

Synthesis of Compounds Related to Muscarufin

II. 3,6-Dihydroxy-2,5-bis-(2-carboxyphenyl)-benzoquinone

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3,6-Di-iodo-2,5-dimethoxybenzoquinone has been converted into 3,6-di-iodo-1,2,4,5-tetramethoxybenzene, which on Ullmann coupling with methyl 2-bromobenzoate afforded 2,3,5,6-tetramethoxy-1,4-bis-(2-carbomethoxyphenyl)-benzene (I). This was transformed further into 3,6-dimethoxy-2,5-bis-(2-carbomethoxyphenyl)-benzoquinone (II) and 3,6-dihydroxy-2,5-bis-(2-carboxyphenyl)-benzoquinone (III). The last mentioned compound is related to the fungal pigments muscarufin and polyporic acid.

In the previous communication¹ the synthesis of 2,5-bis-(2-carbomethoxyphenyl)-benzoquinone was reported. The present paper deals with the synthesis of 3,6-dihydroxy-2,5-bis-(2-carboxyphenyl)-benzoquinone (III), which is interesting as an analogue of both muscarufin and polyporic acid although it has not been found in Nature.

Earlier it had been found difficult to introduce further substituents on the central nuclei of 2,5-dimethoxy-1,4-bis-(2-carbomethoxyphenyl)-benzene and 2,5-bis-(2-carbomethoxyphenyl)-benzoquinone. The most suitable approach to the synthesis of the dihydroxyquinone III was therefore considered to be an Ullmann coupling of methyl 2-bromobenzoate with a *p*-di-iodo compound already possessing the essential features of the central nucleus.

Preliminary experiments aiming at the direct iodination of 1,2,4,5-tetramethoxybenzene to 3,6-di-iodo-1,2,4,5-tetramethoxybenzene were unsuccessful and interest was therefore turned to the use of 3,6-di-iodo-2,5-dimethoxybenzoquinone as a starting material. This compound was prepared in poor yield from iodo-anil *via* di-iodo-dimethoxybenzoquinone di-methyl hemiacetal according to Jackson and Bolton². Reduction with phenyl hydrazine and methylation of the hydroquinone thus obtained gave 3,6-di-iodo-1,2,4,5-tetramethoxybenzene.

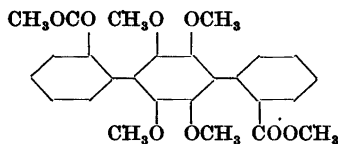
Ullman coupling with methyl 2-bromobenzoate then afforded 2,3,5,6-tetramethoxy-1,4-bis-(2-carbomethoxyphenyl)-benzene (I) in good yield. The product, however, was found to be a mixture of two different types of

crystals, which could not be completely separated. They were readily interconvertible and it may be presumed that they are the *cis*- and *trans*-isomers arising from hindered rotation, the energy barrier between them being low enough to permit rapid equilibration. Similar although stable isomers have been described for 3,6-dibromo-2,5-dihydroxy-1,4-bis-(2,4-dimethylphenyl)-benzene and its derivatives³.

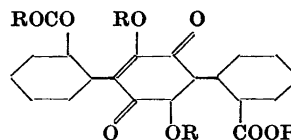
2,3,5,6-Tetramethoxy-1,4-bis-(2-carbomethoxyphenyl)-benzene on cautious treatment with nitric acid yielded 3,6-dimethoxy-2,5-bis-(2-carbomethoxyphenyl)-benzoquinone (II), which on alkaline hydrolysis gave the desired 3,6-dihydroxy-2,5-bis-(2-carboxyphenyl)-benzoquinone (III). This compound is a high melting solid, which can be recrystallised from dioxan giving crystals containing five moles of solvent of crystallisation. It is somewhat soluble in hot water giving a bluish solution and it dissolves readily in aqueous alkali to give an intense violet colour.

The dihydroxyquinone III on reductive acetylation afforded a dilactone diacetate (IV). This behaviour is analogous to that of 2,5-bis-(2-carbomethoxyphenyl)-benzoquinone but is in contrast to that of muscarufin, which on similar treatment is reported to give a triacetate (*cf.* Ref. 1).

