

tions, as $\log P$ against $1/T$, it was found that the curves were all straight lines and all parallel to the curve for water. At present there seems

to be no explanation for this unexpected result.

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

The Synthesis of 3-Hydroxy-2-(3)-benzofuranone and of 4-Hydroxymandelic Acid

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A number of hydroxy acids were recently investigated in regard to the treatment of urinary infections. Mandelic acid was the most effective of these,¹ and this was due in part to the fact that it was excreted unchanged in the urine. It seemed quite possible that the introduction of a phenolic hydroxyl group into this acid might increase its antiseptic action. 2-Hydroxymandelic acid appeared promising, since salicylic acid has been found to pass through the body into the urine largely unchanged,² and because it seemed possible that this hydroxymandelic acid might also be excreted partly unchanged. It was of further interest to determine the influence of the 4-hydroxy group in the bactericidal efficiency of the mandelic acid molecule.

There is but little information on 2-hydroxymandelic acid in the chemical literature. Plöschl³ treated salicylaldehyde with hydrocyanic acid in solution. The crude 2-hydroxymandelonitrile was then treated with concentrated hydrochloric acid for hydrolysis to 2-hydroxymandelic acid. The acid product was a sirup, which like the nitrile was neither purified, nor analyzed. Later Baeyer and Fritsch⁴ obtained crude 2-hydroxymandelic acid by reduction of 2-hydroxyphenylglyoxylic acid with sodium amalgam. They were unable to crystallize the crude sirupy acid, and finally converted it to the crystalline 2-hydroxyphenylacetic acid by further reduction with hydriodic acid. Rosenmund and Schindler⁵ mentioned the reaction of 2-hydroxymandelic acid with acetyl chloride to give a diacetyl derivative of m. p. 68°, but gave neither the source nor a description of their 2-hydroxymandelic acid.

(1) Rosenheim, *Lancet*, **228**, 1032 (1935). See also, Lyon and Dunlop, *Brit. Med. J.*, No. 3909, 1096 (1935); Holling and Platt, *Lancet*, **230**, 769 (1936); Cubitt, *ibid.*, **230**, 922 (1936); *Proc. Staff Meetings of the Mayo Clinic*, **11**, 231 (1936).

(2) Sollmann, "Manual of Pharmacology," 4th ed., W. B. Saunders and Co., 1932, p. 626.

(3) Plöschl, *Ber.*, **14**, 1316 (1881).

(4) Baeyer and Fritsch, *ibid.*, **17**, 974 (1884).

(5) Rosenmund and Schindler, *Arch. pharm.*, **266**, 282 (1928).

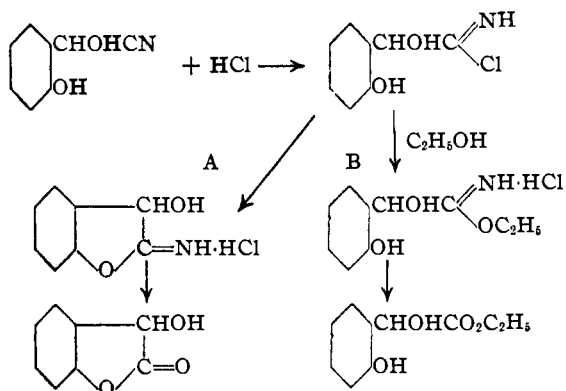
Plöschl's preparation of 2-hydroxymandelic acid was repeated carefully several times. The result was always a very small yield of a colored sirup, which would not crystallize. According to Plöschl, the aqueous solution of the acid on evaporation yielded an oil which crystallized, but a description of the solid was not given. This solid, supposed to be the lactone of 2-hydroxymandelic acid (3-hydroxy-2-(3)-benzofuranone),⁶ was obtained in these experiments, but in all cases, the products were so impure and unsatisfactory that a more detailed examination of the reactions was made.

2-Hydroxymandelonitrile was found to be an oil, which was stable for only about twelve hours at about 0°. Its distillation under high vacuum was hardly satisfactory due to decomposition. To convert certain nitriles to the acids, it has frequently been advantageous to proceed first to the imino ether hydrochloride, then to the ethyl ester and finally to the acid. Consequently, three experiments were made in which the nitrile was treated with dry hydrogen chloride and ethanol. At the ester stage, only one of the three products could be induced to crystallize partially. The analytical data indicated that the crystals were 3-hydroxy-2-(3)-benzofuranone, the lactone of 2-hydroxymandelic acid.

These results suggested that in the one case the reaction designated as A had proceeded to a greater extent than reaction B so that there was sufficient lactone present to crystallize and be isolated.

If this were true, then the lactone should be isolated without difficulty when ethanol was omitted from the reaction. This contention was verified by experiment, and this reaction has provided an excellent method of preparing the pure 3-hydroxy-2-(3)-benzofuranone.

(6) The International Rules numbering has been used for the benzofuran nomenclature.



