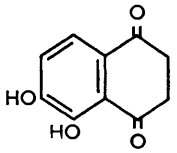
484. *Quinones. Part VI.* Some New Polyhydroxynaphthaquinones.*

By J. F. Garden and R. H. Thomson.

5 : 6- and 5 : 7-Dihydroxy- and 2 : 3 : 5- and 2 : 3 : 6-trihydroxy-1 : 4-naphthaquinone have been synthesised. Some new properties of hydroxynaphthaquinones are described.

We have shown [1] that the compound regarded by Dimroth and Roos [2] as 5 : 6-dihydroxy-1 : 4-naphthaquinone is, in fact, 5-amino-6-hydroxy-1 : 4-naphthaquinone. They obtained it by nitration of 6-hydroxy-1 : 4-naphthaquinone followed by reduction to a trihydroxynaphthylamine and oxidation with ferric chloride. Acetylation of the intermediate trihydroxynaphthylamine gives a tetra-acetyl derivative identical with that obtained by reductive acetylation of the quinone. Authentic 5 : 6-dihydroxy-1 : 4-naphthaquinone (*o*-naphthazarin) (II) has now been prepared from 3 : 5 : 6-trihydroxy-1 : 4-naphthaquinone by reduction with acid stannous chloride.[3] The diketone (I), isolated initially,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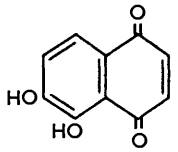
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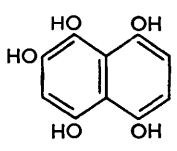
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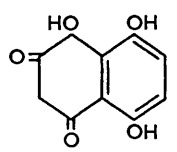
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was converted into (II) by aeration in alkaline solution. In an effort to improve the overall yield of 3 : 5 : 6-trihydroxy-1 : 4-naphthaquinone [3] the intermediate 5-chloro-7 : 8-dimethoxytetralone was condensed with *p*-nitrosodimethylaniline before hydrogenolysis, but removal of chlorine from the resulting 5-chloro-2-hydroxy-7 : 8-dimethoxy-1 : 4-naphthaquinone was difficult. 5 : 6-Dihydroxy-1 : 4-naphthaquinone closely resembles naphthazarin in its behaviour in alkaline solution, the cornflower-blue colour remaining unchanged after several days whereas Dimroth and Roos's compound is unstable and soon becomes red therein. *o*-Naphthazarin also forms a blue solution in aqueous sodium hydrogen carbonate, as does 5-amino-6-hydroxy-1 : 4-naphthaquinone. As 6-hydroxy- and 5 : 7-dihydroxy-1 : 4-naphthaquinone are also soluble in this reagent hydroxyl groups at positions 6 and 7 are evidently strongly acidic (Dimroth and Roos prepared a monopyridine salt from their compound) and are readily distinguished from the chelated hydroxyl groups at positions 5 and 8 which confer solubility only in sodium carbonate. In this respect hydroxynaphthaquinones differ from analogous anthraquinones; the α-hydroxy-derivatives in that series are soluble in sodium carbonate and very rarely (in certain polyhydroxy-derivatives, *e.g.*, 1 : 3 : 6 : 8-tetrahydroxyanthraquinone) in sodium hydrogen carbonate solution.

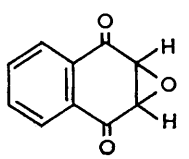
As 5 : 7-dihydroxy-1 : 4-naphthaquinone was required for our work on spinochrome N, this has also been synthesised. In principle it should be possible to derive this from 2(or 3) : 5 : 7-trihydroxy-1 : 4-naphthaquinone by reduction with stannous chloride but the synthesis of both intermediates is somewhat tedious.[4] In the case of the 2 : 5 : 7-isomer (flaviolin) the main difficulty lies in the cyclisation of γ-(2 : 4-dimethoxyphenyl)-butyric acid to the corresponding tetralone, the yield being very low. Where similar difficulty (*i.e.*, cyclisation *meta* to two *ortho*/*para*-directing groups) has been encountered in the formation of anthraquinones from *o*-benzoylbenzoic acids, bromination of the

* Part V, *J.*, 1955, 1089.

[1] Garden and Thomson, *Chem. and Ind.*, 1954, 1146.
[2] Dimroth and Roos, *Annalen*, 1927, **456**, 177.
[3] Bruce and Thomson, *J.*, 1952, 2759; 1954, 1428.
[4] Davies, King, and Roberts, *J.*, 1955, 2782.

