stitute, National Institutes of Health, The Public Health Research Institute of the City of New York, Inc., and the Albert and Mary Lasker Foundation. The cholic acid used in this study was generously supplied by the Ames Co.

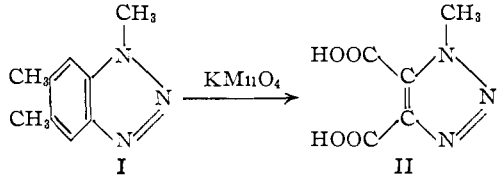
COLUMBIA UNIVERSITY RESEARCH SERVICE
GOLDWATER MEMORIAL HOSPITAL
WELFARE ISLAND, NEW YORK 17, N. Y.

The Preparation of 1,5,6-Trimethylbenzotriazole and 1-Methyl-v-triazole-4,5-dicarboxylic Acid

BY G. W. E. PLAUT[1]

RECEIVED JUNE 9, 1954

During the course of an investigation of riboflavin biosynthesis[2] it was desired to convert one of the products of chemical degradation of the vitamin, 1,2-dimethyl-4-amino-5-methylaminobenzene, to 1,-5,6-trimethylbenzotriazole (I), and the latter to 1-methyl-v-triazole-4,5-dicarboxylic acid (II). These triazole derivatives have not been described previously in the literature.



I II

1,5,6-Trimethylbenzotriazole was prepared in two ways. In the first method 1,2-dimethyl-4-amino-5-methylaminobenzene was treated with nitrous acid by a modification of the procedure of Zincke.[3] The desired product was obtained in 30–40% yield. 1,5,6-Trimethylbenzotriazole also was synthesized by treatment of 5,6-dimethylbenzotriazole with dimethyl sulfate under conditions analogous to those described for the preparation of N-methylbenzotriazoles by Krollpfeiffer, *et al.*[4] The resulting 1,5,6-trimethylbenzotriazole and 2,5,6-trimethylbenzotriazole were separated by passage of hydrogen chloride gas through a dry ether solution of the mixture of these isomeric benzotriazoles. The more basic 1,5,6-trimethylbenzotriazole precipitates as a hydrochloride under these conditions.[4] The starting compound, 5,6-dimethylbenzotriazole, was prepared by the reaction of 1,2-dimethyl-4,5-diaminobenzene with nitrous acid under the conditions described for the synthesis of benzotriazole.[5] The melting points of 1,5,6-trimethylbenzotriazole prepared by either procedure were in agreement and no depression occurred upon mixing.

A second compound, presumably 2,5,6-trimethylbenzotriazole, was recovered from the ether mother liquor after the removal of 1,5,6-trimethylbenzotriazole as the hydrochloride. This compound had a melting point only 6° below that of 1,5,6-trimethylbenzotriazole but showed a marked depression of melting point when mixed with the latter.

It was shown by Bladin[6] that benzotriazole can be converted to v-triazole-4,5-dicarboxylic acid by oxidation with potassium permanganate. When either 1-methylbenzotriazole or 1,5,6-trimethylbenzotriazole was treated in this manner, 1-methyl-v-triazole-4,5-dicarboxylic acid was obtained. This dicarboxylic acid was identified further by thermal decarboxylation to 1-methyl-v-triazole which was characterized as the gold chloride double salt, m.p. 160°.[7]

Experimental

5,6-Dimethylbenzotriazole.—A sample of 11.5 g. of 1,2-dimethyl-4,5-diaminobenzene[8] was dissolved in a mixture of 9.8 ml. of glacial acetic acid and 25 ml. of water. The solution was cooled to 4°. A solution of 6.4 g. of sodium nitrite in 10 ml. of water was added. The temperature rose to 70° and the reaction was then kept at room temperature for 12 hours. The mixture was chilled to 0° for 1 hour and filtered. The residue was washed with 25 ml. of water, filtered and dried *in vacuo* at 50°. The compound was crystallized from 700 ml. of benzene. A total of 6.7 g. of product was obtained, m.p. 156–157°.

