimethylsaccharic acid was esterified with cold ethereal diazomethane, no crystalline dimethylsaccharic acid esters or lactone esters were obtained; instead there was produced an unsaturated dimethyl lactone methyl ester (II) known to have its methyl groups on positions 2 and 5.[6] This

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[5] P. A. Levene and G. M. Meyer, *J. Biol. Chem.*, **74**, 701 (1927).

[6] O. Th. Schmidt, H. Zeiser and H. Dippold, *Ber.*, **70**, 2402 (1937).