The Structure and Synthesis of Nepenthone-A, a Naphthoquinone from *Nepenthes rafflesiana*

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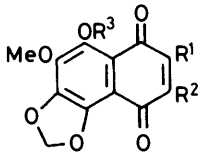
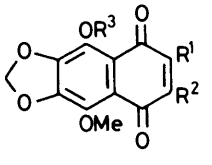
The structure of a naphthoquinone, nepenthone-A, isolated from *Nepenthes rafflesiana* Jack, is shown to be 4,7-dihydroxy-9-methoxy-6-methylnaphtho[2,3-*d*]-1,3-dioxole-5,8-dione (**6**), first by the synthesis of its di-*O*-methyl derivative (**7**), and then by the synthesis of the natural product.

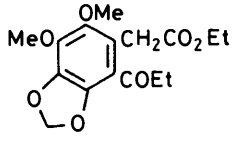
Cannon and his co-workers[1] have extracted the roots of *Nepenthes rafflesiana* Jack and have thereby isolated a number of naphthoquinones. For one of these, which they named nepenthone-A, they were able to propose, chiefly on the grounds of its spectroscopic properties, one of the four structures (**1**), (**2**), (**5**), or (**6**). They undertook to solve the problem by synthesis since suitable crystals for *X*-ray work could not be obtained. The synthetic quinone (**3**) proved to be different to di-*O*-methylnepenthone-A so that the possible structures were now limited to three: (**2**), (**5**), or (**6**). The chemical shifts of the



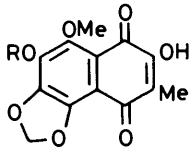
(**1**) R^1 = OH, R^2 = Me, R^3 = H
(**2**) R^1 = Me, R^2 = OH, R^3 = H
(**3**) R^1 = OMe, R^2 = R^3 = Me
(**4**) R^1 = R^3 = Me, R^2 = OMe



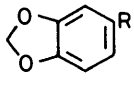
(**5**) R^1 = OH, R^2 = Me, R^3 = H
(**6**) R^1 = Me, R^2 = OH, R^3 = H
(**7**) R^1 = R^3 = Me, R^2 = OMe

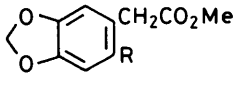


(**8**)



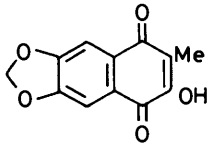
(**9**) R = Me
(**10**) R = Et





(**11**) R = NO_2
(**12**) R = CHO

(**13**) R = H
(**14**) R = COEt



(**15**)

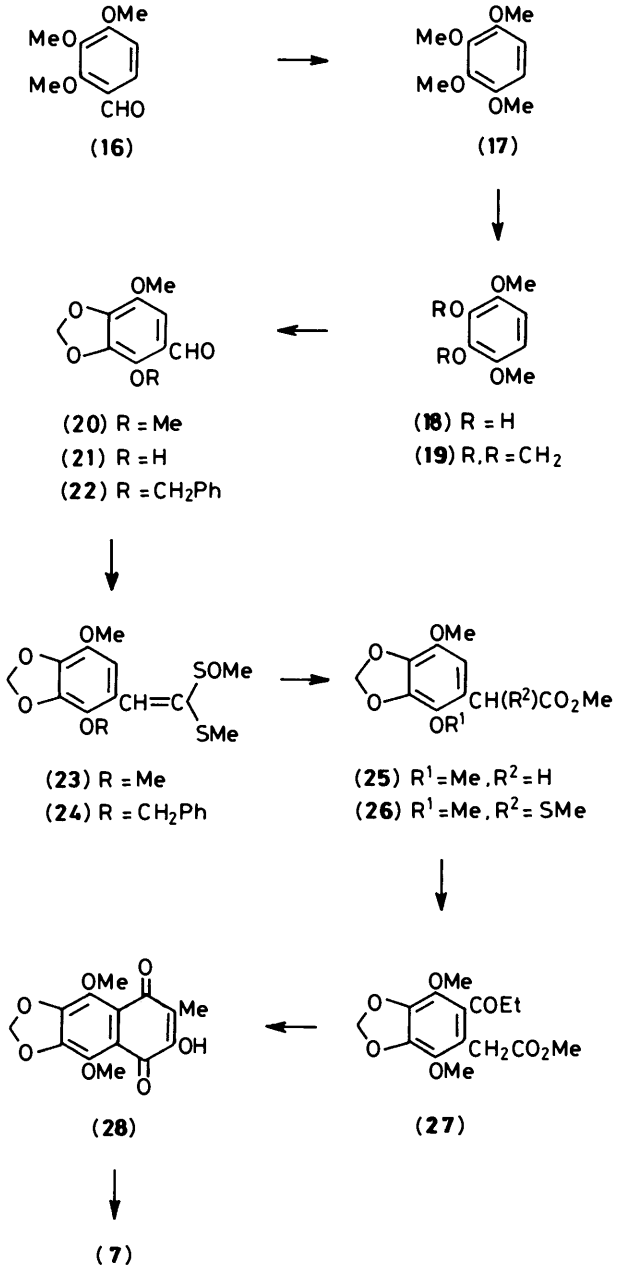
methoxy resonances in the ^{1}H n.m.r. spectrum of the synthetic quinone (**3**) were well separated but two of those in the spectrum of di-*O*-methylnepenthone-A were coincident. Cannon and his co-workers[1] therefore argued that, since the di-*O*-methyl ether (**4**) of compound (**2**), like the synthetic quinone (**3**), contains two methoxy groups in an *ortho* arrangement, the methoxy region of their ^{1}H n.m.r. spectra would be similar. Structure (**2**) was therefore rejected and it followed that nepenthone-A possesses either structure (**5**) or (**6**).

