The Structure of Hydrojuglone Glucoside.

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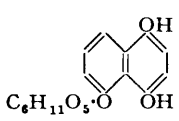
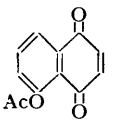
When 5-acetoxy-1 : 4-naphthaquinol (III) reacts with diazomethane the acetyl group is displaced and migrates to the *peri*-position, giving 4-acetoxy-1 : 5-dimethoxynaphthalene (VI; R = Ac). From this and the earlier work of Ruelius and Gauhe and of Daglish it follows that the naturally occurring α-hydrojuglone glucoside is the 4- (VIII) and not the 5-glucoside (I) of 1 : 4 : 5-trihydroxynaphthalene.

It has been found by Daglish (*Biochem. J.*, 1950, **47**, 452) and by Ruelius and Gauhe (*Annalen*, 1951, **571**, 69) that juglone occurs in walnut tissues (*Juglans regia*) as a glucoside of α-hydrojuglone (1 : 4 : 5-trihydroxynaphthalene). They all considered the glucose moiety to be attached at position 5 (cf. I). Ruelius and Gauhe showed that methylation of the glucoside with diazomethane, followed by removal of the glucose residue, gave a dimethoxynaphthol, m. p. 155—156°, identical with that obtained from juglone acetate (II) by catalytic reduction, methylation (with diazomethane), and final hydrolysis. This was regarded as (IV), and the glucoside consequently as (I). However, 5 : 8-dimethoxy-1-naphthol has been obtained by Asano and Hase (*J. Pharm. Soc. Japan*, 1943, **63**, 83;

Chem. Abs., 1952, **46**, 92) by a standard procedure : quinol dimethyl ether was condensed with succinic anhydride in the presence of aluminium chloride, the resulting keto-acid was reduced and cyclised to 5 : 8-dimethoxy-1-tetralone (Thomson, *J.*, 1952, 1822), and the latter dehydrogenated to give a naphthol, m. p. 103—104°. This is authentic (IV).

After various attempts to convert the naphthol of Ruelius and Gauhe into 5 : 8-dimethoxy-1 : 4-naphthaquinone by standard methods had failed, the compound was oxidised with chromium trioxide in acetic acid. This yielded juglone methyl ether (V)


(I)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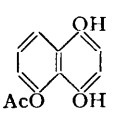
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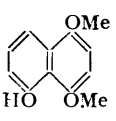
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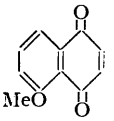
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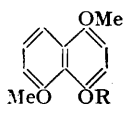
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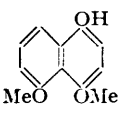
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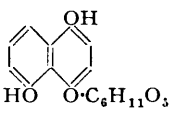
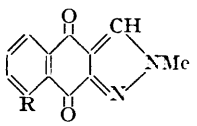

(VIII)


(IX)

together with an unidentified product of high m. p. This indicated that Ruelius and Gauhe's dimethoxynaphthol was in fact (VI; R = H) or (VII); the former structure was confirmed by another synthesis starting from juglone methyl ether. Catalytic reduction of the ether (V) followed by methylation with diazomethane gave the dimethyl ether (VI; R = H) identical with the dimethoxynaphthol obtained from (II). The alternative structure (VII) is ruled out by the fact that 1 : 8-dihydroxynaphthalene forms only a monomethyl ether with diazomethane (Boeseken and Smith, *Rec. Trav. chim.*, 1939, **58**, 125) and by the low solubility of the naphthol in aqueous sodium hydroxide. Since, in the original synthesis, the reduction product (III) can be re-oxidised to the starting material (II), an unusual reaction must take place at the methylation stage. It is known that *O*-acetyl groups can be displaced by reaction with diazomethane in the presence of water to give methyl ethers (Herzig and Tichatschek, *Ber.*, 1906, **39**, 268, 1557) and evidently in this case the neighbouring hydroxyl group functions in the same way, the displaced acetyl group in (III) migrating to the *peri*-position to yield the ether (VI; R = Ac). The mechanism is obscure. Similar migrations of acyl groups during reactions with diazomethane have been observed in compounds containing two *o*-hydroxyl groups : *e.g.*, alizarin 2-acetate reacts with diazomethane to form 1-acetoxy-2-methoxyanthraquinone (Kubota and Perkin, *J.*, 1925, **127**, 1889), and other examples were found amongst derivatives of anthragallol and gallacetophenone (Perkin and Storey, *J.*, 1928, 229; 1929, 1399). In all these cases the hydroxyl groups were close to a carbonyl group which was thought to have an important influence on the reaction. The explanation put forward at that time is inadequate but the postulated cyclic intermediate seems reasonable as the migration occurs only when the hydroxyl groups are in the *ortho*- (in the present case *peri*-) position. The migration of acyl groups in mono- and di-glycerides is also considered to proceed *via* cyclic intermediates.