1,5,6-Trimethylbenzotriazole. Method A.—A solution of 6.7 g. of 5,6-dimethylbenzotriazole in 56 ml. of 2 *N* NaOH was prepared. To this stirred solution 6.7 ml. of dimethyl sulfate was added over a period of 15 minutes. The reaction was then placed in a boiling water-bath for 20 minutes. Upon cooling to 0° an oil formed which solidified. The mixture was filtered and the residue was taken up in 300 ml. of ether. The ether solution was dried with anhydrous $CaSO_4$. HCl gas was passed through the ether solution. A white precipitate was obtained which was washed with ether on the filter. This residue was placed in 125 ml. of boiling water; the hot aqueous solution was adjusted to *p*H 8–9 with concd. NH_4OH and left at room temperature for 12 hours. The resulting precipitate was recrystallized from 800 ml. of water, 4.1 g., m.p. 136–137°.

Anal.[9] Calcd. for $C_9H_{11}N_3$: C, 67.04; H, 6.88; N, 26.01. Found: C, 66.85; H, 6.84; N, 25.97.

The ether mother liquor obtained after the removal of the hydrochloride of 1,5,6-trimethylbenzotriazole was evaporated to dryness. The residue was taken up in 200 ml. of hot water. Sodium hydroxide was added to the hot solution till the reaction was definitely alkaline. The crystals which formed on cooling were washed with water and dried *in vacuo*, 1.2 g., m.p. 130–131°. This is presumably 2,5,6-trimethylbenzotriazole.

Anal. Calcd. for $C_9H_{11}N_3$: C, 67.04; H, 6.88; N, 26.07. Found: C, 67.39; H, 6.53; N, 25.63.

1,5,6-Trimethylbenzotriazole. Method B.—Amounts of 50 mg. of 1,2-dimethyl-4-amino-5-methylaminobenzene hydrochloride[8,10] and 24 mg. of sodium bisulfite were dissolved in 4 ml. of 0.223 *M* acetic acid at 0°. Sodium nitrite (77 mg.) in 3 ml. of water was added to the stirred solution over 1 hour. The reaction was left at 0° for 3 hours. The compound was recrystallized from water, 15 mg., m.p. 136–137°.

1-Methyl-v-triazole-4,5-dicarboxylic Acid. (a) Oxidation of 1,5,6-Trimethylbenzotriazole.—A sample of 0.5 g. of 1,5,6-trimethylbenzotriazole in 91 ml. of water was placed in a boiling water-bath. A dropwise addition of 5.5 g. of $KMnO_4$ in 25 ml. of water was made over a period of 30 minutes with stirring. The reaction was kept in the boiling water-bath for an additional 8 hours. At the end of this time enough methanol was added to discharge the purple color of permanganate. Manganese dioxide was removed and washed with 50 ml. of hot water. The combined fil-

(1) Department of Biochemistry, New York University College of Medicine, New York 16, N. Y. Supported in part by research grants from the Wisconsin Alumni Research Foundation and the National Heart Institute (No. H-1279), United States Public Health Service. This work was done during the tenure of an Established Investigatorship of the American Heart Association.

(2) G. W. E. Plaut and P. L. Broberg, *Federation Proc.*, **13**, 274 (1954).

(3) T. Zincke, *Ann.*, **311**, 290 (1900).

(4) F. Krollpfeiffer, A. Rosenberg and C. Mühlhaussen, *ibid.*, **515**, 113 (1935).

(5) R. E. Damschroder and W. D. Peterson, *Org. Syntheses*, **20**, 16 (1940).

(6) J. A. Bladin, *Ber.*, **26**, 545, 2736 (1893).

(7) O. Dimroth and G. Fester, *ibid.*, **43**, 2222 (1910).

(8) E. Noelting, A. Braun and G. Thesmar, *ibid.*, **34**, 2252 (1901).

(9) Analyses by Micro-Tech Laboratories, Skokie, Ill.