We therefore intended to verify this proposal first by the synthesis of the quinone (**7**), which should be identical with di-*O*-methylnepenthone-A. Cannon and his co-workers[1] had adopted the naphthoquinone synthesis of Bentley *et al.*,[2] for the synthesis of compound (**4**). During this synthesis they observed that treatment of the intermediate (**8**) with an excess of sodium ethoxide in ethanol, followed by oxidation with oxygen, did not give the expected 2-hydroxy-1,4-naphthoquinone (**9**), but the ethyl ether (**10**). Thus nucleophilic attack by ethoxide had occurred at the position *para* to the carbonyl group. Such reactions are well documented[3,4,5] and in the present case the difficulty was readily surmounted by the use of methoxide instead of ethoxide.

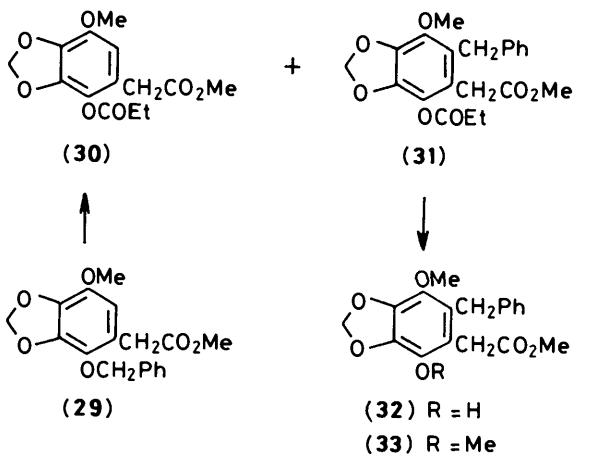
If this type of synthetic route were to be adopted for the quinone (**7**), then it is possible that a similar nucleophilic attack on the proposed intermediate (**27**) (see Scheme 1) would result in cleavage of the methylenedioxy group. The Robinsons[3] observed such a cleavage when 5-nitro-1,3-benzodioxole (**11**) was treated with either sodium methoxide or sodium ethoxide. The cleavage of the methylenedioxy group in substituted derivatives of 1,3-benzodioxole-5-carbaldehyde (piperonal) (**12**) can be achieved with both methoxide and phenoxide.[6] We therefore synthesized the ketone (**14**) by propionylation of the known acetic ester (**13**)[7] with propionic anhydride in the presence of tin(IV) chloride. When the ketone (**14**) was treated with an excess of sodium methoxide in boiling methanol, followed by aeration, a good yield of the quinone (**15**) resulted and no cleavage of the methylenedioxy group could be detected.

