2-Pyrrolealdehyde, 3-Hydroxymethylindole and 2-Hydroxymethylpyrrole

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Received March 29, 1954

In the course of an investigation, it was necessary to prepare 2-pyrrolealdehyde, 3-hydroxymethylindole and 2-hydroxymethylpyrrole. They were prepared by novel and convenient procedures. Some of our findings were at variance with the literature.

The formylation of indole and of thiophene with dimethylformamide has been described previously,[1,2] but the application of this procedure for the formylation of pyrrole does not appear to have been reported. The direct formylation of pyrrole with dimethylformamide gave 2-pyrrolealdehyde in 59% yield, which represents a considerable improvement over previous preparations.

In a recent paper,[3] Leete and Marion described the reduction of 3-indolealdehyde with lithium aluminum hydride to skatole. The expected 3-hydroxymethylindole was not isolated. They prepared this alcohol in good yield by alkaline hydrolysis of gramine methiodide, and definitely established its identity; the compound was described as colorless leaflets which melted at 99–100° after recrystallization from benzene. Madinaveitia[4] reported a melting point of 90° for the same compound. Reduction by us of 3-indolealdehyde with sodium borohydride gave 3-hydroxymethylindole in 86% yield. The authenticity of the product was confirmed by the analytical results, and by the similarity of its infrared spectrum with that reported by Leete and Marion. A study of the melting behavior of our compound reconciled the discrepancy between the previously reported melting points. By varying the rate of heating and the initial temperature of the block, it was possible to obtain apparent melting points anywhere between 85° and 100°. Apparently the compound decomposes at temperatures near its melting point. Starting at 80° and increasing the temperature 2° per minute, the "melting" point obtained was 90–91°.

The reduction of 2-pyrrolealdehyde with sodium borohydride gave a 71% yield of a moderately viscous liquid distilling at 81–83° at 2 mm. The carbon and hydrogen values, molecular weight and molar refractivity were in good agreement with those calculated for 2-hydroxymethylpyrrole. Its infrared absorption spectrum, like that of 3-hydroxymethylindole, showed the N–H bond stretching peak at 2.97 mμ and a shoulder at about 3.05 mμ ascribed to hydrogen-bonded hydroxyl. The same product was obtained in 59% yield by a lithium aluminum hydride reduction of 2-pyrrolealdehyde wherein the hydride was added to the aldehyde; the normal reduction procedure gave lower yields. A similar observation was made by Herz and Courtney[5] on 2-acetylpyrrole. Catalytic hydrogenation over Pd–C was very sluggish. The use of Raney nickel resulted in a low boiling mixture which was not further investigated.

Taggart and Richter[6] reported the preparation of a crystalline material melting at 117.5–118° which they called 2-hydroxymethylpyrrole. It was prepared by sodium amalgam reduction of 2-pyrrolealdehyde. This preparation was repeated by us, and the compound described was obtained in rather low yield. Its molecular weight was 196 by cryoscopy in water. Oxidation with potassium periodate gave 2-pyrrolealdehyde which was identified by its melting point, and a mixed melting point with an authentic sample. In view of this, and considering the high melting point of the compound, it seems likely that it is the pinacol rather than the alcohol. Bimolecular reductions of aromatic aldehydes with metal amalgams are not uncommon.

In view of the reported instability of some of the higher homologs of 2-hydroxymethylpyrrole, it was expected that the first member of the series would be highly unstable. Actually, the distillate was a water-white liquid which could be kept for a week or more in the refrigerator with only slight yellowing and resinification. However, it has not been possible to prepare a derivative of this compound by any of the usual procedures. The same difficulty was noted by Leete and Marion[3] for 3-hydroxymethylindole, and by Herz and Courtney[5] for 2-pyrrolemethylcarbinol, although Taylor[7] was able to acetylate 2-hydroxymethylindole.

Experimental

2-Pyrrolealdehyde.—The procedure of Shabica, *et al.*,[8] for the formylation of indole with N-methylformanilide was modified to accomplish the formylation of pyrrole with dimethylformamide:

To 14.6 g. of dimethylformamide in a 1-liter, 3-neck flask fitted with a stirrer, condenser and drying tube, was added 35.6 g. of phosphorus oxychloride. After 15 minutes, 150 ml. of ethylene dichloride was added, and the solution was cooled in an ice-bath. Pyrrole (6.9 g.) was added in small portions at such a rate that the temperature remained below 10°. Finally, 40 g. of finely divided calcium carbonate was added and the temperature was raised slowly. At about 30–40°, a strongly exothermic reaction with evolution of hydrogen chloride commenced, which could be controlled by vigorous stirring and external cooling. When the initial reaction subsided, the mixture was refluxed for 30 minutes, then cooled in an ice-bath while a solution of 150 g. of sodium acetate in 200 ml. of water was slowly added. The reflux condenser was replaced by a take-off condenser, and the mixture was distilled to remove the ethylene dichloride. The hot solution was filtered, and the filtrate and precipitate were extracted with ether. The ether solution was washed with sodium carbonate, dried and evaporated. The residue was dissolved in petroleum ether (65–110°), treated with Norit, filtered hot, cooled and the solid filtered. By this procedure, 5.8 g. (59%) of light pink crystals which melted at 43–45° was obtained. Two more recrystallizations gave white needles melting at 45–46°, lit.[9] 45°; oxime 165–166°, lit.[9] 164.5°.

Sodium Borohydride Reduction of 3-Indolealdehyde.—A solution of 1.0 g. of sodium borohydride in 15 ml. of methyl alcohol was added in one portion to a stirred suspension of 1.0 g. of 3-indolealdehyde in 15 ml. of methyl alcohol. A temperature rise to 30° was noted, and the suspended material dissolved. After one hour, 25 ml. of water was added, and the mixture was saturated with potassium carbonate and extracted with ether. Removal of the solvent left 0.86 g. (86%) of a white crystalline material. Recrystallization

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(1) F. T. Tyson and J. T. Shaw, This Journal, **74**, 2273 (1952).

(2) E. Campaigne and W. L. Archer, *ibid.*, **75**, 989 (1953).

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

(4) J. Madinaveitia, *J. Chem. Soc.*, 1927 (1937).

(5) W. Herz and C. F. Courtney, This Journal, **76**, 576 (1954).

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

(7) W. I. Taylor, *Helv. Chim. Acta*, **33**, 164 (1950).

(8) A. C. Shabica, E. E. Howe, J. B. Ziegler and M. Tishler, This Journal, **68**, 1156 (1946).

(9) E. Bamberger and G. Djierdjian, *Ber.*, **33**, 536 (1900).

from benzene or from a benzene–petroleum ether solution yielded platelets whose "melting" point depended on the rate of heating as described above. *Anal.* Calcd. for 3-hydroxymethylindole: C, 73.4; H, 6.16. Found: C, 73.2; H, 6.03. The infrared spectrum showed the N–H bond stretching peak at 2.97 mμ, and a shoulder at about 3.05 mμ ascribed to hydrogen-bonded hydroxyl.

The reduction was also carried out in an aqueous dioxane solution, and the same product was obtained.

Sodium Borohydride Reduction of 2-Pyrrolealdehyde.—A solution of 2.0 g. of sodium borohydride in 10 ml. of water was added over a period of ten minutes to a stirred solution of 1.8 g. of 2-pyrrolealdehyde in 30 ml. of water. The temperature rose to 42°. After one hour, the solution was saturated with potassium carbonate and extracted with ether. The ether solution was dried and evaporated, and the residue was distilled at 81–83° at 2 mm. The distillate was a colorless, moderately viscous oil; yield 1.3 g. (71%) *Anal.* Calcd. for 2-hydroxymethylpyrrole: C, 61.8; H, 7.27. Found: C, 61.9; H, 7.14; n^{20}_{D} 1.5425; d^{20}_{4} 1.130; $(R)_D$ calcd. 27.3, found 27.1; mol. wt. calcd. 97, found 104, 106 by cryoscopy in water. It was noted that the aqueous solution became slightly turbid during the measurements. By analogy with the reported behavior of 3-hydroxymethylindole,[3] probably self-condensation was occurring. The infrared spectrum showed the N–H and bonded O–H bands as described above.

Lithium Aluminum Hydride Reduction of 2-Pyrrolealdehyde.—A slurry of 0.8 g. of lithium aluminum hydride in ether was added dropwise to a stirred solution of 2.0 g. of 2-pyrrolealdehyde in 50 ml. of dry ether. The mixture was stirred for 15 minutes after the addition was completed, and the excess hydride and the organic salt were decomposed with a slight excess of water. The ether solution was filtered, dried and evaporated. Distillation of the residue gave 1.2 g. (59%) of 2-hydroxymethylpyrrole.

Acknowledgment.—The authors are indebted to Miss C. M. Brown and Mrs. Harriette Huff for the analytical determinations, and to Dr. H. J. Eding for the infrared spectra.

