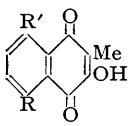
276. *Naturally Occurring Quinones: A Synthesis of Droserone.*

By R. H. Thomson.

Droserone has been synthesised and its structure established as 3 : 5-dihydroxy-2-methyl-1 : 4-naphthaquinone.

Two colouring matters occur in the outer layers of the bulb of *Drosera Whittakeri*, a plant growing in the Adelaide district of Australia. These pigments were first examined by Rennie (*J.*, 1887, **51**, 371; 1893, **63**, 1083), who showed that the yellow substance, droserone, was probably a dihydroxymethylnaphthaquinone, whilst the more abundant red material (hydroxydroserone) contained an additional hydroxyl group. Many years later Macbeth *et al.* confirmed Rennie's findings, and deduced the positions of the hydroxyl and methyl groups by comparing the natural products with a large number of hydroxynaphthaquinones, making particular use of absorption spectra and reduction potentials. It was thus shown that hydroxydroserone had the structure 3 : 5 : 8-trihydroxy-2-methyl-1 : 4-naphthaquinone (I), whilst droserone, which formed a monoboroacetate and a monopyridine salt, was considered to be either 3 : 5- or 3 : 8-dihydroxy-2-methyl-1 : 4-naphthaquinone (II or III) (Macbeth, Price, and Winzor, *J.*, 1935, 325; Macbeth and Winzor, *J.*, 1935, 334; Lugg, Macbeth, and Winzor, *J.*, 1936, 1457). Hydroxydroserone was synthesised by condensation of 3 : 6-dihydroxy-2-methoxytoluene with maleic anhydride (Winzor, *J.*, 1935, 336) and the structure (I) thereby established, but it was not found possible to distinguish between (II) and (III).



(I; R = R' = OH.)
(II; R = OH, R' = H.)
(III; R = H, R' = OH.)

The hydroxyjuglones originally prepared by Mylius (*Ber.*, 1885, **18**, 463) have recently been characterised as 2 : 5- and 3 : 5-dihydroxy-1 : 4-naphthaquinones (Thomson, *J. Org. Chem.*, 1948, **13**, 870). By treatment of these compounds with acetyl peroxide (Fieser and Oxford, *J. Amer. Chem. Soc.*, 1942, **64**, 2060), a methyl group has now been introduced into the vacant position in the quinonoid ring: 3 : 8-*dihydroxy*-2-*methyl*-1 : 4-*naphthaquinone* (III), m. p. 193°, was prepared from 2 : 5-dihydroxy-1 : 4-naphthaquinone and afforded a *diacetate*, m. p. 164°; similarly, the 3 : 5-dihydroxy-compound (II), m. p. 181° (diacetate, m. p. 119°), was prepared from the unmethylated quinone. The properties of (II) agreed with those recorded for droserone (Macbeth, *et al.*, *loc. cit.*), and their diacetates were identical (mixed m. p.) and gave concordant absorption characteristics, although only a minute amount of the "natural" material was available for examination. The absorption curves, determined by use of a Beckman Model DU spectrophotometer, showed the following maxima (solvent, 95% ethanol):

	$\lambda_{max.}$, mμ.	241	265	346
3 : 5-Diacetoxy-2-methyl-1 : 4-naphthaquinone	log *E*	4·150	4·118	3·552
Droserone diacetate	log *E*	4·155	4·125	3·566

It is noteworthy that the theoretical value for the reduction potential of droserone (with which the value determined experimentally was in good agreement) was calculated from the reduction potential of "hydroxyjuglone" on the assumption that the hydroxyl groups occupied the same relative positions in both compounds (Lugg, Macbeth, and Winzor, *loc. cit.*). This assumption is now seen to be correct, for the hydroxyjuglone obtained by Macbeth *et al.* has proved to be 3 : 5-dihydroxy-1 : 4-naphthaquinone (Thomson, *loc. cit.*).

3 : 5-Dihydroxy-1 : 4-naphthaquinone is best prepared from 3-chlorojuglone. Peroxide alkylation of the latter with acetyl peroxide, followed by treatment of the 3-*chloro*-5-*hydroxy*-2-*methyl*-1 : 4-*naphthaquinone* obtained with sodium hydroxide, provides an alternative route to

droserone, but the overall yield is lower. It also appeared to be of interest to convert juglone into droserone *via* plumbagin (5-hydroxy-2-methyl-1 : 4-naphthaquinone). Plumbagin has been synthesised by two methods, each involving a large number of stages (Fieser and Dunn, *J. Amer. Chem. Soc.*, 1936, **58**, 572; Dieterle, *Scientia Pharm.*, 1938, **9**, 121), so a one-stage synthesis from juglone by peroxide alkylation seemed attractive. Results, however, were disappointing. The product, obtained in very poor yield, was a mixture of mono- and di-methyljuglones which were exceedingly difficult to separate. Careful sublimation yielded a minute amount of material, m. p. 76—77°, which appeared to be plumbagin. Similar unsatisfactory results have been obtained by monoalkylation of other quinones having more than one free position in the quinonoid ring (private communication from Professor L. F. Fieser).

Experimental.