" unreactive " ring has, on occasion, greatly assisted the ring closure.[5] However this device did not succeed in the present instance, the yield of bromodimethoxytetralone being very poor. This route to 5 : 7-dihydroxy-1 : 4-naphthaquinone was not pursued. The most direct method, *i.e.*, condensation of maleic anhydride with resorcinol or 4-chlororesorcinol (cf. ref. 6) also failed, presumably for the same reason. Another approach to flaviolin, namely, alkaline oxidation of 1 : 3 : 6 : 8-tetrahydroxynaphthalene, could not be carried through as attempts to obtain the latter by alkali fusion of chromotropic acid invariably disrupted the molecule and only 2 : 4-dihydroxybenzoic acid could be isolated (cf. ref. 7). Finally the desired compound was obtained by reduction of naphthapurpurin with alkaline sodium stannite. Probably the quinol (III) formed initially reacts in the tautomeric form (IV) from which the " benzyl " hydroxyl group is removed. The resultant tetrahydroxynaphthalene was taken into ether and oxidised directly with silver oxide. For convenience naphthapurpurin triacetate was used as starting material; this is readily prepared by oxidation of naphthazarin to 1 : 4 : 5 : 8-naphthadiquinone followed by Thiele acetylation of the crude material.[8] This type of reduction has been effected in the anthraquinone series (*e.g.*, purpurin ⟶ xanthopurpurin [9]) where much milder conditions suffice. The new quinone is unstable in the presence of acids, becoming green, but acetylation in the presence of sodium acetate afforded a diacetate which showed typical 1 : 4-naphthaquinone ultraviolet absorption. With the synthesis of 5 : 7-dihydroxy-1 : 4-naphthaquinone all the possible dihydroxy-1 : 4-naphthaquinones are now known.

Most of the polyhydroxynaphthaquinones occurring in sea urchins (in which we are interested) contain two hydroxyl groups in the quinone ring. 2 : 3-Dihydroxy-1 : 4-naphthaquinone itself has been obtained by several methods,[10] most of which are of limited value. Weygand's procedure,[11] an unusual benzoin condensation of phthalaldehyde with glyoxal in the presence of cyanide ion, is of general application but is limited by the inaccessibility of substituted phthalaldehydes. Shchukina *et al.*[12] have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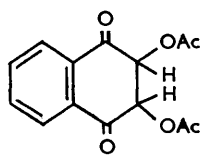
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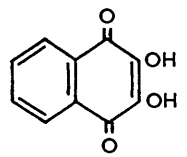
(VII)

converted 1 : 4-naphthaquinone into its 2 : 3-dihydroxy-derivative *via* the epoxide (V) and the glycol diacetate (VI), which on aeration in alkaline solution is smoothly converted into the quinone (VII). This is a more flexible method and enables two hydroxyl groups to be introduced into any *Bz*-substituted naphthaquinone provided the epoxides can be obtained. The latter are prepared under alkaline conditions which have not been successfully applied to *Bz*-hydroxylated naphthaquinones whilst acid reagents (including trifluoroperoxyacetic acid) are ineffective. It is therefore necessary to protect such hydroxyl groups, which has hitherto been difficult, especially for strongly chelated *peri*-hydroxyl groups. Only three such quinones (naphthazarin,[13] flaviolin,[14] and cordeauxiaquinone [15]) have been

[5] Jacobson and Adams, *J. Amer. Chem. Soc.*, 1924, **46**, 1312.
[6] Cooke and Dowd, *Austral. J. Chem.*, 1953, **6**, 53.
[7] Meyer and Hartman, *Ber.*, 1905, **38**, 3945.
[8] Zahn and Ochwat, *Annalen*, 1928, **462**, 72; Fieser and Dunn, *J. Amer. Chem. Soc.*, 1937, **59**, 1019.
[9] G.P. 212,697; Hill and Richter, *J.*, 1936, 1714.
[10] " Encyclopaedia of Organic Chemistry," Vol. XII, B, p. 3178. Elsevier, Amsterdam, 1952.
[11] Weygand, *Ber.*, 1942, **75**, 625.
[12] Shchukina, Vinogradova, and Shemyakin, *J. Gen. Chem.* (*U.S.S.R.*), 1951, **21**, 1661.
[13] Brass, Pfluger, and Honsberg, *Ber.*, 1936, **69**, 87.
[14] Astill and Roberts, *J.*, 1953, 3302.
[15] Lister, Eugster, and Karrer, *Helv. Chim. Acta*, 1955, **38**, 215.