The natural product must therefore be (VIII) unless a similar migration of the glucose residue occurs during the reaction of the glucoside with diazomethane. This is very unlikely. There are many examples of the treatment of glycosides with diazomethane [*e.g.*, Hasagawa, *Acta phytochim.* (*Tokyo*), 1940, **11**, 299; Zemplen and Bognár, *Ber.*, 1941, **74**, 1785; Kuhn and Löw, *Ber.*, 1944, **77**, 196] but no anomalies have been reported, and we found that phenyl and 2-naphthyl tetra-*O*-acetyl-β-D-glucoside were unaffected when treated with excess of moist ethereal diazomethane. The natural product has been synthesised by Daglish (*J. Pharm. Pharmacol.*, 1952, **4**, 539) from both α- and β-hydrojuglone and, in very low yield, from juglone but none of these syntheses establishes the structure. Under the conditions used β-hydrojuglone would rapidly enolise and, in the case of juglone, reduction evidently occurred at some stage, probably before glucoside formation. We have failed to prepare juglone glucoside, which is not surprising as even

methylation has never been achieved. In support of structure (I) Daglish (*loc. cit.*, 1950) drew attention to the reducing properties of the glucoside and the similarity of its ultraviolet absorption curve to that of the acetate (III). As naphthols in general show reducing properties (and Daglish's material was not pure) simple tests with ammoniacal silver nitrate, etc., are not very significant, and as the light absorption is broadly similar to that of 1 : 5-dihydroxy- and 1 : 4 : 5-trihydroxy-naphthalene (Daglish, *J. Amer. Chem. Soc.*, 1950, **72**, 4859) it does not exclude structure (VIII). The occurrence of this glucoside in walnut tissues interferes with the determination of ascorbic acid by titration with 2 : 6-dichlorophenol-indophenol (Daglish, *Biochem. J.*, 1950, **47**, 462; Wokes and Melville, *ibid.*, 1949, **45**, 343, and earlier papers). The dye titrations were carried out under acid conditions (pH <4), and the titre increased as the pH was lowered. We find that 1 : 5-dihydroxynaphthalene will also reduce 2 : 6-dichlorophenol-indophenol under similar conditions, the reduction being very rapid at low pH. The dye titrations are therefore not at variance with structure (VIII). [N.B. The large discrepancy in the m. p. of α-hydrojuglone glucoside reported by the English and the German workers does not affect the foregoing discussion as the same dimethoxynaphthol was obtained in each laboratory.]

It is of interest that the abnormal reaction of the acetate (III) with diazomethane proceeds more smoothly than is the case with 1 : 4-naphthaquinols in general. Smith and Webster (*J. Amer. Chem. Soc.*, 1937, **59**, 666) were unable to obtain 1 : 4-dimethoxy-2-methylnaphthalene from 2-methylnaphthaquinol, and Moore and Waters (*J.*, 1953, 3405) obtained the diazole (IX; R = H) by reaction of diazomethane with 1 : 4-naphthaquinol. We found that treatment of α-hydrojuglone with excess of diazomethane gave a dark oil from which a diazole (IX; R = OMe) was isolated in low yield. No other product could be identified. Perkin and Storey (*loc. cit.*) noted that methylations with diazomethane were occasionally accompanied by oxidation.