(10) R. Kuhn and K. Reinemund, *Ber.*, **67**, 1932 (1934).

trates were adjusted to *p*H 2–3 with nitric acid; 25% $AgNO_3$ was added till the precipitation was complete. The white silver salt was washed with water to remove all excess HNO_3 and $AgNO_3$. The silver salt was suspended in 35 ml. of water and treated exhaustively with H_2S. Silver sulfide was removed and the filtrate concentrated to dryness *in vacuo*. The dried residue was crystallized from 3 ml. of *n*-butyl alcohol. The resulting product was collected by filtration, washed with petroleum ether and dried *in vacuo* at 55° for 2 hours. One hundred twenty mg. of 1-methyl-v-triazole-4,5-dicarboxylic acid, m.p. 174–175° dec., was obtained. An additional 70 mg. of product could be obtained from the mother liquor by the careful addition of petroleum ether, m.p. 170° dec.

Anal. Calcd. for $C_5H_5O_4N_3$: C, 35.09; H, 2.95; O, 37.39; N, 24.56. Found: C, 35.02; H, 3.02; O, 37.28; N, 24.68.

(b) Oxidation of 1-methylbenzotriazole[4] was performed as under (a), m.p. 175–176° dec.; mixture of 1-methyl-v-triazole-4,5-dicarboxylic acid from (a) and (b), m.p. 174–175° dec.

INSTITUTE FOR ENZYME RESEARCH
UNIVERSITY OF WISCONSIN
MADISON, WISCONSIN

N-Methyl-2-pyrrolealdehyde and N-Methyl-2-hydroxymethylpyrrole

BY EDWARD E. RYSKIEWICZ AND ROBERT M. SILVERSTEIN

RECEIVED JULY 6, 1954

The formylation of pyrrole with dimethylformamide to give 2-pyrrolealdehyde, and the reduction of the aldehyde to 2-hydroxymethylpyrrole, was reported recently.[1]

A compound previously reported[2] as 2-hydroxymethylpyrrole was shown to be the pinacol formed by a bimolecular reduction of 2-pyrrolealdehyde.

This communication records the formylation of N-methylpyrrole with dimethylformamide to give N-methyl-2-pyrrolealdehyde, and the reduction of this aldehyde with sodium borohydride to the previously unreported N-methyl-2-hydroxymethylpyrrole. The elemental analysis, molar refractivity and infrared spectrum were in accord with the postulated structure. All efforts, however, to prepare a derivative of this simplest alcohol of the N-methylpyrrole series were unsuccessful, as was also the case for 2-hydroxymethylpyrrole.[1] Treatment with acetic anhydride in pyridine, benzoyl chloride and 2,4-dinitrobenzoyl chloride in pyridine and in ether with potassium carbonate, dilute aqueous potassium permanganate, picric acid, trinitrobenzene, α-naphthyl isocyanate and triphenylmethyl chloride in pyridine gave polymeric material. Shaking an ether solution of the alcohol with aqueous sodium bisulfite to remove traces of the aldehyde also resulted in polymerization of the alcohol.

Unequivocal proof of the identity of the alcohol was obtained by preparing the same compound by two other routes. The preparation of 3-hydroxymethylindole by Leete and Marion[3] by alkaline hydrolysis of gramine methiodide led us successfully to apply this technique to the methiodide of N-methyl-2-dimethylaminomethylpyrrole. A crossed-Cannizzaro reaction of N-methyl-2-pyrrolealdehyde yielded the same product. Satisfactory agreement of the boiling points, refractive indices, and infrared spectra established that the products obtained from these three diverse procedures were identical.

(1) R. M. Silverstein, E. E. Ryskiewicz and S. W. Chaikin, THIS JOURNAL, **76**, 4485 (1954).

(2) M. S. Taggart and G. H. Richter, *ibid.*, **56**, 1385 (1934).

(3) E. Leete and L. Marion, *Can. J. Chem.*, **31**, 775 (1953).

Experimental

N-Methyl-2-pyrrolealdehyde.—The procedure which was used for the formylation of pyrrole[1] was applied to N-methylpyrrole. The product was obtained in 25% yield; boiling point 73–75° (11 mm.), lit.[4] 75–76° (12 mm.); semicarbazone 206–208°, lit.[5] 207–208°.