3 : 5-*Dihydroxy*-2-*methyl*-1 : 4-*naphthaquinone* (II).—(*a*) Acetyl peroxide (0·75 g.) was added to a suspension of 3 : 5-dihydroxy-1 : 4-naphthaquinone (1 g.) in glacial acetic acid (10 c.c.). The mixture was warmed over a free flame until effervescence commenced and then transferred to the steam-bath. The effervescence subsided after a few minutes. Heating was continued for 1 hour, and the orange-red solution then allowed to cool. The crude product which separated (0·39 g., m. p. 172—174°) was recrystallised from light petroleum (b. p. 100—120°), 50% aqueous acetic acid, and finally from glacial acetic acid, 3 : 5-dihydroxy-2-methyl-1 : 4-naphthaquinone forming yellow needles, m. p. 181° (yield, 26%) (Found : C, 64·8; H, 4·05. Calc. for $C_{11}H_8O_4$: C, 64·7; H, 3·9%). The diacetate was obtained by boiling (II) with twice its weight of acetic anhydride, containing a trace of concentrated sulphuric acid, for 2 minutes. It crystallised from light petroleum (b. p. 50—60°) in pale yellow needles, m. p. 119°; mixed m. p. with droserone diacetate, 119° (Found : C, 62·2; H, 4·1. Calc. for $C_{15}H_{12}O_6$: C, 62·5; H, 4·15%).

(*b*) To a hot solution of 3-chloro-5-hydroxy-2-methyl-1 : 4-naphthaquinone (see below) (0·5 g.) in alcohol (40 c.c.), an aqueous solution of sodium hydroxide (20 c.c., 10%) was added. The initial violet colour changed to red in about 1 minute. After being warmed on the water-bath for 1 hour, the solution was diluted with cold water (80 c.c.), acidified with hydrochloric acid, and set aside for 3 hours. The brownish-yellow precipitate was collected, dried in a vacuum, and extracted with light petroleum (b. p. 100—120°). The residue, after removal of the solvent, was recrystallised from 50% aqueous acetic acid, and then from glacial acetic acid, forming yellow needles, m. p. 181° (yield, 24%).

3 : 8-*Dihydroxy*-2-*methyl*-1 : 4-*naphthaquinone* (III).—This was prepared as described above for (II) but from 2 : 5-dihydroxy-1 : 4-naphthaquinone (0·92 g.) and acetyl peroxide (0·69 g.) in glacial acetic acid (9 c.c.). The product which crystallised on cooling (0·45 g., m. p. 179—181°) was recrystallised first from glacial acetic acid, and then several times from alcohol, from which 3 : 8-*dihydroxy*-2-*methyl*-1 : 4-*naphthaquinone* separated in minute light orange plates, m. p. 193° (yield, 23%) (Found : C, 64·8; H, 3·7. $C_{11}H_8O_4$ requires C, 64·7; H, 3·9%). The *diacetate* crystallised from methyl alcohol in pale yellow needles, m. p. 164° (Found : C, 62·2; H, 4·1. $C_{15}H_{12}O_6$ requires C, 62·5; H, 4·15%).

3-*Chlorojuglone*.—Chlorine (3·6 g.) was passed into a cold suspension of juglone (8·7 g.) in glacial acetic acid (100 c.c.). The suspension was then shaken for 20 minutes; the juglone passed into solution and the yellow dichloride began to separate. After being kept for 2 hours, the mixture was poured into cold water (800 c.c.). The yellow precipitate of juglone dichloride was collected, drained rapidly, and suspended in alcohol (100 c.c.), and the suspension heated under reflux for 20 mins. 3-Chlorojuglone was collected on cooling, and recrystallised from alcohol in orange needles, m. p. 166° (yield, 66%).

3-*Chloro*-5-*hydroxy*-2-*methyl*-1 : 4-*naphthaquinone*.—3-Chlorojuglone (1 g.) in glacial acetic acid (10 c.c.) was treated with acetyl peroxide (0·63 g.) in the usual manner. After being heated on the steam-bath for ¾ hour, the solution was concentrated to half bulk, and the crystals which deposited on cooling were recrystallised first from glacial acetic acid and then twice from aqueous acetic acid. The *quinone* separated in glistening orange-yellow leaflets, m. p. 125° (yield, 35%) (Found : C, 59·4; H, 3·2. $C_{11}H_7O_3Cl$ requires C, 59·3; H, 3·15%). The *acetate* crystallised from alcohol in light-yellow microcrystals, m. p. 144° (Found : C, 58·7; H, 3·4. $C_{13}H_9O_4Cl$ requires C, 59·0; H, 3·4%).

Peroxide Alkylation of Juglone.—A solution of juglone (5 g.) in glacial acetic acid (45 c.c.) was treated with acetyl peroxide (3·72 g.) in the usual way. After 1 hr.'s heating the solution was diluted with water and steam-distilled. The distillate (4000 c.c.) was acidified and extracted with ether, the extract washed, dried ($CaCl_2$), and the solvent removed. The orange-red residue was sublimed at 75—80°, and the sublimate resublimed at 60°, the process taking several days. The second sublimate when crystallised twice from aqueous methanol formed orange-yellow needles (*ca.* 2 mg.), m. p. 76—77° (plumbagin has m. p. 78—79°). Peroxide alkylation of juglone acetate gave a similar mixture of methyljuglones. Steam-distillation of the reaction mixture, which required several days, gave a very dilute aqueous solution of the mixed acetates, which were hydrolysed on standing.

Juglone acetate also hydrolyses with ease : when 0·2 g. was dissolved in a few c.c. of alcohol or dioxan and the solution poured into water (1 l.), the pale yellow solution obtained became orange-yellow on standing overnight, and ether extraction (without previous acidification) after 48 hours gave a mixture of juglone and a smaller amount of juglone acetate.

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