[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Cleavage of Trigonelline

BY JOHN WEIJLARD, MAX TISHLER AND JOHN P. MESSERLY

In the search of simple methods for cleaving betaines of pyridine carboxylic acids, the methods applicable to the cleavage of quaternary ammonium halides, of tertiary amines and of other betaines were investigated. The demethylation of trigonelline to nicotinic acid was not effected by inorganic sulfides, sulfites and thiosulfate reagents known to cleave quaternary ammonium halides,[1] nor could the conversion be accomplished using reagents effective in cleaving tertiary amines, as cyanogen bromide[2] and nitrous acid.[3] Unlike betaine itself, which is converted to methyl-N-dimethylaminoacetate[4] by heating at 290°, trigonelline does not undergo thermal rearrangement to methyl nicotinate. Trigonelline shows a remarkable stability toward nitric, chromic and chloric acids since attempts to demethylate trigonelline by oxidation with acidic oxidizing agents were unsuccessful.

In connection with the structure of trigonelline, E. Jahns[5] briefly reported that he obtained complete alteration of it by heating with hydrochloric acid for one day at 260–270°. On examination of this work, we found that an excellent yield of nicotinic acid can be obtained if a mixture of the two is heated at 250° for twenty-seven hours.[6]

A more convenient and practical method for demethylating trigonelline, whereby nicotinic acid is obtained in excellent yields, consists of heating a mixture of trigonelline and pyridine hydrochloride at about 200°. In this reaction methyl chloride is not evolved as in the cleavage of trigonelline by hydrochloric acid. Instead *trans*-methylation occurs—the by-product being N-methylpyridinium chloride. The formation of the latter in the reaction mixture was established by treating the nicotinic acid-free mother liquor with hydrobromic acid and bromine and isolating the well-defined dibromide of N-methylpyridinium bromide.[7] Quinoline hydrochloride is apparently effective in demethylating trigonelline. However, under the conditions of reaction, decarboxylation of nicotinic acid to pyridine occurs.

The betaine of N-methyl-α-picolinic acid reacts with pyridine hydrochloride at lower temperatures. Since α-picolinic acid readily loses carbon dioxide under these conditions, pyridine and not α-picolinic acid is the product.

The limits and scope of this demethylation reaction have not been investigated. It is interesting to note, however, that pyridine hydrochloride is known to cleave alkyl phenol ethers. Although aniline hydrochloride is also effective in cleaving phenol ethers under certain conditions,[8] it does not demethylate trigonelline.

Experimental

Cleavage of Trigonelline

(a) **By Pyridine Hydrochloride.**—Two grams of trigonelline hydrate were mixed with 6 g. of pyridine hydrochloride and held in a vessel open to the atmosphere at 200–204° for two hours. The reaction mixture was dissolved in 125 cc. of water, about 5 g. of sodium hydroxide was added and the solution was distilled until the excess pyridine had been removed. The pyridine-free solution was neutralized with dilute sulfuric acid and heated to boiling, a hot solution of 2 g. of copper sulfate in 20 cc. of water was added, and the mixture was cooled to room temperature. The copper nicotinate was filtered off, washed with water, suspended in 100 cc. of water and decomposed with hydrogen sulfide. After filtering the mixture, the filtrate and washings were taken to dryness; yield 1.33 g. nicotinic acid, 83%. After one crystallization in water, the acid melted at 235–237°. *Anal.* Calcd. for $C_6H_5NO_2$: C, 58.53; H, 4.09; N, 11.38. Found: C, 58.88; H, 4.21; N, 11.58. The over-all yield of pure acid was 72%.

(b) **By Concentrated Hydrochloric Acid.**—The best yields of nicotinic acid were obtained by heating 1 g. of trigonelline in 15 cc. of concentrated hydrochloric acid in a sealed tube at 250° for twenty-seven hours. After removing the hydrochloric acid from the reaction mixture by distillation, the residue was worked up in the manner described above. The yield of pure nicotinic acid was 83%.

Isolation of N-Methylpyridinium Bromide Dibromide.—For identifying the by-product in the pyridine hydrochloride reaction, the aqueous, pyridine-free solution of the product, prepared as above from 3 g. of trigonelline and 9 g. of pyridine hydrochloride, was neutralized with hydrobromic acid and treated with copper bromide to remove the nicotinic acid. After removal of the excess copper by treatment with hydrogen sulfide, the solution was concentrated to 25 cc. under reduced pressure and 10 cc. of 40% hydrobromic acid were added. After further concentration to dryness, the residue was taken up in hydrobromic acid and concentrated again to dryness in order to remove all chlorides.

The residue was dissolved in 50 cc. of water, air saturated with bromine was passed through at 30–35° until the solution was saturated with bromine. The solution was chilled at 2° overnight. A heavy brown oil was separated from the solution and washed with water, then dissolved in 15 cc. of warm alcohol. Upon cooling and scratching, crystallization occurred. The orange-yellow crystals were collected on a filter and washed with cold alcohol, then ether; yield 1.80 g., m. p. 65–66°.

Anal. Calcd. for $C_6H_6NBr_3$: C, 21.57; H, 2.41; N, 4.20. Found: C, 21.77; H, 2.46; N, 4.18.

Other Attempts at Demethylation.—No nicotinic acid was formed when aqueous solutions of trigonelline were boiled with sodium sulfide, sodium thiosulfate, sodium sulfite, or ammonium sulfide. With cyanogen bromide[2] a bromo compound of unknown structure was obtained

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[1] Snyder and Speck, THIS JOURNAL, **61**, 668, 2895 (1939).