A better yield was obtained from a simpler procedure based on the method of Rogers[6] for the formylation of 2,4-diphenylpyrrole with N-methylformanilide:

To 7.3 g. of dimethylformamide in a flask fitted with a stirrer, condenser and drying tube, was added 17.8 g. of phosphorus oxychloride. After 10 minutes, the flask was placed in a 60° bath, and 4.1 g. of N-methylpyrrole was added dropwise over a period of 30 minutes. The mixture was stirred at 60° for an additional hour, then poured on 100 g. of ice. Hydrolysis was completed by adding 75 g. of sodium acetate and heating the mixture just to boiling. The mixture was cooled and extracted with ether. The ether solution was washed with sodium carbonate, dried and evaporated, and the residue was distilled at 73–75° at 11 mm.; yield 2.7 g. (48%).

Sodium Borohydride Reduction of N-Methyl-2-pyrrolealdehyde.—A solution of 2.0 g. of sodium borohydride in 15 ml. of methyl alcohol was added portionwise to a stirred solution of 2.04 g. of N-methyl-2-pyrrolealdehyde in 10 ml. of methyl alcohol. The temperature was held below 55° by intermittent cooling. After one hour, 25 ml. of water was added. The solution was saturated with potassium carbonate, and extracted with ether. After the ether solution was dried and the ether was removed, the residue was distilled at 98–100° at 11 mm. The distillate was a moderately viscous, colorless oil; yield 1.26 g. (61%). *Anal.* Calcd. for N-methyl-2-hydroxymethylpyrrole: C, 64.8; H, 8.11; $(R)_D$, 32.2. Found: C, 64.5; H, 8.11; $(R)_D$ 31.9; $n^{20}D$ 1.5268, d^{20}_4 1.070. The infrared spectrum showed the hydrogen-bonded hydroxyl band at 3.00 μ. After two weeks in the refrigerator, the liquid crystallized. Two recrystallizations from a petroleum ether–benzene mixture gave white crystals melting at 28–30°.

Hydrolysis of N-Methyl-2-dimethylaminomethylpyrrole Methiodide.—The quaternary ammonium salt was prepared as described by Herz and Rogers.[7] Attempted alkaline hydrolysis of this compound under the very mild conditions used by Leete and Marion[3] for gramine methiodide was not successful. The desired alcohol was obtained, albeit in poor yield, as follows: To a stirred refluxing mixture of 125 ml. of 10% sodium hydroxide and 125 ml. of benzene was added, over a period of 20 minutes, 7.0 g. of N-methyl-2-dimethylaminomethylpyrrole methiodide in 75 ml. of water. After refluxing for an additional hour, the benzene layer was separated. The residue following evaporation of the benzene weighed 0.60 g. The aqueous alkaline solution was refluxed and stirred with another 125-ml. portion of benzene for three hours. An additional 1.1 g. of residue was thus extracted. Distillation of the combined residues gave 0.30 g. (11%) of a moderately viscous oil which distilled at 95° at 11 mm., $n^{20}D$ 1.5268. The infrared spectrum was identical with that of the product obtained by sodium borohydride reduction of N-methyl-2-pyrrolealdehyde.

Crossed-Cannizzaro Reaction of N-Methyl-2-pyrrolealdehyde.—A procedure for the preparation of *p*-tolylcarbinol[8] was adapted for our purpose: To a solution of 3.0 g. of potassium hydroxide in 6 ml. of methyl alcohol was added a mixture of 2.33 g. of N-methylpyrrolealdehyde and 2 ml. of formalin (37% formaldehyde). The mixture was allowed to stand overnight at room temperature, held at 60° for one hour, diluted with 20 ml. of water, saturated with potassium carbonate and extracted with ether. The ether solution was dried, the solvents removed and the residue was distilled at 11 mm. in a Claisen flask. A forerun of 1.0 g.

(4) E. Fischer, *Ber.*, **46**, 2504 (1913).

(5) H. Fischer and H. Orth, "Die Chemie des Pyrrols," Vol. I, Edwards Bros., Ann Arbor, Mich., 1943, p. 175.

(6) M. A. T. Rogers, *J. Chem. Soc.*, 596 (1943).

(7) W. Herz and J. L. Rogers, THIS JOURNAL, **73**, 4921 (1951).

(8) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 590.