successfully methylated and previous attempts to methylate juglone,[16] the simplest example, failed. We now find that methyl iodide–silver oxide in chloroform solution (but not in dimethylformamide [17]) is a convenient methylating reagent for this purpose and 5-hydroxy-, 6-hydroxy-, and 5 : 8-dihydroxy-1 : 4-naphthaquinone have been smoothly converted into their methyl ethers. The yield of naphthazarin dimethyl ether is only moderate but the procedure is more convenient than that of Brass *et al.*[13] who used methyl toluene-*p*-sulphonate. By use of the Russian method, the 2 : 3-dihydroxy-derivatives of these ethers were prepared from which the 2 : 3 : 5-(new) and 2 : 3 : 6-trihydroxy-1 : 4-naphthaquinones were obtained by demethylation. 5 : 8-Dimethoxy-1 : 4-naphthaquinone 2 : 3-epoxide was obtained earlier [18] but was regarded as the 2-hydroxy-derivative on account of its solubility in aqueous sodium hydroxide. However the epoxide is genuine (there is no OH band in its infrared spectrum in chloroform solution) but readily hydrolyses in alkaline solution to form 2-hydroxy-5 : 8-dimethoxy-1 : 4-naphthaquinone which was also obtained by methylation of naphthapurpurin and subsequent hydrolysis. Simple 2-hydroxy-1 : 4-naphthaquinones form red solutions in aqueous sodium hydroxide, but we have noticed that the colour usually shifts towards orange-yellow when a *peri*-methoxyl group is introduced. The effect is more striking when two such groups are present: 2-hydroxy-5 : 8-dimethoxy-1 : 4-naphthaquinone gives an amber solution in alkali, and 2 : 3-dihydroxy-5 : 8-dimethoxy-1 : 4-naphthaquinone a red colour, whereas 2 : 3-dihydroxy-1 : 4-naphthaquinone itself forms a blue alkaline solution.

Certain substituents attached to a quinone ring, *e.g.*, halogen or alkylthio-groups, are readily replaced by hydroxyl on treatment with alkali, but a second hydroxyl group cannot be introduced adjacent to the first in this way. Acid hydrolysis should be more effective. This was examined briefly but the results were discouraging and anomalous. By using sulphuric acid it was possible to replace one substituent in 2 : 3-dichloronaphthazarin and in 2 : 3-dibenzylthio-1 : 4-naphthaquinone; the latter with hydrobromic acid unexpectedly yielded a little 2-hydroxy-1 : 4-naphthaquinone. Hydrolysis of 2-phenylthio-1 : 4-naphthaquinone with hydrobromic acid proceeded normally but no definite products could be isolated after acid hydrolysis of 2-acetoxy-3-*p*-tolylthio-1 : 4-naphthaquinone.

Experimental

5-Amino-6-hydroxy-1 : 4-naphthaquinone.—6-Hydroxy-5-nitro-1 : 4-naphthaquinone was prepared by Dimroth and Roos's method.[8] It crystallised from glacial acetic acid in yellow *needles*, m. p. 285—289° (decomp.) (54%) (Found: C, 54·6; H, 2·4; N, 6·4. $C_{10}H_5O_5N$ requires C, 54·8; H, 2·3; N, 6·4%). The nitroquinone (5·5 g.) was added in portions to a stirred solution of stannous chloride (55 g.) in concentrated hydrochloric acid (110 ml.) at 60° After 5 min. the solution became colourless and, on cooling, 5-amino-1 : 4 : 6-trihydroxynaphthalene hydrochloride separated. This was dissolved in water (1050 ml.) and oxidised by the slow addition of ferric chloride (12 g.) in water (350 ml.). The dark red solution was set aside and the precipitate collected next day. 5-Amino-6-hydroxy-1 : 4-naphthaquinone crystallised from a large volume of water in dark red, almost black, crystals with a metallic lustre, m. p. 196—200° (48%). They formed a cornflower-blue solution in aqueous sodium hydrogen carbonate. Reductive acetylation yielded a tetra-acetyl derivative forming plates, m. p. 201—202° (from ethanol), identical with the product obtained by acetylation of 5-amino-1 : 4 : 6-trihydroxynaphthalene hydrochloride. The aminohydroxyquinone (0·3 g.) in acetic anhydride (5 ml.) was heated under reflux for 5 min., allowed to cool slowly, and set aside for 5 days. The *diacetyl derivative* was collected and recrystallised from benzene in red needles, m. p. 187° (decomp.) (Found: C, 61·8; H, 4·2; N, 5·3. $C_{14}H_{11}O_5N$ requires C, 61·55; H, 4·05; N, 5·1%). A mixture of the aminohydroxyquinone (0·3 g.), benzoyl chloride (0·3 ml.), and pyridine (3 ml.) was stirred for 15 min., red needles of 5-amino-6-benzoyloxy-1 : 4-naphthaquinone being deposited. These were collected and rearrangement was effected by warming

[16] Fierz-David, Blangey, and Krannichfeldt, *ibid.*, 1947, **30**, 827.
[17] Kuhn, Trischmann, and Lõw, *Angew. Chem.*, 1955, **67**, 32.
[18] Bruce and Thomson, *J.*, 1955, 1089.

them in glacial acetic acid (4 ml.) at 35°. On cooling, *5-benzamido-6-hydroxy-1 : 4-naphthaquinone* separated and was recrystallised from the same solvent, forming red needles, m. p. 165—170° (decomp.) (Found : C, 69·35; H, 4·0; N, 4·7. $C_{17}H_{11}O_4N$ requires C, 69·6; H, 3·8; N, 4·8%).