Certain properties of 3-hydroxy-2-(3)-benzofuranone are described in the experimental section. In particular, and as might be expected, the pure lactone partially hydrolyzed to 2-hydroxymandelic acid when dissolved in water; and when an alkaline solution of the acid was acidified, the lactone was partially formed from the liberated acid.

The isomeric 4-hydroxymandelic acid has been described in the literature, but each of the four methods,⁷ by which it was obtained have certain disadvantages. For this research, 4-hydroxymandelic acid was synthesized from 4-hydroxybenzaldehyde through the intermediates: nitrile, imino ether hydrochloride and ethyl ester. This method was found to be quite satisfactory.

Aqueous solutions of 2-hydroxymandelic acid (and its lactone) and 4-hydroxymandelic acid have been tested *in vitro* against *E. Typhi* and *Staphylococcus aureus* by Dr. W. L. Sampson of the Merck Institute for Therapeutic Research. By comparing these two acids with mandelic acid, it was found that the phenolic hydroxyl group did not augment the bactericidal power of the acid.

Experimental

All analyses were micro determinations carried out by Mr. D. Hayman and Mr. S. Adler.

For satisfactory results, the details of the following preparations must be carefully observed.

2-Hydroxymandelonitrile.—Ten grams of pure salicylaldehyde was dissolved in a 10% aqueous solution of 8.6 g. of sodium bisulfite. To this was added 50 ml. of ether, and the liquids were cooled to 0–5° and stirred mechanically. A 20% aqueous solution of 4.1 g. of sodium cyanide was added from a dropping funnel, after which the stirring

(7) (1) The direct hydrolysis of *p*-hydroxymandelonitrile to the acid [Henry, *Chem. News*, **85**, 301 (1902)]. (2) The reduction of *p*-hydroxyglyoxylic acid [Ellinger and Kotake, *Z. physiol. Chem.*, **65**, 409 (1910)]. (3) The reaction of nitrous acid on *p*-hydroxyphenylaminoacetic acid [Fromherz, *ibid.*, **70**, 356 (1910)]. (4) The hydrolysis of 4- α -dibenzoyloxyphenylacetamide [Alay and Rabout, *Bull. soc. chim.*, [4] **11**, 392 (1912)].

was continued for one hour. The layers were separated, and the aqueous layer extracted with ether. The combined ethereal solutions were washed twice with 30 ml. of 10% sodium bisulfite solution each time. After removal of the ether *in vacuo* at 20°, ca. 35 ml. of dry benzene was added, and then removed *in vacuo* at 20–25°. The residue was pumped out for two to three hours at 1 mm. pressure. The yield of nitrile was 10 to 11 g. (82–90%). It was a light green tinted viscous oil. The yield was increased by further extraction of the aqueous layer.

All efforts to crystallize this oil were unsuccessful. It could be kept only about twelve hours at temperatures of 0 to 10° or lower, and after this the slow decomposition and resinification increased until the oil had become a deep red thick resin. The odor of hydrocyanic acid was noticeable.

A carefully pumped out (1 mm. pressure or lower) analytical specimen of the freshly prepared nitrile gave, on immediate analysis: found, C, 63.71, 63.57; H, 5.01, 5.10; N, 9.0. Calcd. for C₈H₇NO₂: C, 64.40; H, 4.73; N, 9.40.

When a sample of the freshly prepared nitrile was placed in a still of the alembic type at a pressure of 10⁻³ to 10⁻⁵ mm., a few drops distilled on warming the flask to about 50°. However, this slight warming caused a marked increase in the pressure of the system. Hydrocyanic acid was detected and vapors (probably salicylaldehyde) were condensed in the trap. This warming also increased the resinification of the sample. The few drops of distillate on immediate analysis gave, found: C, 64.31; H, 5.28.

3-Hydroxy-2-(3)-benzofuranone (Lactone of 2-Hydroxymandelic Acid).—Ten grams of freshly prepared nitrile that had been well pumped out at 1 mm. was dissolved in 50 ml. of anhydrous ether. This solution was cooled in an ice-bath, and dry hydrogen chloride bubbled through until a little over the theoretical amount was absorbed. The red solution was kept at 10° overnight, and then the ether was decanted from the salt. The flask was placed in a desiccator over sodium hydroxide and evacuated to 5 mm. for four hours. To the imino ether hydrochloride was added 400 ml. of water, and the flask was shaken mechanically until the solution was almost clear. A red lump of tar remained. The solution was filtered and allowed to stand at 25° for five hours. It was again filtered to remove flocculent material, and then extracted with ether five times. The residue that remained after removal of the ether by distillation was pumped out until it crystallized. The lactone was recrystallized from dry benzene until the constant value, m. p. 107–108°, was reached. The yield was 30% (based on salicylaldehyde).

Anal. Calcd. for C₈H₆O₃: C, 64.00; H, 4.03. Found: C, 64.23, 64.32; H, 4.27, 4.29.