Consequently we sought to synthesize the ketone (**27**) as a precursor to the quinone (**7**). We therefore required 4,7-dimethoxy-1,3-benzodioxole (**19**) (see Scheme 1) as starting material. Dallacker[8] has described a synthesis of this compound from *o*-vanillin but the method is unattractive on account of its length. We have previously shown[9] that treatment of 1,2,3,4-tetramethoxybenzene (**17**)[10] with 1 mol equiv. of boron trichloride at room temperature for a short time gives 2,3,6-trimethoxyphenol in 86% yield. When the amount of boron trichloride is increased to 3 mol equiv. and the reaction time is extended to 5 h then 3,6-dimethoxybenzene-1,2-diol (**18**)[11] can be extracted from the crude product with aqueous sodium tetraborate in 80% yield. 1,2,3,4-Tetramethoxybenzene (**17**) is easily prepared by Baeyer–Villiger oxidation of the readily available 2,3,4-trimethoxybenzaldehyde (**16**)[12] and subsequent hydrolysis and methylation. Methylenation[13] of the diol (**18**) then gave the required benzodioxole (**19**).

Formylation of the benzodioxole (**19**) with *N*-methylformanilide and phosphoryl chloride gave the aldehyde (**20**) which was condensed with methyl methylthiomethyl sulphoxide[14] in the presence of Triton B, thus affording the sulphoxide (**23**). On treatment of a methanolic solution of the sulphoxide (**23**) with hydrogen chloride a mixture of the acetic ester (**25**) and its *S*-methyl derivative (**26**) resulted. On boiling this mixture with W-2 Raney nickel in methanol the *S*-methyl

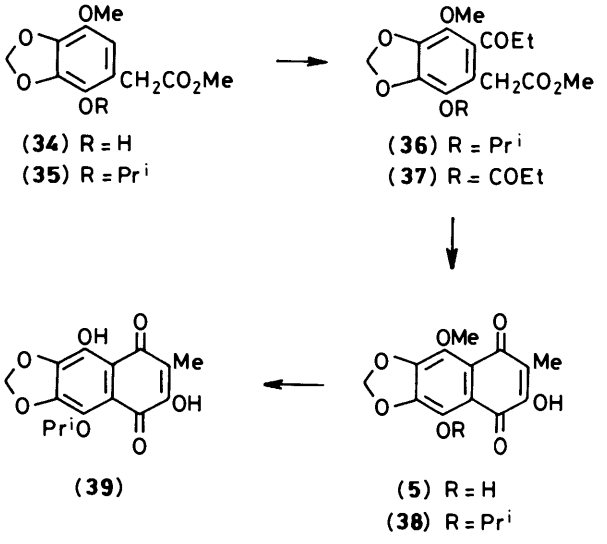


Scheme 1.



Scheme 2.

obtained. The minor product proved to be the proprionate (**30**) of the debenzylated starting material. On hydrolysis it furnished the phenol (**34**) (see Scheme 3). The other product was assigned structure (**31**). The spectroscopic data were in accord with this



Scheme 3.

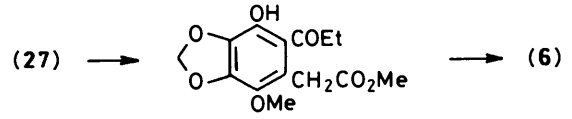
component (**26**) was hydrogenolysed to the acetate (**25**).[1] Propionylation of the acetate (**25**) was achieved with the mixed anhydride formed from propionic acid and trifluoroacetic anhydride. Ring-closure and oxidation of the resultant ketone (**27**) gave the quinone (**28**) which, on methylation, provided compound (**7**) which had the same properties as those recorded for di-*O*-methylnepenthone-A and it subsequently proved to be identical with an authentic sample of this substance.

We now embarked on the synthesis of the quinones (**5**) and (**6**) which were therefore the possible structures for nepenthone-A. We first undertook the synthesis of the quinone (**5**). Boron trichloride-induced demethylation of the aldehyde (**20**) gave the *o*-hydroxy aldehyde (**21**) which was converted into its benzyl ether (**22**). The acetic ester (**29**) (Scheme 2) was then secured *via* the intermediate sulphoxide (**24**). When this compound was allowed to react with propionic acid in the presence of trifluoroacetic anhydride, two products were structure and on hydrolysis it furnished the phenol (**32**) which was converted into the methyl ether (**33**). The ^{13}C n.m.r. spectra of both compounds (**32**) and (**33**) contained signals near δ 32 which were assigned to the methylene carbon of the diphenylmethane entity. In the ^{1}H n.m.r. spectra the analogous methylene protons resonated near δ 4.0. Thus the trifluoroacetic acid present in the reaction mixture had induced debenzylation of compound (**29**) and most of the resultant phenol (**34**) had undergone electrophilic substitution by the benzyl cation followed by *O*-propionylation thus affording compound (**31**). The remaining phenol had merely undergone *O*-propionylation, hence affording compound (**30**).