1 : 2 : 3 : 4-Tetrahydro-5 : 6-dihydroxy-1 : 4-dioxonaphthalene.—3 : 5 : 6-Trihydroxy-1 : 4-naphthaquinone (0·6 g.) was added to a hot solution of stannous chloride (3 g.) in 5N-hydrochloric acid (130 ml.) and boiled under reflux for 30 min. The solution was filtered and repeatedly extracted with chloroform whilst still warm. More hydrochloric acid (20 ml.; 6N) was added to the aqueous phase which was then refluxed for 30 min. and again extracted with chloroform. The process was repeated once more. Evaporation of the combined, dried ($CaCl_2$) extracts left a residue which crystallised from light petroleum (b. p. 100—120°) in pale fawn needles, m. p. 186° (decomp.) (27%) (Found : C, 62·35; H, 4·2. $C_{10}H_8O_4$ requires C, 62·45; H, 4·2%). The *diketone* formed a green solution in aqueous sodium hydroxide which became cornflower-blue on being kept. Treatment with cold acetic anhydride containing a drop of concentrated sulphuric acid afforded *1 : 4 : 5 : 6-tetra-acetoxynaphthalene* in needles, m. p. 178° (from aqueous acetic acid) (Found : C, 60·1; H, 4·3; Ac, 43·0. $C_{18}H_{16}O_8$ requires C, 60·0; H, 4·5; Ac, 47·5%).

5 : 6-Dihydroxy-1 : 4-naphthaquinone.—A brisk current of air was passed through a solution of the above diketone (0·5 g.) in 2N-aqueous sodium hydroxide (10 ml.) for 10 min. After filtration, the blue solution was acidified with hydrochloric acid, extracted with chloroform, and dried ($CaCl_2$). Removal of the solvent under reduced pressure left the *quinone* which separated from light petroleum (b. p. 100—120°) in red needles, m. p. 180—183° (decomp.) (66%) (Found : C, 63·1; H, 3·35. $C_{10}H_6O_4$ requires C, 63·1; H, 3·2%). Light absorption : $\lambda_{max.}$ (in EtOH) at 226, 263, and 461 mμ (log ε 4·15, 4·01, and 3·51 respectively), $\nu_{C:O}$ (in $CHCl_3$) 1666 (m) and 1644 (s) $cm.^{-1}$. *o*-Naphthazarin forms an intensely red solution in concentrated sulphuric acid and a red solution in pyridine which becomes deep blue on dilution with water. It gives a green ferric reaction and a deep blue precipitate with methanolic lead acetate. Acetylation with acetic anhydride, perchloric acid being used as catalyst, afforded yellow needles, m. p. 138—140°, but consistent analytical figures could not be obtained. Reductive acetylation gave the tetra-acetate, m. p. 178°, described above.

8-Chloro-3-hydroxy-5 : 6-dimethoxy-1 : 4-naphthaquinone.—10% Aqueous sodium hydroxide (3 ml.) was added to a solution of 5-chloro-1 : 2 : 3 : 4-tetrahydro-7 : 8-dimethoxy-1-oxonaphthalene (1·5 g.) and *p*-nitrosodimethylaniline (2·5 g.) in alcohol (100 ml.). After 4 days the violet precipitate (1·3 g.) was collected, washed with a little cold methanol, and dried. This dianil was then heated under reflux in a solution of concentrated sulphuric acid (6 ml.) and water (100 ml.) for 1 hr. The *hydroxy-quinone* was precipitated and was collected on cooling. It was combined with an additional amount obtained by chloroform extraction of the filtrate and purified by dissolution in dilute aqueous sodium hydrogen carbonate (charcoal). Acidification afforded golden needles which sublimed at 125°/0·02 mm. in yellow needles, m. p. 209° (26·1%) (Found : C, 53·4; H, 3·4; Cl, 12·9. $C_{12}H_9O_5Cl$ requires C, 53·6; H, 3·4; Cl, 13·3%). Light absorption : $\lambda_{max.}$ (in EtOH) 362 and 446—450 mμ (log ε 3·61 and 3·39 respectively). The *acetate* crystallised from glacial acetic acid in yellow needles, m. p. 187° (Found : C, 53·9; H, 3·7; Cl, 10·9. $C_{14}H_{11}O_6Cl$ requires C, 54·1; H, 3·6; Cl, 11·3%).

Naphthapurpurin Triacetate (cf. ref. 8).—Lead tetra-acetate (12·5 g.) was added gradually to a suspension of finely divided naphthazarin (5 g.) in glacial acetic acid (70 ml.) until the red colour had become yellow-brown. The dark purple diquinone was collected, washed with light petroleum, and added in portions to a stirred mixture of acetic anhydride (25 ml.) and concentrated sulphuric acid (1 ml.). The temperature rose to 40°. After 2 hr. the mixture was poured on ice, and the light orange precipitate crystallised from alcohol (charcoal) in orange-brown needles, m. p. 160° (3 g.). This material was sufficiently pure for reduction.

