

[CONTRIBUTION FROM THE OTHO S. A. SPRAGUE MEMORIAL INSTITUTE AND THE DEPARTMENTS OF PATHOLOGY AND MEDICINE, THE UNIVERSITY OF CHICAGO]

## Substituted Dialuric and Hydurilic Acids<sup>1</sup>

BY C. M. MARBERG AND D. W. STANGER

In the study of the ideational background underlying certain psychoses in which there is a barrier to communication, there is need for a drug which will permit the physician to establish contact with the patient. Intravenously, sodium-5,5-isoamylethylbarbituric acid has this property<sup>2</sup> to a limited extent. It has the disadvantage that the interview is terminated after a few minutes by the hypnotic effect of the drug. As part of a program to investigate some barbituric acid derivatives from this point of view, we decided to prepare and study the bibarbituric acids, 5,5'-diethylhydurilic and 5,5'-diisoamylhydurilic acid. As by-products in one method of preparation of these compounds, we also obtained the 5-hydroxy barbituric acids, ethyldialuric and isoamylodialuric acids.

Upon intraperitoneal injection of aqueous solutions of the sodium salts of these barbituric acid derivatives into rats, the following results were obtained. Sodium diethylhydurilate, in a dose of 500 mg. per kg. caused no depression. Sodium diisoamylhydurilate, up to 200 mg. per kg., caused no depression, but caused death by circulatory failure in a dose of 500 mg. per kg. Sodium ethyldialurate and sodium isoamylodialurate caused no depression in doses as high as 2 g. per kg. The results of further pharmacological tests will be published in detail elsewhere.

It was first planned to prepare the 5,5'-disubstituted bibarbituric acids from a tetraethyl ester prepared by the reaction of a monobromo-monoalkyl-substituted malonic diethyl ester and the sodium salt of a monoalkyl-substituted malonic diethyl ester. This should permit the ultimate synthesis of unsymmetrical as well as symmetrical dialkyl bibarbituric acids. Two difficulties were encountered. First, the yield of the bimalonic tetraethyl ester was poor, 21 to 24% in the case of the symmetrical diethyltetracarboethoxyethane. This is in agreement with the work of Bischoff,<sup>3</sup> who obtained only a 17% yield of the same ester. Second, attempts to prepare diethylbibarbituric

acid, 5,5'-diethylhydurilic acid, from the symmetrical diethyltetracarboethoxyethane by condensation with urea in the usual manner with sodium ethylate were unsuccessful; unchanged ester was recovered. Conrad and Bischoff<sup>4</sup> failed to condense symmetrical tetracarboethoxyethane with urea in the presence of phosphorus oxychloride or phosphorus pentachloride.

The oxidation of the 5-monosubstituted barbituric acids to form 5,5'-disubstituted hydurilic acids, reported by Aspelund,<sup>5</sup> appeared to offer the best method. The preparation of the 5-ethyldialuric and 5,5'-diethylhydurilic acids was repeated and two new compounds, 5-isoamylodialuric and 5,5'-diisoamylhydurilic acids were prepared. For characterization, a benzoyl derivative of the 5-isoamylodialuric acid was prepared and the acid was also hydrolyzed to the isoamyltartronic acid.

### Experimental Part

**5-Ethylbarbituric Acid.**—This acid was prepared according to the method of Fischer and Dilthey as described by v. Merkatz.<sup>6</sup> Our product melted at 196–196.5°.

**5-Ethyldialuric Acid.**—This acid was prepared according to the method of Aspelund<sup>5</sup> and melted at 224.5–225°.

**5,5'-Diethylhydurilic Acid.**—This acid was prepared according to the directions of Aspelund<sup>5</sup> and melted with decomposition at 328°. Aspelund reports that it melts above 310° with previous darkening and evolution of gas.

**5-Isoamylbarbituric Acid.**—This acid was prepared by the Fischer–Dilthey synthesis following Volwiler's<sup>8</sup> directions, and melted at 246–246.5°.

**5-Isoamylodialuric Acid.**—The preparation of this acid was carried out according to the method of Aspelund<sup>5</sup> with slight modifications. A mixture of 2.1 g. of monoisoamylbarbituric acid and 25 cc. of 3% hydrogen peroxide was refluxed for an hour. The crystals obtained on cooling weighed 1.57 g. when dry and melted at 179.5–180°. Concentration of the mother liquor to 5 cc. increased the yield by 0.46 g., m. p. 176.5°.

Twelve and seven-tenths grams of isoamylbarbituric acid was ground to a fine paste with a small amount of water and transferred to a 1-liter Erlenmeyer flask with 100 cc. of water. After adding 1.5 cc. of concentrated sulfuric acid, the barbituric acid was oxidized by the slow addition of 0.2 N potassium permanganate solution from a dropping funnel. The flask was well shaken during the addition

(1) Presented before the Division of Medicinal Chemistry at the meeting of the American Chemical Society, Boston, Massachusetts, September 12, 1939.

(2) Bleckwenn, *Arch. Neurol. Psychiatry*, **24**, 365–372 (1930).

(3) Bischoff, *Ber.*, **21**, 2085 (1888).

(4) Conrad and Bischoff, *Ann.*, **214**, 70 (1882).

(5) Aspelund, *J. prakt. Chem.*, **136**, 329–344 (1933).

