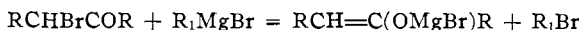


Summary

The reaction between an organic magnesium halide and an α -bromo ketone, in which the carbonyl group is relatively inactive, is represented by the equation



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[CONTRIBUTION FROM THE INSECTICIDE DIVISION, BUREAU OF CHEMISTRY AND SOILS]

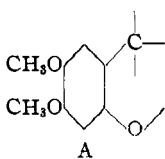
TOXICAROL. III. A RELATION BETWEEN TOXICAROL AND THE ROTENONE GROUP OF FISH POISONS

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It has been shown¹ that rotenone, deguelin and tephrosin are structurally related in that, among other things, all three compounds possess the atomic grouping represented by formula A.



As toxicarol, the other member of this group of fish poisons, is characterized by properties so similar to those possessed by the first three, it has been assumed that, in all probability, this substance has some structure common to the others. Proof of this assumption has recently been obtained as a result of a series of experiments which are described in what follows.

Permanganate oxidation of dehydrotoxicarol in acetone has yielded risic and 2-hydroxy-4,5-dimethoxybenzoic acids. In this reaction the yield of the benzoic acid was essentially the same as that obtained from dehydrodeguelin,¹ but the risic acid, although always present, was obtained in small and variable quantities.

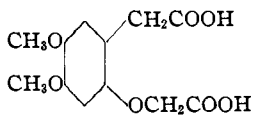
When dehydrotoxicarol was boiled gently with an alcoholic potassium hydroxide solution, the material formed an acid apparently analogous to deguelic² and derrisic³ acids, although it was impossible to obtain it in a crystalline condition. However, when the acidic material was separated from the reaction mixture, dissolved in aqueous alkali, and oxidized with potassium permanganate, risic acid was obtained. If, instead of potassium permanganate, hydrogen peroxide was used as an oxidizing agent, a good yield of derric acid was obtained. These products are the same as those formed under identical conditions with deguelic and derrisic acids, derived, respectively, from deguelin and rotenone.

¹ Clark, *THIS JOURNAL*, **53**, 3431 (1931).

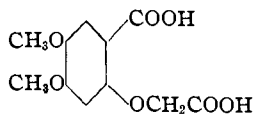
² Clark, *ibid.*, **53**, 316 (1931).

³ Butenandt and Hildebrandt, *Ann.*, **477**, 249 (1930).

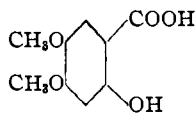
Recently LaForge⁴ has presented evidence to show that derric and risic acids have respectively the structures represented by the formulas B and C. For comparative purposes the formula for 2-hydroxy-4,5-dimethoxybenzoic acid, D, is also given.



B. Derric acid



C. Risic acid



D. 2-Hydroxy-4,5-dimethoxybenzoic acid

It thus follows that toxicarol has the same atomic grouping represented by formula A, as have rotenone, deguelin and tephrosin. As the products B, C and D are obtained in a similar manner from all four substances, it is possible that the skeletons in each, immediately adjacent to the methoxylated benzene ring, which gives rise to the side chains in the three acids, are in each case essentially the same, but with the information at present available concerning this point, it is considered unjustifiable to postulate any further statement than that which is given above.

Experimental

Permanganate Oxidation of Dehydrotoxicarol.—A mechanically stirred suspension of 5 g. of dehydrotoxicarol in 350 cc. of acetone, cooled to 0°, was oxidized with 18 g. of potassium permanganate. The reagent was added in 2-g. portions from time to time as the acetone became colorless. When the specified quantity of permanganate had been added and the reaction was completed, the manganese dioxide was removed by filtration and thoroughly extracted with boiling water. The aqueous extract was filtered, acidified to Congo red with sulfuric acid and concentrated under reduced pressure to approximately 100 cc. The concentrate was allowed to stand overnight for the 2-hydroxy-4,5-dimethoxybenzoic acid to separate. The yield was 0.7 g. When the experiment was repeated 1 g. of the product was obtained.