5 : 7-Dihydroxy-1 : 4-naphthaquinone.—A solution of sodium stannite was prepared by mixing warm solutions of stannous chloride (2·5 g.) in concentrated hydrochloric acid (5 ml.), and sodium hydroxide (7·5 g.) in water (15 ml.). After cooling and addition of a little Celite, the mixture was filtered and added to naphthapurpurin triacetate (0·5 g.). The alkaline solution was boiled under reflux for 5 hr., added to iced concentrated hydrochloric acid (25 ml.) and rapidly extracted with ether. The ether layer was shaken with saturated brine (containing a little sodium dithionite) and then filtered through anhydrous magnesium sulphate on to silver oxide (3 g.) mixed with a little of the desiccant. After the suspension had been shaken for

30 min. it was filtered and evaporated. The residual *quinone* crystallised from toluene in orange needles, decomp. 165—170° (30%) (Found: C, 63·1; H, 3·05. $C_{10}H_6O_4$ requires C, 63·1; H, 3·2%). Light absorption: $\lambda_{max.}$ (in EtOH) 265 and 431 mμ (log ε 4·12 and 3·63 respectively), $\nu_{C=O}$ (in $CHCl_3$) 1675 (m) and 1642 (s) cm.$^{-1}$. The quinone gave a violet-red colour in aqueous sodium hydrogen carbonate and a green solution in concentrated sulphuric acid. Stirring in the cold with acetic anhydride and anhydrous sodium acetate afforded a *diacetate*, golden-yellow plates, m. p. 126—127° (decomp.) (Found: C, 61·7; H, 3·9. $C_{14}H_{10}O_6$ requires C, 61·3; H, 3·7%). Light absorption: $\lambda_{max.}$ (in EtOH) 233 and 342 mμ (log ε 4·5 and 3·6 respectively). Stirring the acetylation mixture in the cold with zinc dust yielded 1 : 4 : 5 : 7-*tetra-acetoxynaphthalene* which separated from ethyl acetate–light petroleum (b. p. 100—120°) in needles, m. p. 181° (Found: C, 60·3; H, 4·5. $C_{18}H_{16}O_8$ requires C, 60·0; H, 4·5%).

2 : 3 : 5-*Trihydroxy*-1 : 4-*naphthaquinone*.—A suspension of juglone (5 g.) in chloroform (125 ml.) was shaken vigorously with silver oxide (10 g.) and methyl iodide (7·5 ml.) for 1 hr. Two further additions of silver oxide (5 g.) and methyl iodide (4 ml.) were made at intervals of 1 hr. and shaking was continued until a test portion of the chloroform solution no longer gave a violet colour with aqueous sodium hydroxide. The mixture was filtered and the residue extracted with warm chloroform. Evaporation of the combined filtrates left juglone methyl ether which crystallised from methanol in orange needles, m. p. 187° (92%). To a solution of this quinone (5 g.) in alcohol (250 ml.) at 45° was added 30% hydrogen peroxide (20 ml.) and 30% aqueous sodium carbonate (17 ml.). Heat was evolved and the yellow colour faded. After being shaken at 45° for 5 min., the mixture was cooled and diluted with water (200 ml.), and kept at 0° overnight. The precipitate was collected, and further material was obtained by repeated extraction of the filtrate with ether. 5-*Methoxy*-1 : 4-*naphthaquinone* 2 : 3-*epoxide* separated from methanol in needles, m. p. 109° (57%) (Found: C, 64·8; H, 4·1. $C_{11}H_8O_4$ requires C, 64·7; H, 4·0%). The oxide (2 g.) in acetic anhydride (15 ml.) containing concentrated sulphuric acid (0·9 ml.) was stirred at room temperature for 10 min., with occasional cooling in ice, after which a solid mass separated. The product was collected, and washed with ether containing a little alcohol and with water. 2 : 3-*Diacetoxy*-1 : 2 : 3 : 4-*tetrahydro*-5-*methoxy*-1 : 4-*dioxonaphthalene* crystallised from methanol in needles, m. p. 185° (decomp.) (80%) (Found: C, 58·4; H, 4·8. $C_{15}H_{14}O_7$ requires C, 58·8; H, 4·6%). Hydrolysis and oxidation of the diacetate (0·5 g.) was effected by passing a brisk stream of air through its solution in aqueous sodium hydroxide (15 ml., 10%). After 10 min. the blue solution was filtered and acidified with dilute sulphuric acid. The precipitated 2 : 3-*dihydroxy*-5-*methoxy*-1 : 4-*naphthaquinone* formed red crystals, m. p. 229° (decomp.) (from glacial acetic acid) (70%) (Found: C, 59·9; H, 3·8. $C_{11}H_8O_5$ requires C, 60·0; H, 3·7%). Light absorption: $\lambda_{max.}$ (in EtOH) 382·5 and 540 mμ (log ε 3·46 and 3·23 respectively). The *diacetate* formed yellow needles, m. p. 201° (from benzene) (Found: C, 59·1; H, 3·9. $C_{15}H_{12}O_7$ requires C, 59·2; H, 3·95%). The dihydroxymethoxyquinone (0·8 g.) was demethylated by addition to a stirred melt of anhydrous aluminium chloride (24 g.) and sodium chloride (4·8 g.) at 140°. The temperature was quickly raised to 180—190° and maintained for 2 min. After cooling, the mixture was decomposed with 18% hydrochloric acid (360 ml.). The precipitated quinone was filtered off and a little more was obtained by chloroform extraction of the filtrate. 2 : 3 : 5-*Trihydroxy*-1 : 4-*naphthaquinone* crystallised from light petroleum (b. p. 100—120°) in red needles, m. p. 234° (decomp.) (45%) (Found: C, 58·1; H, 3·25. $C_{10}H_6O_5$ requires C, 58·2; H, 3·0%). Light absorption $\lambda_{max.}$ (in EtOH), 397 and 567 mμ (log ε 3·56 and 3·42 respectively). The *triacetate* crystallised from light petroleum (b. p. 100—120°) in yellow needles, m. p. 140° (Found: C, 57·7; H, 3·7. $C_{16}H_{12}O_8$ requires C, 57·8; H, 3·65%).