Experimental

4 : 8-*Dimethoxy*-1-*naphthol*.—(*a*) Ruelius and Gauhe's procedure (*loc. cit.*) was modified as follows: Juglone acetate (2·16 g.) in chloroform (30 c.c.) and methanol (30 c.c.) was hydrogenated over Adams catalyst (0·2 g.). When hydrogen uptake was complete, the solution was cooled in ice and then decanted into dry ice-cold ethereal diazomethane (from 10 g. of nitrosomethylurea). Next day the solution was evaporated to dryness *in vacuo*. The residual pale orange solid (a portion crystallised from aqueous alcohol had m. p. 117°) was dissolved in warm ethanol (20 c.c.), heated on a steam-bath for 5 min. with aqueous sodium hydroxide (10 c.c.; 2N), and then poured on ice and hydrochloric acid. The crude naphthol was collected, washed, dried, sublimed at 120—130°/0·05 mm., and crystallised from ethanol in leaflets, m. p. 155—156° (46%). (When a portion of the naphthaquinol solution was shaken with silver oxide juglone acetate was regenerated.)

(*b*) Juglone methyl ether (0·4 g.) in chloroform (30 c.c.) and methanol (30 c.c.) was hydrogenated as above and the resulting naphthaquinol solution (a portion shaken with silver oxide yielded starting material) decanted into excess of diazomethane in dry ether. Removal of the solvents next day left crude naphthol which was sublimed at 120°/0·05 mm. and crystallised from ethanol in leaflets, m. p. 155—156° (30%), identical with those obtained as in (*a*) above. The acetate had m. p. and mixed m. p. 119°.

(*c*) The same naphthol was obtained by reaction of 1 : 4 : 5-trihydroxynaphthalene in aqueous potassium hydroxide under nitrogen with a large excess of methyl sulphate. Ether-extraction of the alkaline solution yielded a crude solid from which 4 : 8-dimethoxy-1-naphthol was obtained by sublimation.

Oxidation.—A solution of chromium trioxide (0·5 g.) in water (2 c.c.) was added to a suspension of the naphthol (0·5 g.) in glacial acetic acid (10 c.c.) and the mixture gently warmed for 2—3 min. until dissolution was complete and yellow crystals began to separate. These were collected after 3 hr. and the filtrate was diluted with water and extracted with chloroform. The extract was shaken with aqueous sodium hydrogen carbonate, dried, and evaporated, leaving a residue which crystallised from alcohol in fine orange-brown needles, m. p. 186° (170 mg.), undepressed on admixture with juglone methyl ether. The yellow crystals, m. p. *ca.* 270° (55 mg.), were insoluble in aqueous alkali but dissolved in warm alcoholic sodium hydroxide.

5′-*Methoxy*-1-*methylnaphthaquinono*(3′ : 2′-3 : 4)*pyrazole.*—1 : 4 : 5-Trihydroxynaphthalene (2 g.) in ether (30 c.c.) was treated with ethereal diazomethane (from 20 g. of nitrosomethylurea) and left overnight. Removal of the solvent left a dark red oil which largely dissolved when stirred with fresh ether (30 c.c.). The insoluble portion crystallised from light petroleum (b. p. 100—120°) to give yellow crystals, m. p. 208° (120 mg.) (Found : C, 64·7; H, 4·2; N, 11·2. $C_{13}H_{10}O_3N_2$ requires C, 64·5; H, 4·2; N, 11·5%). This *compound* was insoluble in aqueous sodium hydroxide and gave no ferric chloride colour. The ether-soluble portion was extracted with aqueous sodium hydroxide. Acidification then gave a brown solid, none of which sublimed *in vacuo*, indicating the absence of (IV) and (VI; R = H). No recognisable compound was isolated.

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