The crude acid was purified by boiling a slightly alkaline 1% solution of its potassium salt with hydrogen peroxide until most of the dark color was discharged, after which the liquid was acidified with acetic acid and filtered through norit. The filtrate was then heated to boiling, and the pure acid was separated by adding dilute sulfuric acid to the clear solution. It crystallized as colorless and, for the most part, twinned plates which melted with decomposition at 210°. When it was mixed with an authentic sample of 2-hydroxy-4,5-dimethoxybenzoic acid, no depression of the melting point occurred. It also gave a deep blue color with ferric chloride.

The mother liquors from the crude acid just described contained risic acid which was separated by extracting the liquid with ether. The yield of the crude acid from 5 g. of dehydrotoxicarol was in one experiment 0.1 g. and in another 0.15 g. The acid was purified by crystallization from butyl alcohol followed by a recrystallization from water. The latter process was accomplished by acidifying a hot slightly alkaline solution of the potassium salt with sulfuric acid.

The risic acid melted at 256°, and when it was mixed with an authentic sample of the acid no depression of the melting point occurred. It also possessed the optical properties characteristic of risic acid. These data, determined by George L. Keenan of the Food

⁴ LaForge, THIS JOURNAL, 53, 3896 (1931).

and Drug Administration of the U. S. Department of Agriculture, are as follows. The acid crystallized from water consists of colorless square plates and rods with square ends. Most of the rods have straight extinction, although occasionally some are found that possess inclined extinction. The elongation is negative, and the indices of refraction are as follows: η_{α} , 1.450 (± 0.002) lengthwise; η_{β} , indeterminate and η_{γ} , 1.695 (± 0.005) crosswise.

Treatment of Dehydrotoxicarol with Boiling Alcoholic Potassium Hydroxide. Ristic Acid.—A suspension of 2 g. of dehydrotoxicarol in 75 cc. of a potassium hydroxide solution, made by dissolving 15 cc. of an aqueous solution of 7.5 g. of potassium hydroxide in 60 cc. of absolute alcohol, was boiled gently for thirty minutes. The dehydrotoxicarol soon dissolved, forming a dark colored solution which, after the specified time, was poured upon 100 g. of crushed ice in a separatory funnel. The mixture was diluted with water to a volume of 500 cc., acidified with sulfuric acid, and extracted with ether. The extract was washed with water and dried, after which the solvent was removed. The residue was dissolved in 20 cc. of 1% potassium hydroxide and oxidized with a solution of 4 g. of potassium permanganate in 50 cc. of hot water. After the manganese dioxide was removed, the filtrate was concentrated to 15 cc. and acidified with sulfuric acid, causing the organic acid to separate at once. In several experiments in which 2 g. of starting material was used, the yield was small and variable. Usually it was of the order of 0.1 to 0.2 g. of ristic acid. After the crude material was purified by the method outlined before, it possessed the same properties as recorded for ristic acid above.

Derric Acid.—Two and five-tenths grams of dehydrotoxicarol was treated with alcoholic potassium hydroxide, and the acidic product was separated from the reaction mixture as outlined in the preceding paragraph.

The residue from the ethereal extract was dissolved in 25 cc. of 10% potassium hydroxide solution and treated with 10 cc. of 30% hydrogen peroxide. The solution was boiled gently until frothing ceased, then it was cooled, acidified with sulfuric acid and extracted with ether. After drying, the ethereal solution was concentrated to approximately 10 cc. and allowed to crystallize. Three-tenths gram of derric acid separated, which, after recrystallization from *n*-butyl ether, melted at 167–168°. When it was mixed with pure derric acid, no depression of the melting point occurred and the substance possessed the optical properties characteristic of derric acid.⁵

Summary

1. Dehydrotoxicarol has yielded derric, ristic and 2-hydroxy-4,5-dimethoxybenzoic acids.
2. This fact demonstrates that toxicarol contains the same atomic grouping, represented by formula A in the text, as does rotenone, deguelin and tephrosin.

WASHINGTON, D. C.

⁵ Clark, THIS JOURNAL, 53, 2369 (1931).