2 : 3 : 6-*Trihydroxy*-1 : 4-*naphthaquinone*.—6-Hydroxy-1 : 4-naphthaquinone (5 g.) was methylated by shaking it vigorously in chloroform (125 ml.) for 1 hr. with silver oxide (20 g.) and methyl iodide (15 ml.). The product formed yellow needles, m. p. 136° (from light petroleum) (80%), and was converted, as described above, into 6-*methoxy*-1 : 4-*naphthaquinone* 2 : 3-*epoxide* which crystallised from methanol in prisms, m. p. 109° (77%) (Found: C, 64·5; H, 3·8. $C_{11}H_8O_4$ requires C, 64·7; H, 4·0%). Acetylation as before yielded 2 : 3-*diacetoxy*-1 : 2 : 3 : 4-*tetrahydro*-6-*methoxy*-1 : 4-*dioxonaphthalene* in rosettes, m. p. 192° (from methanol) (75%) (Found: C, 58·6; H, 5·0. $C_{15}H_{14}O_7$ requires C, 58·8; H, 4·6%). Aeration in alkaline solution then yielded 2 : 3-*dihydroxy*-6-*methoxy*-1 : 4-*naphthaquinone* which crystallised from glacial acetic acid in red needles, m. p. 214—217° (decomp.) (60%) (Found: C, 60·0; H, 3·9. $C_{11}H_8O_5$ requires C, 60·0; H, 3·7%). The *diacetate* formed yellow needles, m. p. 169° (from

light petroleum) (Found : C, 59·4; H, 4·1. $C_{15}H_{12}O_7$ requires C, 59·2; H, 3·95%). Demethylation of the dihydroxymethoxyquinone with aluminium chloride–sodium chloride yielded 2 : 3 : 6-trihydroxy-1 : 4-naphthaquinone which was sublimed at 175°/0·03 mm. and then crystallised from light petroleum (b. p. 100—120°), forming red needles, m. p. 300—305° (decomp.) (50%) (Weygand *et al.*[19] give m. p. 300°).

3-*Hydroxy*-6-*methoxy*-1 : 4-*naphthaquinone*.—A mixture of 6-methoxy-1 : 4-naphthaquinone 2 : 3-epoxide (3·3 g.), acetic anhydride (17 ml.) and concentrated sulphuric acid (1·5 ml.) was stirred for 15 min. at room temperature without external cooling. The solid product was collected, washed well with water, and dissolved in N-sodium hydroxide (60 ml.). The solution was stirred for 10 min. and acidified with sulphuric acid. The precipitate separated from glacial acetic acid as red crystals (1·8 g.) of indefinite m. p. which were chromatographed in chloroform on a column of alumina. Two bands appeared. Elution of the lower band with chloroform gave a quinone separating from glacial acetic acid in golden needles, m. p. 214° (decomp.) (1·1 g.) (Found : C, 64·7; H, 3·9. Calc. for $C_{11}H_8O_4$: C, 64·7; H, 3·95%). (Fieser *et al.*[20] give m. p. 220—222° for 3-hydroxy-6-methoxy-1 : 4-naphthaquinone; the 2-hydroxy-isomer[21] has m. p. 197—200°.) The *acetate* formed yellow needles, m. p. 123° (from methanol) (Found : C, 63·3; H, 4·2. $C_{13}H_{10}O_5$ requires C, 63·4; H, 4·1%). Elution of the upper band on the column with chloroform–glacial acetic acid yielded 2 : 3-dihydroxy-6-methoxy-1 : 4-naphthaquinone, m. p. 214—217° (0·5 g.).