We therefore prepared the phenol (**34**) (see Scheme 3) by hydrogenolytic debenzylation of compound (**29**). The derived isopropyl ether (**35**) now underwent smooth proprionylation, and ring-closure and oxidation of the resultant ketone (**36**) provided the quinone (**38**). We have previously observed that

isopropyl ethers in an *ortho*-relationship to a carbonyl group can be cleaved in the presence of methyl ethers in a similar situation.[15] It did not prove to be the case here, however, since on treatment of the quinone (**38**) with boron trichloride it was the methyl ether which underwent cleavage and the quinone (**39**) resulted. It may be that boron trichloride is better able to co-ordinate at the methoxy-substituted *peri*-position. The quinone (**38**) was unaffected by titanium(IV) chloride.[15]

When the phenol (**34**) was allowed to react for a prolonged period (7 days) with propionic acid and trifluoroacetic anhydride both *O*- and *C*-propionylation took place and a good yield of the ketone (**37**) resulted. This compound, on ring-closure and oxidation, furnished the quinone (**5**) which was different in m.p. and spectroscopic properties from nepenthone-A which must therefore have structure (**6**). This last-mentioned quinone was obtained (see Scheme 4) when the ketone (**27**) was



(**40**)

Scheme 4.

selectively demethylated with boron trichloride and the resultant *o*-hydroxypropiophenone (**40**) was ring-closed and oxidized. The synthetic quinone (**6**) proved to be identical in all respects with an authentic sample of nepenthone-A which therefore must possess this structure.

Experimental

M.p.s were determined on a Kofler hot-stage apparatus. Light petroleum was a fraction b.p. *ca.* 55—65 °C. All organic extracts were washed with saturated brine, and were then dried over anhydrous sodium sulphate, prior to evaporation under reduced pressure. Radial chromatography was carried out on a Harrison Research Chromatotron with plates coated with Merck Kieselgel $60PF_{254}$. Silica gel was B.D.H. 60—120 mesh, and alumina was Fluka neutral (Brockmann activity I). N.m.r. spectra were recorded at 60 MHz on a Hitachi–Perkin-Elmer R24 B instrument (^1H), at 80 MHz (^1H) or 20.1 MHz (^{13}C) on a Bruker WP-80 instrument, at 300 MHz (^1H) or 75.5 MHz (^{13}C) on a Bruker AM-300 instrument. Mass spectra (35 eV) were recorded with a Hewlett-Packard 5986 instrument. I.r. spectra were recorded on a Perkin-Elmer 283 spectrophotometer and electronic spectra were measured with a Hewlett-Packard 8450A instrument.

Methyl 5-(1-*Oxopropyl*)-1,3-*benzodioxol*-6-*ylacetate* (**14**).—Tin(IV) chloride (2.7 ml) was added dropwise at room temperature to a solution of methyl 1,3-benzodioxol-5-ylacetate (**13**) (2.0 g)[7] and propionic anhydride (1.47 g) in 1,2-dichloroethane (5.0 ml). The mixture was stirred at room temperature for 1.5 h and then poured into cold dilute hydrochloric acid. The suspension was extracted with ethyl acetate and the extract was washed successively with dilute hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and finally with saturated brine. The crude product crystallized from cyclohexane (charcoal) as plates (1.0 g, 39%) of the *ketone* (**14**), m.p. 123—123.5 °C (Found: C, 62.35; H, 5.7%; M^+, 250. $C_{13}H_{14}O_5$ requires C, 62.4; H, 5.65%; *M*, 250); $\delta_H(CDCl_3, 60\ MHz)$ 1.16 (3 H, t, $COCH_2Me$), 2.83 (2 H, q, $COCH_2Me$), 3.59 (3 H, s, OMe), 3.77 (2 H, s, CH_2CO_2Me), 5.88 (2 H, s, OCH_2O), 6.58 (1 H, s, 7-H), and 7.10 (1 H, s, 4-H).