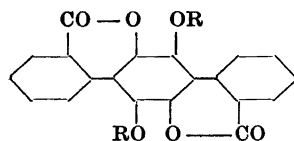
The controlled action of hydrobromic acid on 2,3,5,6-tetramethoxy-1,4-bis-(2-carbomethoxyphenyl)-benzene afforded a dimethoxy dilactone (V) and even when the dihydroxyquinone III itself was heated lactonisation occurred to give a quinonoid dilactone (VI), which was however far less resistant to hydrolysis than the above mentioned dilactones; it dissolved fairly rapidly in cold, dilute aqueous alkali.



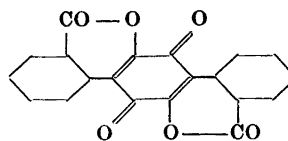
I



II R = CH₃-
III R = H-



IV R = CH₃CO-
V R = CH₃-



VI

EXPERIMENTAL

All melting points are uncorrected.

3,6-Di-iodo-2,5-dimethoxy-1,4-dihydroxybenzene. Bromo-anil was treated with an excess of sodium or potassium iodide (in successive portions) in boiling acetone or ethanol^{4,5}. A crude iodo-anil was obtained, which was extracted with hot acetic acid to remove part of the bromo-iodoquinones present, and then recrystallised from large

volumes of ethyl acetate or benzene. The yield of purified iodo-anil was 20–40 %, large scale preparations giving the smaller yields. Treatment with sodium methoxide in methanol⁵ (equivalent amount or a moderate excess) afforded the amorphous di-iodo-dimethoxybenzoquinone dimethyl hemiacetal, which on heating with acetic anhydride³ gave 3,6-di-iodo-2,5-dimethoxybenzoquinone (overall yield from iodo-anil 10–35 %). It was found to be most important to use a thoroughly purified iodo-anil; with less pure material large amounts of ill-defined by-products were obtained and the yield of di-iodo-dimethoxyquinone was considerably diminished.

3,6-Di-iodo-2,5-dimethoxybenzoquinone (7.2 g) was suspended in hot (90°) acetic acid and phenyl hydrazine (2.5 ml) added dropwise with shaking until the nitrogen evolution ceased. After cooling to room temperature the product (5.2 g) was collected and recrystallised from acetic acid to give needles, which slowly darkened in the air, m.p. 240° (decomp.). (Found: C 22.9; H 1.9; I 60.1. Calc. for $C_8H_8O_4I_2$: C 22.8; H 1.9; I 60.2.)

3,6-Di-iodo-1,2,4,5-tetramethoxybenzene. 3,6-Di-iodo-2,5-dimethoxy-1,4-dihydroxybenzene was dissolved in a mixture of ethanol and excess dimethyl sulphate. The solution was stirred under an atmosphere of coal gas and a 50 % solution of sodium hydroxide in water added. On addition of water the methylated product separated in almost quantitative yield. Recrystallisation from methanol (charcoal) gave long needles, m.p. 136–137°. (Found: C 27.2; H 2.8; I 55.6. Calc. for $C_{10}H_{12}O_4I_2$: C 26.7; H 2.7; I 54.4.)

2,3,5,6-Tetramethoxy-1,4-bis-(2-carbomethoxyphenyl)-benzene, (I). 3,6-Di-iodo-1,2,4,5-tetramethoxybenzene (11 g), methyl 2-bromobenzoate (21 g) and copper bronze (60 g) were mixed intimately and heated to 200°; a reaction then brought the temperature up to ca. 270°. The reaction mixture was allowed to cool and was then exhaustively extracted with chloroform in a Soxhlet apparatus. The solvent was removed and the residue distilled *in vacuo* yielding besides dimethyl diphenate and a small amount of methyl benzoate a fraction b.p. 200–300°, 1 mm (6.6 g), which solidified to a mixture of needles and prisms on trituration with methanol. On recrystallisation from the same solvent it became evident that the two forms were crystalline modifications of the same compound. The prisms (m.p. around 130°) were apparently more stable above 30°, but below this temperature needles (m.p. about 120°) dominated in the mixture. It was not, however, possible to obtain a perfectly homogeneous sample; even after seeding and rapid separation of the various crops contaminated crystals were obtained. The interconvertibility of the forms is shown by the fact that a sample mainly consisting of one form could give a product in which the other form predominated. The product obtained after six recrystallisations from various solvents was sublimed *in vacuo* and analysed (m.p. 122–129°). (Found: C 66.5; H 5.7. Calc. for $C_{24}H_{26}O_8$: C 66.9; H 5.6.)