2 : 3-*Dihydroxy*-5 : 8-*dimethoxy*-1 : 4-*naphthaquinone*.—A stirred solution of sublimed naphthazarin (2 g.) in chloroform (70 ml.) was heated under reflux on a water-bath for 8 hr. with freshly prepared silver oxide (5 g.) and methyl iodide (4 ml.). Four further additions of silver oxide (5 g.) and methyl iodide (4 ml.) were made at intervals of 3 hr. Silver compounds were then removed by filtration and the procedure repeated until a test portion of the chloroform solution gave no colour when shaken with aqueous sodium hydroxide. After filtration, the chloroform was passed through a column of alumina and evaporated. The residual naphthazarin dimethyl ether crystallised from light petroleum (b. p. 100—120°) as orange needles, m. p. 155° (31%). It was converted into the *oxide* as before, yielding yellow needles, m. p. 195° (from light petroleum) (60%) (Found : C, 61·45; H, 4·15. $C_{12}H_{10}O_5$ requires C, 61·5; H, 4·3%). A mixture of the oxide (0·87 g.), acetic anhydride (9 ml.), and concentrated sulphuric acid (0·8 ml.) was set aside for 24 hr. The solution was then poured into ice-water (50 ml.), and the precipitate collected, washed with a little cold methanol, and dried. Recrystallisation from methanol afforded 2 : 3-*diacetoxy*-1 : 2 : 3 : 4-*tetrahydro*-5 : 8-*dimethoxy*-1 : 4-*dioxonaphthalene* as needles, m. p. 182° (38%) (Found : C, 57·3; H, 5·0. $C_{16}H_{16}O_8$ requires C, 57·15; H, 4·8%). A solution of this compound (0·4 g.) in 10% alcoholic potassium hydroxide (8 ml.) was aerated for 10 min., poured into water (30 ml.), and acidified with dilute sulphuric acid. Evaporation of the dried (Na_2SO_4) ethereal extract of this solution left 2 : 3-*dihydroxy*-5 : 8-*dimethoxy*-1 : 4-*naphthaquinone* which crystallised from benzene in red crystals, m. p. 211—213° (decomp.) (Found : C, 57·35; H, 3·95. $C_{12}H_{10}O_6$ requires C, 57·6; H, 4·0%). The quinone gave a red solution in aqueous sodium hydroxide and in concentrated sulphuric acid. The *diacetate* crystallised from light petroleum (b. p. 80—90°) as yellow needles, m. p. 127° (Found : C, 57·7; H, 4·25. $C_{16}H_{14}O_8$ requires C, 57·5; H, 4·2%).

2-*Hydroxy*-5 : 8-*dimethoxy*-1 : 4-*naphthaquinone*.—(*a*) A solution of 5 : 8-dimethoxy-1 : 4-naphthaquinone 2 : 3-epoxide (0·35 g.) in N-sodium hydroxide (10 ml.) was kept at 30—35° for 5 min., filtered, and acidified with dilute sulphuric acid. The *product* was isolated by chloroform-extraction and crystallised from light petroleum (b. p. 100—120°) in orange needles, m. p. 200° (decomp.) (57%) (Found : C, 61·8; H, 4·3. $C_{12}H_{10}O_5$ requires C, 61·5; H, 4·35%). Light absorption : $\lambda_{max.}$ (in EtOH) 421 mμ (log ε 3·78). (*b*) Naphthapurpurin was methylated as described for naphthazarin. The crude trimethyl ether (0·5 g.) (it was difficult to purify) was dissolved in N-sodium hydroxide (15 ml.) by warming at 60° for a few minutes, and acidified. The precipitate obtained was sublimed at 135°/0·03 mm. and then crystallised from light petroleum, forming orange needles, m. p. and mixed m. p. 198—200° (decomp.).

2-*Chloro*-3-*hydroxynaphthazarin*.—To a solution of 2 : 3-dichloronaphthazarin (0·2 g.) in concentrated sulphuric acid (3 ml.), water (3 ml.) was added. The suspension was heated gently under reflux for 30 min., cooled, diluted with water, and extracted with ether. The

[19] Weygand, Vogelbach, and Zimmermann, *Ber.*, 1947, **80**, 391.
[20] Fieser and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 3615.
[21] Buu-Hoï and Cagniant, *Compt. rend.*, 1942, **214**, 87.

ether solution was then extracted with 5% aqueous sodium hydrogen carbonate, from which *2-chloro-3-hydroxynaphthazarin* was precipitated on acidification. It formed red crystals, m. p. 183—187° (subl. and decomp.) (from light petroleum) (65%) (Found: C, 50·1; H, 2·15; Cl, 14·5. $C_{10}H_5O_5Cl$ requires C, 49·9; H, 2·1; Cl, 14·7%).