6-*Hydroxy*-7-*methylnaphtho*[2,3-d]-1,3-*dioxole*-5,8-*dione* (**15**).—The ketone (**14**) (500 mg) and sodium methoxide [from sodium (100 mg)] were heated under reflux in anhydrous methanol (11 ml) under dry nitrogen for 35 min. The solution was then diluted with methanol (30 ml) and a brisk stream of air was passed through it for 45 min. The solution was poured into dilute hydrochloric acid and extracted with ethyl acetate. This extract was washed with aqueous sodium carbonate and acidification and isolation of the crude product with ethyl acetate gave the *quinone* (**15**) (410 mg, 88%) which formed deep orange needles from chloroform, m.p. 226–227 °C (Found: C, 61.9; H, 3.4%; M^+, 232. $C_{12}H_8O_5$ requires C, 62.05; H, 3.5%; *M*, 232); $\delta_H(CD_3SOCD_3, 80\ MHz)$ 1.86 (3 H, s, Me), 6.21 (2 H, s, OCH_2O), and 7.24 and 7.28 (each 1 H, s, ArH).

1,2,3,4-*Tetramethoxybenzene* (**17**).—A solution of 2,3,4-trimethoxybenzaldehyde (**16**) (30.0 g)[12] in dichloromethane (600 ml) was added slowly to a stirred solution of *m*-chloroperoxybenzoic acid (85%, 32.7 g) in dichloromethane (600 ml). After 5 h the solution was concentrated under reduced pressure to a quarter of its original volume and then cooled in ice. The precipitated *m*-chlorobenzoic acid was filtered off and washed with a little ice-cold dichloromethane. The solvent was removed from the filtrate under reduced pressure and the residue was dissolved in ethyl acetate. This solution was washed in turn with saturated aqueous sodium hydrogen carbonate until effervescence ceased, with water, and finally with saturated brine. The crude product in methanol (300 ml) was stirred with aqueous sodium hydroxide (10%; 250 ml) with ice-cooling under nitrogen for 1.5 h. After acidification, isolation of the product with ethyl acetate gave the crude phenol (21.8 g) which was methylated with methyl sulphate (12.4 ml) and potassium carbonate (18.0 g) in boiling acetone (250 ml) during 17 h. Work-up gave the crude product which was filtered through a plug of alumina with light petroleum as eluant. The ether (**17**) (17.8 g, 59%) formed needles from light petroleum, m.p. 87.5—88 °C (lit.,[10] 89 °C).

3,6-*Dimethoxybenzene*-1,2-*diol* (**18**).—Boron trichloride (14.1 g) in dichloromethane (30 ml) was added dropwise at 0 °C to a stirred solution of 1,2,3,4-tetramethoxybenzene (**17**) (8.0 g) in dichloromethane (80 ml). The solution was stirred at room temperature for 5 h and then poured into ice–water and extracted with ethyl acetate. The extract was washed several times with saturated aqueous sodium tetraborate and these washings were acidified and extracted with ethyl acetate. Removal of the solvent gave the diol (**18**) (5.54 g, 80%) pure enough for the next step. A sample formed prisms (from dichloromethane–light petroleum), m.p. 105—106 °C (lit.,[11] 105—106 °C); $\delta_H(CDCl_3, 80\ MHz)$ 3.84 (6 H, s, 2 × OMe), 5.41 (2 H, s, 2 × D_2O-exchangeable OH), and 6.38 (2 H, s, ArH).

4,7-*Dimethoxy*-1,3-*benzodioxole* (**19**).—The phenol (**18**) (10.50 g) and anhydrous caesium fluoride (28.3 g) were shaken with anhydrous *N,N*-dimethylformamide (120 ml) and then dibromomethane (10.9 g) was added and the mixture was stirred and heated at 120—130 °C (bath) under dry nitrogen for 6 h. The solution was poured into ice–water and then extracted with ether. The extract was washed in turn with water, aqueous sodium hydroxide, and finally with saturated brine. The crude product was filtered through a plug of alumina with 5% ethyl acetate–light petroleum as eluant. The dioxole (**19**) (5.9 g, 52%) formed needles (from dichloromethane–light petroleum), m.p. 76.5—77.5 °C (lit.,[8] 78.5 °C).

4,7-*Dimethoxy*-1,3-*benzodioxole*-5-*carbaldehyde* (**20**).—Phosphoryl chloride (7.24 g) was added dropwise at 0 °C to a mixture of the foregoing dioxole (**19**) (5.50 g) and *N*-methylformanilide

(4.49 g). The mixture was stirred at room temperature for 48 h and ice and an excess of aqueous sodium acetate were added. The mixture was extracted with ethyl acetate and the extract was washed in turn with dilute hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and finally with saturated brine. The crude product was crystallized from methanol and was obtained as needles (5.52 g, 87%), m.p. 101.5—102.5 °C (lit.,[8] 102.5 °C); $\delta_H(CDCl_3, 60$ MHz) 3.80 and 3.96 (each 3 H, s, OMe), 5.95 (2 H, s, OCH_2O), 6.94 (1 H, s, ArH), and 10.02 (1 H, s, CHO).