Titration experiments indicated that 3-hydroxy-2-(3)-benzofuranone partially hydrolyzed when dissolved in warm water. When an aqueous solution of the lactone was treated with the required amount of calcium hydroxide dissolved in a large amount of water, an insoluble calcium salt formed. *Anal.* Calcd. for C₁₆H₁₄O₃Ca: Ca, 10.71. Found: Ca, 10.18, 9.97.

When the lactone was dissolved in 0.5% sodium hydroxide solution, and allowed to stand at 25°, a brown insoluble precipitate formed. This precipitate contained only a trace (0.14%) of sodium.

Anal. Found: C, 64.17; H, 5.00. The filtrate on acidification, extraction, etc., yielded a red oil.

Anal. Found: C, 60.21; H, 4.23.

When the lactone was dissolved in a 1% sodium carbonate solution and refluxed one hour, hydrolysis was complete, as was evidenced by a lack of extractable material. The alkaline solution, after acidification, extraction, etc., yielded a partially crystalline residue.

Anal. Found: C, 59.48; H, 4.83. Calcd. for the lactone: C, 64.00; for the acid, C, 57.12. Thus, these residues were mixtures of the lactone and the acid.

Obviously, the lactone partially hydrolyzed to the acid in water solution and, conversely, the acid, liberated in solution from its salt, partially formed the lactone.

4-Hydroxymandelonitrile.—Ten grams (0.082 mole) of 4-hydroxybenzaldehyde was dissolved in a warm 10% solution of 10 g. of sodium bisulfite, and cooled to 0°. The solution was covered with 50 ml. of ether, and with mechanical stirring, a 20% solution of 4.2 g. (0.086 mole) of sodium cyanide was added over a period of thirty minutes. After stirring thirty minutes longer at 0°, the layers were separated, and the aqueous one extracted further with ether. The combined extracts were washed with a 10% sodium bisulfite solution, dried over calcium chloride and then distilled at 25° or lower *in vacuo*. The nitrile was dried at 1 mm. for one to two hours. This yield of nitrile was 90%; m. p. 99–102°.⁸

Ethyl 4-Hydroxymandelate.—Eleven grams of the nitrile was dissolved in 50 ml. of anhydrous ether, and 4.6 ml. of absolute ethanol was added. Dry hydrogen chloride was bubbled through the solution at 0–5° until a little over the theoretical amount had been absorbed. After standing overnight at 10°, the ether was decanted from the imino ether hydrochloride. The salt was dried and freed of excess hydrogen chloride in a vacuum desiccator. The yield of the salt was 11.5 g.

The crude imino ether hydrochloride was shaken mechanically with 300 ml. of water until the solution was almost clear. The insoluble material was filtered, and the solution was allowed to stand at 25° for five hours. The

(8) Buck, *THIS JOURNAL*, **55**, 3388 (1933), described analytically pure 4-hydroxymandelonitrile of m. p. 98°, which was obtained in 38% yield (pure) by a technique differing in detail from this procedure.

solution was then extracted with ether, and on solvent removal, there remained 5.5 g. (34.2% as based on 4-hydroxybenzaldehyde) of ethyl 4-hydroxymandelate of m. p. 124–126°. On recrystallization (with norite) from dry benzene the constant value of m. p. 128.5–129° was obtained.

Anal. Calcd. for C₁₁H₁₂O₄: C, 61.19; H, 6.17. Found: C, 61.09; H, 6.25.

4-Hydroxymandelic Acid (Monohydrate and Anhydrous).—Three and one-half grams of the pure ethyl ester was dissolved in 110 ml. of 2% sodium hydroxide solution, and the mixture refluxed for one hour. The light brown solution was cooled and acidified with hydrochloric acid. The first ether extract removed all the colored impurities and about 0.1 g. of the acid (m. p. 79–82°). After twenty more ether extractions, and distillation of the solvent, there remained 2.4 g. (72%) of 4-hydroxymandelic acid monohydrate of m. p. 82–84°. On dissolving in benzene, and reprecipitating with petroleum ether, it melted at 83–84°.

Anal. Calcd. for C₈H₈O₄·H₂O: H₂O, 9.67. Found: H₂O, 9.66.

Anhydrous 4-hydroxymandelic acid (from the monohydrate by warming *in vacuo* at 60°) melted at 109.5–110.5°.⁹

Anal. Calcd. for C₈H₈O₄: C, 57.12; H, 4.80. Found: C, 57.42; H, 5.08.

Summary

Pure 3-hydroxy-2-(3)-benzofuranone has been made from salicylaldehyde. When this lactone was dissolved in water, it hydrolyzed partially to 2-hydroxymandelic acid. 4-Hydroxymandelic acid has been synthesized from 4-hydroxybenzaldehyde through the intermediate nitrile, imino ether hydrochloride and ethyl ester.

2- and 4-hydroxymandelic acids were not more bactericidal against *E. Typhi* and *Staphylococcus aureus in vitro* than mandelic acid.

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(9) By other methods, Fromherz⁷ found m. p. 83–84° for the monohydrate and m. p. 107–108° (Ellinger and Kotake⁷ m. p. 105–106°) for the anhydrous acid.