

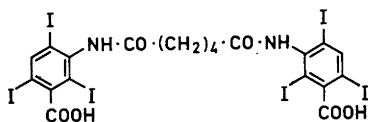
Synthesis of α,α' -Bis-(3,5-diiodo-4-hydroxyphenyl)-sebacic Acid

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Most X-ray contrast media consist of acids containing an iodinated aryl group. When two such acids are joined by an aliphatic chain, compounds possessing good X-ray diagnostic properties and low toxicity may result.

Adipic acid di-(3-carboxy-2,4,6-triiodo-anilide) (Biligradin) is such a compound, having found clinical use as a cholecystographic agent ¹.



The present note describes the synthesis of a similar type of compound, *viz.* α,α' -bis-(3,5-diiodo-4-hydroxyphenyl)-sebacic acid

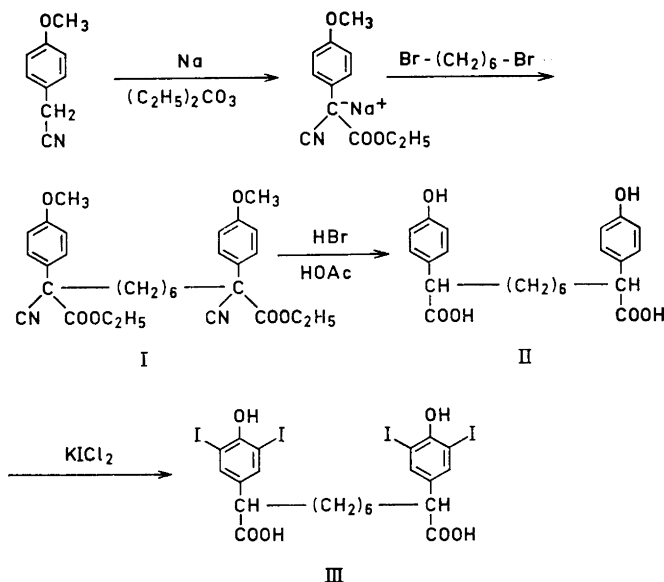
(III), which was prepared by the sequence of reactions depicted schematically below.

The acids II and III contain two asymmetric carbon atoms, hence the product of the synthesis may consist either of pure racemate or of the meso form, or may be a mixture of both. The product obtained seemed to be uniform. The acid II was partially resolved using (+)-dehydroabietylamine as the optically active base, affording a product exhibiting a small positive rotation at 589 m μ . The optical rotatory dispersion curve, however, showed a considerable rotation at lower wavelengths. Consequently, the acids II and III must have the racemic and not the meso form.

Pharmacological tests in mice showed that acid III had no affinity for any specific part of the test organism, but it exhibited a rather high general toxicity.

a,a'-Bis-(ethoxycarbonyl)-*a,a'*-bis(4-methoxyphenyl)-sebaconitrile (I). 4-Methoxybenzyl cyanide was treated with sodium and the resulting sodium salt was treated with 1,6-dibromohexane, according to the procedure outlined by Wideqvist ².

To a boiling, stirred solution of 29.5 g (0.2 mole) of 4-methoxybenzyl cyanide in 100 ml of diethyl carbonate was added in small portions



4.6 g (0.2 mole) of sodium shavings. After all the sodium had reacted, the ethanol formed was distilled off and 22.4 g (0.1 mole) of 1,6-dibromohexane was added dropwise to the boiling, stirred solution. The reaction mixture was boiled for a further 5 h, cooled, and treated with 100 ml of ice-water. The alkaline mixture was neutralised with acetic acid, the organic phase was separated, dried with sodium sulphate, and the volatile matter distilled off under vacuum. The residual reddish-brown oil neither crystallised nor could it be distilled without decomposition. It was heated to 240° at 0.5 mm Hg pressure, in order to remove all of the more volatile matter, and the resulting product was used as such in the next step without further purification.

a,a'-Bis-(4-hydroxyphenyl)-sebacic acid (II). 43 g of the crude product I was refluxed for 6 h with 220 ml of 48 % hydrobromic acid and 110 ml of glacial acetic acid. The reaction mixture was then poured onto 1 kg of crushed ice and extracted with 4 × 100 ml of ether. The combined ethereal solution was dried with sodium sulphate and the solvent distilled off, leaving a residue which crystallised upon triturating with a little benzene. The crude product was dissolved in alkali, the solution treated with active carbon and the acid precipitated out with dilute hydrochloric acid. The product thus

obtained was further purified through recrystallisation from a large quantity of water (ca. 100 ml/g crude product). Obtained 29 g (91 %) of pure white crystals, m.p. 171.5–172.5°. Further recrystallisation did not raise the melting point. (Found: C 68.2; H 6.78. Calc. for $C_{22}H_{34}O_6$: C 68.4; H 6.78).

a,a'-Bis-(3,5-diiodo-4-hydroxyphenyl)-sebacic acid (III). 11.5 g (0.03 mole) of the acid II, prepared as above, was dissolved in a small excess of 5 N sodium hydroxide and heated under vigorous stirring first with 500 ml of conc. hydrochloric acid and then immediately with 65 ml of 2 M $KICl_2$. The resulting yellow-white precipitate was filtered off after one hour and dissolved in sodium bicarbonate solution. After treatment with a saturated bisulphite solution, a light yellow product fell out, which, after recrystallisation from aqueous ethanol, afforded 17 g (63 %) of yellow needles melting at 240–241° (decomp.). (Found: C 30.4; H 2.62; I 55.7. Calc. for $C_{22}H_{22}I_4O_6$: C 29.7; H 2.49; I 57.0).

1. Priewe, H. *Chem. Ber.* **87** (1954) 651.
2. Wideqvist, S. *Arkiv Kemi Mineral. Geol.* **24 B** (1947) No. 14.

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