4,7-*Dimethoxy*-5-[2-(*methylsulphinyl*)-2-(*methylthio*)*ethenyl*]-1,3-*benzodioxole* (**23**).—A methanolic solution of Triton B (0.5 ml, 40%) was added to a solution of the foregoing aldehyde (**20**) (700 mg) and methyl methylthiomethyl sulphoxide (475 mg) in anhydrous tetrahydrofuran (5 ml). The solution was heated under reflux under dry nitrogen for 4 h and then poured into water. Isolation with ethyl acetate gave the crude product which was purified by radial chromatography with 50% ethyl acetate–light petroleum as eluant. The *sulphoxide* (**23**) (761 mg, 72%) crystallized from dichloromethane–light petroleum as prisms, m.p. 104—105 °C (Found: C, 49.4; H, 4.95; S, 20.2%; M^+, 316. $C_{13}H_{16}O_5S_2$ requires C, 49.35; H, 5.1; S, 20.25%; *M*, 316); $\delta_H(CDCl_3, 80$ MHz) 2.32 (3 H, s, SMe), 2.75 (3 H, s, SOMe), 3.90 and 3.96 (each 3 H, s, OMe), 6.02 (2 H, s, OCH_2O), 7.65 (1 H, s, vinyl H), and 7.87 (1 H, s, ArH).

Methyl 4,7-*Dimethoxy*-1,3-*benzodioxol*-5-*ylacetate* (**25**).—The sulphoxide (**23**) (300 mg) was dissolved in anhydrous methanol (10 ml) and cooled to −5 °C and a stream of dry hydrogen chloride was passed through the solution for 5 min. The solution was poured into saturated aqueous sodium hydrogen carbonate and the crude product was isolated with ethyl acetate. The residue left on removal of the solvent was heated under reflux with W-2 Raney nickel (5.0 g) in methanol (20 ml) for 1 h. The Raney nickel was filtered off and most of the methanol was removed under reduced pressure. The solution was diluted with water and the product was isolated with ethyl acetate. The *ester* (**25**) (145 mg, 60%) crystallized from light petroleum as needles, m.p. 52.5—53.5 °C (Found: C, 56.5; H, 5.5%; M^+, 254. $C_{12}H_{14}O_6$ requires C, 56.7; H, 5.55%; *M*, 254); $\delta_H(CDCl_3, 80$ MHz) 3.55 (2 H, s, CH_2CO_2Me), 3.70, 3.85, and 3.89 (each 3 H, s, OMe), 5.96 (2 H, s, OCH_2O), and 6.36 (1 H, s, ArH).

Methyl 4,7-*Dimethoxyl*-5-(1-*oxopropyl*)-1,3-*benzodioxol*-6-*ylacetate* (**27**).—The ester (**25**) (806 mg) in propionic acid (2.34 ml) was treated at 0 °C with trifluoroacetic anhydride (4.42 ml) and the solution was then stirred at room temperature for 18 h. Work-up gave a crude product which was purified by radial chromatography with 15% ethyl acetate–light petroleum as eluant. The *ketone* (**27**) crystallized from light petroleum as prisms (875 mg, 89%), m.p. 74—75 °C (Found: C, 57.85; H, 5.85%; M^+, 310. $C_{15}H_{18}O_7$ requires C, 58.05; H, 5.85%; *M*, 310); $\delta_H(CDCl_3, 80$ MHz) 1.12 (3 H, t, $COCH_2Me$), 2.78 (2 H, q, $COCH_2Me$), 3.55 (2 H, s, CH_2CO_2Me), 3.68, 3.88, and 3.91 (each 3 H, s, OMe), and 5.99 (2 H, s, OCH_2O).

6-*Hydroxy*-4,9-*dimethoxy*-7-*methylnaphtho*[2,3-d]-1,3-*dioxole*-5,8-*dione* (**28**).—Ring-closure and oxidation of the ketone (**27**) (100 mg) in a manner similar to that described above for the synthesis of the quinone (**15**) gave the *quinone* (**28**) (42 mg, 44%) as pale orange needles (from acetone–light petroleum), m.p. 197—198 °C (Found: C, 57.9; H, 4.3%; M^+, 292. $C_{14}H_{12}O_7$ requires C, 57.55; H, 4.15%; *M*, 292); $\delta_H(CDCl_3, 80$ MHz) 2.01 (3 H, s, Me), 3.98 and 4.06 (each 3 H, s, OMe), 6.15 (2 H, s, OCH_2O), and 7.44 (1 H, s, D_2O-exchangeable OH).