(6) Von Merkatz, *Ber.*, **52**, 869 (1919).

(7) Stem corrections have been applied to all melting points recorded in this paper.

(8) Volwiler, *This Journal*, **47**, 2239 (1925).

and heated from time to time to decolorize the permanganate. When 400 cc. had been used and the suspension in the flask was at the boiling point, the further addition was continued until the brown color no longer could be discharged by boiling. This required an additional 200 cc. together with 1 cc. of concentrated sulfuric acid. When the suspension was cool, the brown solid was collected on a Büchner funnel, well washed with water and dried; yield 8.4 g. The filtrate and washings were combined and concentrated to 50 cc. On cooling, crystals of crude isoamyldialuric acid were obtained; yield 4.4 g. The acid was purified by boiling an aqueous solution with norite, filtration and crystallization: yield 3.4 g., m. p. 179.5°. The melting point of a mixture of the isoamyldialuric acid obtained by this procedure with that obtained by the peroxide oxidation showed no depression.

*Anal.* Calcd. for  $C_9H_{14}O_4N_2 \cdot 2H_2O$ :  $H_2O$ , 14.40. Found:  $H_2O$ , 14.12. Calcd. for  $C_9H_{14}O_4N_2$ : C, 50.46; H, 6.59; N, 13.08. Found: C, 50.56; H, 6.36; N, 12.86.

**Hydrolysis of 5-Isoamyldialuric Acid.**—One-half gram of the acid was added to a solution of 2 g. of sodium hydroxide in 4 cc. of water. Foaming and vigorous evolution of ammonia resulted, and the flask was placed in a steam oven overnight. The residue was dissolved in water, the solution made acid to congo red paper with hydrochloric acid and extracted with ether. The ether extract was concentrated to a small volume, a few cc. of benzene added, and the solution boiled to remove the ether. On cooling, 0.22 g. of isoamyltartronic acid was obtained, which melted with evolution of gas at 134.5°. The melting point of a mixture of this acid and isoamyltartronic acid prepared by the hydrolysis of bromo-isoamylmalonic diethyl ester, method of Braun and Nelles,<sup>9</sup> showed no depression.

**5-Benzoyl-5-isoamyldialuric Acid.**—One-half gram of 5-isoamyldialuric acid was added to 5 cc. of benzoyl chloride and the mixture was heated slowly to 200–210° in an oil-bath. Solution was almost immediate, followed

(9) Braun and Nelles, *Ber.*, **66B**, 1466 (1933).

by gradual evolution of hydrogen chloride. On cooling, crystals were obtained by scratching the walls of the flask with a stirring-rod. The reaction mixture was transferred to a centrifuge tube with ligroin and the crystals were washed several times with this solvent. The slightly brown crystals were dissolved in alcohol, boiled with norite, filtered, and the filtrate diluted with water. After standing for several days the crystals which formed were collected; yield 0.5 g. and m. p. 210.5–216°.

*Anal.* Calcd. for  $C_{16}H_{18}O_6N_2$ : N, 8.80. Found: N, 8.88.

**5,5'-Diisoamylhydurilic Acid.**—This acid which was present in the insoluble residue from the preparation of 5-isoamyldialuric acid by the permanganate method was dissolved in acetone and filtered from the manganese oxide. The acetone was diluted with water and the crystals which formed on standing were collected and air-dried; yield 5.3 g. The acid darkened and melted with decomposition at 290°.

*Anal.* Calcd. for  $C_{18}H_{26}O_6N_4 \cdot 2H_2O$ :  $H_2O$ , 8.37. Found:  $H_2O$ , 8.34. Calcd. for  $C_{18}H_{26}O_6N_4$ : C, 54.81; H, 6.65; N, 14.21. Found: C, 54.82; H, 6.52; N, 14.06.

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### Summary

A new bibarbituric acid derivative, 5,5'-diisoamylhydurilic acid, and a new 5-hydroxybarbituric acid, isoamyldialuric acid, have been prepared. Solutions of the sodium salts of these compounds and of the corresponding ethyl compounds have no appreciable effect when injected into rats.

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## Vapor Pressures and Accommodation Coefficients of Four Non-Volatile Compounds. The Vapor Pressure of Tri-*m*-cresyl Phosphate over Polyvinyl Chloride Plastics

BY FRANK H. VERHOEK AND A. L. MARSHALL

The vapor pressures and accommodation coefficients of the non-volatile organic compounds useful as plasticizers are data of fundamental importance in interpreting the losses of plasticizers which occur from plastics under certain conditions. Such data are given below for pure samples of di-*n*-butyl phthalate, tri-*m*-cresyl phosphate, tri-*p*-cresyl phosphate, and dibenzyl sebacate. The experimental methods employed were: measurements of the rate of effusion of

saturated vapor through various tubes and through a small hole in a thin plate; measurements of the rate of evaporation from a free surface; measurements of the vapor pressure by a static method similar to that of Hickman, Hecker and Embree.<sup>1</sup> The vapor pressures of tri-*m*-cresyl phosphate over polyvinyl chloride plastics in which it served as plasticizer were determined by the static method.

(1) Hickman, Hecker and Embree, *Ind. Eng. Chem., Anal. Ed.*, **9**, 264 (1937).