[2] von Braun, *Ber.*, **47**, 2312 (1914); **63**, 490 (1930).

[3] Speyer and Walther, *ibid.*, **63**, 852 (1930).

[4] Willstätter, *ibid.*, **35**, 585 (1902).

[5] E. Jahns, *ibid.*, **20**, 2840 (1887).

[6] Apparently H. Maier-Bode and J. Altpeter, "Das Pyridine und Seine Derivate in Wissenschaft und Technik," 1934, p. 224 failed to mention Jahns' findings. Their statement that trigonelline is not attacked by concentrated hydrochloric acid at 260° is incorrect.

[7] Trowbridge and Diehl, THIS JOURNAL, **19**, 565 (1897).

[8] Prey, *Ber.*, **74B**, 1219 (1941).

which did not form nicotinic acid when subjected to acid or to alkaline hydrolysis.

Nitrous acid treatments[3] did not effect demethylation. Trigonelline is apparently stable toward boiling nitric acid, even in the presence of oxidizing catalysts. Concentrated sulfuric acid at 300° and 65% oleum at 125°, with or without mercury as catalyst, also do not alter trigonelline. Chlorates, bromates, chromates and hypochlorites were also tried under a variety of conditions, without the formation of nicotinic acid.

Aniline hydrochloride was substituted for pyridine hydrochloride in the above outlined experiment with negative result. When quinoline hydrochloride was used, pyridine was produced which indicated demethylation with accompanying decarboxylation. Betaine N-methyl-α-picolinic acid reacts with pyridine hydrochloride already at 140° with formation of pyridine.

Summary

Pyridine hydrochloride effects the cleavage of methyl betaines of pyridinecarboxylic acids. With trigonelline the products are nicotinic acid and N-methylpyridinium chloride.

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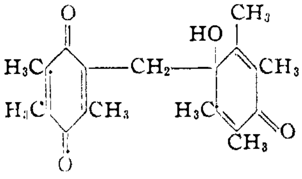
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Reaction between Quinones and Metallic Enolates. XIX.[1] The Structure of Diduroquinone

BY LEE IRVIN SMITH, ROY W. H. TESS AND GLENN E. ULLYOT

Duroquinone, in the presence of alkaline reagents in polar solvents, is converted into an orange dimer, diduroquinone.[2,3] The dimer was shown by Rugheimer and Hänkel[3] to contain a hydroxyl group, to yield durohydroquinone upon reduction, and to give duroquinone upon pyrolysis. These properties were considered to support structure I for the substance, rather than structure II, even though the compound could not be dehydrated.



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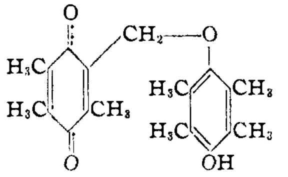
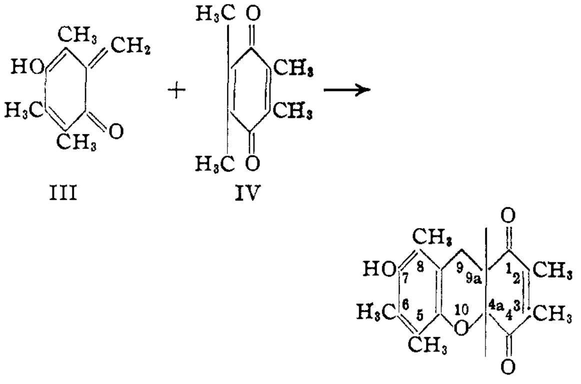


II

Diduroquinone was encountered very early in the work described in this series of papers[4] and although it was felt that neither structure I nor II adequately represented the substance, no clue to a more satisfactory structure for the dimer was found until recently. Through considerations advanced in connection with the mechanism whereby methylated quinones are converted into coumarins[5] it appeared that the structure of diduroquinone might be V, formed as a result of a diene reaction between duroquinone IV and its tautomer III, as shown.



III IV

V

The properties of diduroquinone described in the present paper support the structure V, which represents the substance as a *p*-hydroxychroman of a special type. The similarity of the adsorption spectrum of diduroquinone (Fig. 1)[6] to those of hydroduroquinone, its monoethers, various 5-hydroxycoumarans, and 6-hydroxychromans, all of which show absorption maxima between 280 and 300 mμ,[7] indicates the presence in the dimer of a benzenoid ring carrying a hydroxyl group and an ether group para to each other. Chemical evidence that diduroquinone is a *p*-hydroxychroman is supplied by the fact that the substance can be oxidized to a quinone VI, which can be reduced to an orange hydroquinone VII. The hydroquinone VII can be dehydrated, regenerating diduroquinone.

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(1) XVIII, THIS JOURNAL, **65**, 2131 (1943).

(2) v. Pechmann, *Ber.*, **21**, 1417 (1888); **22**, 2115 (1889).

(3) Rugheimer and Hänkel, *ibid.*, **29**, 2176 (1896).

(4) (a) Smith and Dobrovolny, THIS JOURNAL, **48**, 1420 (1926); (b) **48**, 1693 (1926).

(5) Smith, Arnold and Nichols, *ibid.*, **65**, 2131 (1943).

(6) A Beckman Quartz Spectrophotometer was used.

(7) (a) Morton, "The Application of Absorption Spectra to the Study of Vitamins, Hormones, and Coenzymes," Adam Hilger, Ltd. 1942, 2nd ed., pp. 108–115. (b) Webb, Smith, *et al.*, *J. Org. Chem.*, **4**, 389 (1939).