4,6,9-*Trimethoxy*-7-*methylnaphtho*[2,3-d]-1,3-*dioxole*-5,8-*dione* (*Di*-O-*methylnepenthone-A*) (**7**).—Methylation of the quinone (**28**) with iodomethane and potassium carbonate in *N*,*N*-dimethylformamide for 18 h in the usual way gave a crude product which was purified by radial chromatography with 30% ethyl acetate–light petroleum as eluant. Synthetic *di*-O-*methylnepenthone-A* (**7**) crystallized from dichloromethane–light petroleum as yellow needles, m.p. 169—171 °C (lit.,[1] 165—167 °C), undepressed on admixture with an authentic sample (Found: C, 58.85; H, 4.5. $C_{15}H_{14}O_7$ requires C, 58.85; H, 4.6%); *m*/*z* (35 eV) 307 (15%), 306 (100, M^+), 291 (47), 276 (13), 273 (23), 263 (30), 261 (24), and 245 (28); $\delta_H(CDCl_3, 80$ MHz) 1.99 (3 H, s, Me), 3.99 (3 H, s, OMe), 4.02 (6 H, s, 2 × OMe), and 6.14 (2 H, s, OCH_2O); $\nu_{max.}$(KBr) 1 650 (C=O) cm^{-1}; $\lambda_{max.}$(MeOH) 219, 271, 305, and 387 nm (ε 25 700, 21 900, 9 100, and 3 600, respectively). It was identical (mixed m.p., mass spectrum, and R_F values on t.l.c. in three different solvent systems) with an authentic sample.

4-*Hydroxy*-7-*methoxy*-1,3-*benzodioxole*-5-*carbaldehyde* (**21**).—Boron trichloride (3.32 g) in dichloromethane (6 ml) was added dropwise at −10 °C to a stirred solution of the aldehyde (**20**) (2.96 g) in dichloromethane (25 ml). The solution was stirred at room temperature for 15 min and then poured into water–ice. Isolation with ethyl acetate gave the crude product which crystallized from ethyl acetate (charcoal) as plates of the *aldehyde* (**21**) (1.80 g, 70%), m.p. 179—180 °C (Found: C, 55.35; H, 4.1%; M^+, 196. $C_9H_8O_5$ requires C, 55.1; H, 4.1%; *M*, 196); $\delta_H(CDCl_3, 80$ MHz) 3.90 (3 H, s, OMe), 6.14 (2 H, s, OCH_2O), 6.72 (1 H, s, ArH), 9.71 (1 H, s, CHO), and 10.79 (1 H, s, D_2O-exchangeable OH).

4-*Benzyloxy*-7-*methoxy*-1,3-*benzodioxole*-5-*carbaldehyde* (**22**).—The aldehyde (**21**) (1.92 g), benzyl bromide (2.02 g), and anhydrous potassium carbonate (1.65 g) were stirred in dry *N*,*N*-diemethylformamide (30 ml) at 75 °C (bath) under dry nitrogen for 3 h. The mixture was diluted with water and extracted with ethyl acetate and the solvent and excess of benzyl bromide were removed by steam distillation. The pot residue was isolated with ethyl acetate and the crude product was crystallized from dichloromethane–light petroleum to give the *aldehyde* (**22**) (2.61 g, 93%) as needles, m.p. 109—110 °C (Found: C, 67.2; H, 5.0%; M^+, 286. $C_{16}H_{14}O_5$ requires C, 67.15; H, 4.95%; *M*, 286); $\delta_H(CDCl_3, 80$ MHz) 3.88 (3 H, s, OMe), 5.28 (2 H, s, CH_2Ph), 6.11 (2 H, s, OCH_2O), 7.06 (1 H, s, ArH), 7.36 (5 H, s, Ph), and 10.18 (1 H, s, CHO).