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The Rosenmund Reduction of Trichloroacetyl Chloride

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RECEIVED APRIL 27, 1954

It has been claimed that trichloroacetyl chloride is a product of the oxidation of tetrachloroethylene in the presence of light, chlorine or peroxides.[1] The Rosenmund reduction of trichloroacetyl chloride would be of interest as a method of preparing chloral. When the acyl halide was reduced under modified Rosenmund conditions dichloroacetyl chloride was produced in 50–60% yields. No chloral was found. If the reduction were carried out under ordinary Rosenmund conditions[2] (in xylene at 110° using 2% palladium–barium sulfate catalyst, and a quinoline-S regulator) wherein 0.25 millimole of hydrogen chloride was evolved per minute, the acid evolution abruptly stopped when 2 moles of hydrogen chloride had appeared per mole of acid chloride (6 hr.). The product did not contain any material having a boiling point below 125°. When the reaction was stopped after the evolution of 1 mole of hydrogen chloride per mole of acid chloride, the product was a complex mixture of high-boiling substances. Attempts to obtain the reduction in refluxing *n*-heptane produced no acid.

Experimental[3]

Rosenmund Reduction of Trichloroacetyl Chloride.—A suspension of 40 g. (0.22 mole) of trichloroacetyl chloride,[4] 4 g. of 2% palladium–barium sulfate catalyst, 0.4 ml. of quinoline-S regulator and 190 ml. of Insectisol (a highly refined petroleum fraction which was refluxed over sodium, distilled, and the fraction, b.p. 190–220°, collected) was heated to 140°. Hydrogen was passed through the stirred mixture at such a rate that a millimole of hydrogen chloride per minute was collected in the aqueous exit gas scrubber. After 0.22 mole of HCl had been titrated (5 hr.) the mixture was cooled, filtered, and distilled. The fraction, 15.5 g. (50%), b.p. 104–106° (729 mm.),[5] was collected.

Anal. Calcd. for C_2HOCl_3: mol. wt., 147.4; Cl, 72.17. Found: mol. wt. (titration of hydrolysis products in 0.1 *N* NaOH), 146; Cl, 71.0.

The preparation of the dichloroacetanilide in benzene at room temperature[6] gave colored products difficult to purify. When prepared in acetone[7] at −5 to −10° using a 10% excess of aniline (mole ratio of acid chloride: aniline, 1:2.2) and recrystallized from 95% ethanol, the anilide, m.p. 117.5–118.5°, was obtained in 72% yield calculated on the acid chloride.

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[1] F. Kirkbride, U. S. Patent 2,321,823, June 15, 1943; E. Hart and M. Matheson, U. S. Patent 2,472,946, June 14, 1949.

[2] E. Hershberg and J. Cason, *Org. Syntheses*, **21**, 84 (1941).

[3] All melting points uncorrected.

[4] H. Brown, THIS JOURNAL, **60**, 1325 (1938).

[5] E. Gustus and P. Stevens, *ibid.*, **55**, 374 (1933).

[6] E. Votocek and J. Burda, *Ber.*, **48**, 1002 (1915).

[7] P. McKie, *J. Chem. Soc.*, **123**, 2213 (1923).

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The Preparation of Chalcones from Hydroxy and Methoxy Aldehydes and Ketones[1]

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RECEIVED NOVEMBER 13, 1953

Four new methoxylated chalcones,[2] of possible interest as model substances for the investigation of the structure of lignin, have been prepared from hydroxy and methoxy aldehydes and ketones. The crude products were either semisolids or oils which were purified by repeated recrystallization. The recovery of significant amounts of starting materials from each preparation was not unexpected, since condensations of this nature are reversible and the yields of pure products were relatively low. The physical properties, derivatives and analyses of the chalcones are given in Table I.

Rapid cooling of the alcoholic solution of 2′-hydroxy-3,3′,4-trimethoxychalcone produced an intimate mixture of two crystalline varieties which proved to be polymorphic forms which were separable by fractional recrystallization. Controlled cooling of the clarified solution to 50–55° during recrystallization of this chalcone produced only the crystalline prismatic variety. The isolation of minute quantities of 3′,4′,8-trimethoxyflavanone and veratric acid from the reaction mixture indicated that acid isomerization of the 2′-hydroxychalcone[3] and oxidation of the aldehyde

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[1] This note is based on a portion of a thesis submitted by Herbert E. Smith in partial fulfillment of the requirements for the degree of Master of Science at Bradley University.

[2] The number system used for the substituted chalcones is that of *Chemical Abstracts*.

[3] St. von Kostanecki and W. Szabranski, *Ber.*, **37**, 2634 (1904).