2-Benzylthio-3-hydroxy-1 : 4-naphthaquinone.—To a solution of 2 : 3-dibenzylthio-1 : 4-naphthaquinone (0·5 g.) in glacial acetic acid (15 ml.), 1 : 1 v/v sulphuric acid (3 ml.) was added. The red solution was heated under reflux for 3 hr., cooled, poured into water, and extracted with ether. The extract was washed with aqueous sodium carbonate (5%) from which the *hydroxyquinone* was precipitated by acidification. It crystallised from light petroleum (b. p. 80—90°) in red needles, m. p. 152° (0·21 g.) (Found: C, 68·8; H, 4·1; S, 10·4. $C_{17}H_{12}O_3S$ requires C, 68·9; H, 4·1; S, 10·8%). The *acetate* formed yellow needles, m. p. 138° (from light petroleum) (Found: C, 67·2; H, 4·4. $C_{19}H_{14}O_4S$ requires C, 67·4; H, 4·2%). Evaporation of the ether solution left starting material (0·15 g.). Under the same conditions hydrolysis with phosphoric acid–acetic acid gave the same result (lower yield) but the dibenzylthioquinone was unaffected by hydrochloric acid–acetic acid. Hydrolysis of the starting quinone (0·5 g.) in refluxing glacial acetic acid (4 ml.) containing 48% hydrobromic acid (3·1 ml.) gave, after 2 hr., a crude product which sublimed at 125°/0·03 mm. in orange crystals, m. p. 190° (70 mg.). These formed an acetate, m. p. and mixed m. p. with 2-acetoxy-1 : 4-naphthaquinone, 128°.

Hydrolysis of 2-Phenylthio-1 : 4-naphthaquinone.—A suspension of the quinone (0·5 g.) in glacial acetic acid (3 ml.) containing 48% hydrobromic acid (3 ml.) was refluxed for 2 hr., cooled, poured into water, and extracted with ether. After being washed with aqueous sodium carbonate, the ether solution was dried and evaporated. The residue was sublimed at 55°/0·01 mm. and then crystallised from aqueous methanol in plates, m. p. 60°, identical with diphenyl disulphide. Acidification of the alkaline extract yielded a product which was sublimed at 125°/0·02 mm., to give orange crystals, m. p. and mixed m. p. with 2-hydroxy-1 : 4-naphthaquinone, 188—190° (40 mg.).

2-Acetoxy-3-p-tolylthio-1 : 4-naphthaquinone.—Toluene-ω-thiol (0·35 g.) was added to a suspension of 2-acetoxy-1 : 4-naphthaquinone (0·56 g.) in ethanol (12 ml.). The mixture was gently warmed to effect complete dissolution and left overnight. A quinol separated and recrystallised from light petroleum (b. p. 80—90°) in needles, m. p. 158° (0·46 g.). This was dissolved in ethanol (5 ml.) and poured into a stirred solution of ferric chloride (10 ml., 70%). The resultant *quinone* was collected and crystallised from light petroleum (b. p. 80—90°) in yellow needles, m. p. 105° (0·32 g.) (Found: C, 67·4; H, 4·1; S, 8·5. $C_{18}H_{14}O_4S$ requires C, 67·4; H, 4·2; S, 9·4%). The products of acid hydrolysis could not be purified.

γ-(5-Bromo-2 : 4-dimethoxyphenyl)butyric Acid.—Bromine (1·1 mol.) was added to a stirred solution of γ-(2 : 4-dimethoxyphenyl)butyric acid (5 g.) in glacial acetic acid (15 ml.) at 10—12°. The mixture was left overnight at room temperature, refluxed for 3 min., cooled, and poured into water. The *product* was collected and crystallised from light petroleum (b. p. 80—90°) in needles, m. p. 107° (80%) (Found: C, 47·5; H, 5·0; Br, 26·4. $C_{12}H_{15}O_4Br$ requires C, 47·6; H, 5·05; Br, 26·6%).

8-Bromo-5 : 7-dimethoxy-1-tetralone.—The above acid (4·4 g.) was added to polyphosphoric acid (44 g.) at 165°. After 5 minutes' stirring, the mixture was cooled and poured into water. The ketone, isolated with ether, distilled at 140° (bath)/0·3 mm. (0·28 g.) and formed a 2 : 4-*dinitrophenylhydrazone* which separated from acetic acid in orange needles, m. p. 205° (Found: C, 46·7; H, 3·8; N, 12·4. $C_{18}H_{17}O_6N_4Br$ requires C, 46·4; H, 3·6; N, 12·0%).

Alkali Fusion of Chromotropic Acid.—A mixture of chromotropic acid (sodium salt, 15 g.), potassium hydroxide (75 g.), and water (1·5 ml.) was heated at 290° for 15 min. The cooled melt was dissolved in water, acidified, and extracted with ether, and this extract in turn extracted with aqueous sodium hydrogen carbonate. Acidification of the alkaline solution afforded 2 : 4-dihydroxybenzoic acid, m. p. and mixed m. p. 210° (1·3 g.).

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