3,6-Dimethoxy-2,5-bis-(2-carbomethoxyphenyl)-benzoquinone, (II). Nitric acid (15 ml, *d* 1.42) was slowly added to a suspension of finely powdered 2,3,5,6-tetramethoxy-1,4-bis-(2-carbomethoxyphenyl)-benzene (0.50 g) in water (5 ml) and methanol (5 ml). The colour of the mixture turned yellowish red and the crystals dissolved. After some minutes water (50 ml) was added and after 1 h the crystalline precipitate was collected (0.43 g), and recrystallised from *n*-butyl ether and from methanol to give coarse yellow needles m.p. 178–180°. (Found: C 65.9; H 4.9. Calc. for $C_{24}H_{26}O_8$: C 66.0; H 4.6.)

3,6-Dihydroxy-2,5-bis-(2-carboxyphenyl)-benzoquinone, (III). 3,6-Dimethoxy-2,5-bis-(2-carbomethoxyphenyl)-benzoquinone (0.24 g) was added to a solution of sodium hydroxide (2 g) in water (5 ml) and ethanol (15 ml). It slowly dissolved giving a violet solution which was heated on the water bath (20 min.), cooled and acidified. The reddish precipitate was collected (0.17 g) and recrystallised from dioxan giving orange prisms, which slowly crumbled in the air giving off dioxan. They were found to contain ca. five moles of dioxan of crystallisation. (Found: 47.4 % loss of weight on drying *in vacuo* at 130°. Calc. for 5 moles of dioxan: 48.7 %.) When heated the dried material sublimed slowly above 280°, began to decompose at ca. 350° and melted with decomposition at about 370–375°. The dried material was analysed. (Found: C 63.4; H 3.3. Calc. for $C_{20}H_{12}O_8$: C 63.2; H 3.2.)

3,6-Dihydroxy-2,5-bis-(2-carboxyphenyl)-benzoquinone dilactone, (VI). On sublimation or prolonged heating *in vacuo* at 200° 3,6-dihydroxy-2,5-bis-(2-carboxyphenyl)-benzoquinone turned yellow; apparently water was given off and a dilactone formed. This compound decomposed above 350° and dissolved, although not as rapidly as the parent dihydroxyquinone, in aqueous alkali giving a violet solution. The sublimed product was analysed. (Found: C 69.6; H 2.6. Calc. for $C_{20}H_8O_8$: C 69.8; 2.3.)

3,6-Diacetoxy-2,5-dihydroxy-1,4-bis-(2-carboxyphenyl)-benzene dilactone, (V), (or possibly the isomeric *5,6-diacetoxy-2,3-dihydroxy* compound). A small amount of the dihydroxyquinone III was heated under reflux for 0.5 h with acetic anhydride, fused sodium acetate and zinc dust. The white precipitate was collected and recrystallised from large volumes of acetic anhydride giving small needles, m.p. ca. 340° (decomp.) (Found: C 66.3; H 3.3. Calc. for $C_{24}H_{14}O_8$: C 67.0; H 3.3.)

3,6-Dimethoxy-2,5-dihydroxy-1,4-bis-(2-carboxyphenyl)-benzene dilactone, (V), (or the isomer, as pointed out for the previous substance). *2,3,5,6-Tetramethoxy-1,4-bis-(2-carbomethoxyphenyl)-benzene* (0.25 g) was heated to boiling with hydrobromic acid (2 ml, *d* 1.48) and acetic acid (7 ml). The crystals dissolved immediately but after a few minutes a white precipitate appeared. Heating was continued for a total of 7 min. and the mixture allowed to cool. The precipitate (0.20 g) was recrystallised from acetic acid giving small needles, m.p. ca. 316°. (Found: C 70.4; H 4.2. Calc. for $C_{22}H_{14}O_8$: C 70.6; H 3.8.)

If the demethylation procedure was extended over several hours complete demethylation apparently occurred. The product obtained was rather sensitive to air and was partially oxidised on attempts to recrystallise it from acetic acid; it was not further investigated.

The author is indebted to *Statens Tekniska Forskningsråd* for a fellowship.

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Received July 3, 1956.