4-*Benzyloxy*-7-*methoxy*-5-[2-(*methylsulphinyl*)-2-(*methylthio*)*ethenyl*]-1,3-*benzodioxole* (**24**).—In a manner similar to that described for the preparation of compound (**23**), the aldehyde (**22**) (2.46 g) was allowed to react with methyl methylthiomethyl sulphoxide (1.24 g). Purification of the crude product by radial chromatography gave the *sulphoxide* (**24**) (2.03 g, 60%) as spars (from dichloromethane–light petroleum), m.p. 91—92 °C (Found: C, 58.4; H, 5.3; S, 16.4%; M^+, 392. $C_{19}H_{20}O_5S_2$ requires C, 58.15; H, 5.3; S, 16.4%; *M*, 392); $\delta_H(CDCl_3, 80$ MHz) 2.22 (3 H, s, SMe), 2.69 (3 H, s, SOMe), 3.88 (3 H, s, OMe), 5.16 (2 H, s, CH_2Ph), 6.04 (3 H, s, OCH_2O), 7.34—7.37 (5 H, m, Ph), 7.60 (1 H, s, vinyl H), and 7.88 (1 H, s, ArH).

Methyl 4-*Benzyloxy*-7-*methoxy*-1,3-*benzodioxol*-5-*ylacetate* (**29**).—The sulphoxide (**24**) (1.87 g) was treated in methanol with hydrogen chloride in a manner similar to that described for the preparation of compound (**25**). The crude product was boiled in methanol with Raney nickel for 1 h. Radial chromatography of the crude product with 20% ethyl acetate–light petroleum as eluant gave from a band of higher R_F the *ester* (**29**)

(847 mg, 54%) as prisms (from light petroleum), m.p. 76—77 °C (Found: C, 65.55; H, 5.3%; M^+, 330. $C_{18}H_{18}O_6$ requires C, 65.45; H, 5.5%; *M*, 330); δ_H($CDCl_3$, 80 MHz) 3.53 (2 H, s, CH_2CO_2Me), 3.63 (3 H, s, CO_2Me), 3.86 (3 H, s, OMe), 5.13 (2 H, s, CH_2Ph), 5.98 (2 H, s, OCH_2O), 6.36 (1 H, s, ArH), and 7.34—7.36 (5 H, m, Ph). Further elution supplied *methyl* 4-*hydroxy*-7-*methoxy*-1,3-*benzodioxol*-5-*ylacetate* (**34**) (300 mg, 26%) as plates (from dichloromethane–light petroleum), m.p. 89—89.5 °C (Found: C, 54.95; H, 5.25%; M^+, 240. $C_{11}H_{12}O_6$ requires C, 55.0; H, 5.05%; *M*, 240); δ_H($CDCl_3$, 80 MHz) 3.61 (2 H, s, CH_2CO_2Me), 3.75 (3 H, s, CO_2Me), 3.84 (3 H, s, OMe), 5.98 (2 H, s, OCH_2O), 6.29 (1 H, s, ArH), and 6.68 (1 H, s, D_2O-exchangeable OH).

Attempted Propionylation of Methyl 4-*Benzyloxy*-7-*methoxy*-1,3-*benzodioxol*-5-*ylacetate* (**29**).—Treatment of the acetate (**29**) (653 mg) with trifluoroacetic anhydride and propionic acid for 2.5 h in a manner similar to that described for the synthesis of compound (**27**) gave a crude product which was subjected to radial chromatography with 20% ethyl acetate–light petroleum as eluant. The band of higher R_F afforded methyl 6-benzyl-7-methoxy-4-propionyloxy-1,3-benzodioxol-5-ylacetate (**31**) as a thick oil (412 mg, 54%); *m*/*z* 386 (M^+); δ_H($CDCl_3$, 80 MHz) 1.25 (3 H, t, $OCOCH_2Me$), 2.58 (2 H, q, $OCOCH_2Me$), 3.45 (2 H, s, CH_2CO_2Me), 3.54 (3 H, s, CO_2Me), 3.86 (3 H, s, OMe), 4.04 (2 H, s, $ArCH_2Ph$), 5.98 (2 H, s, OCH_2O), and 7.02—7.20 (5 H, m, Ph). Further elution gave methyl 7-methoxy-4-propionyloxy-1,3-benzodioxol-5-ylacetate (**30**) (164 mg, 28%) as a thick oil; *m*/*z* 296 (22%, M^+), 180 (100), 208 (92), 240 (67), and 181 (34); δ_H($CDCl_3$, 80 MHz) 1.26 (3 H, t, $OCOCH_2Me$), 2.60 (2 H, q, $OCOCH_2Me$), 3.47 (2 H, s, CH_2CO_2Me), 3.66 (3 H, s, CO_2Me), 3.88 (3 H, s, OMe), 5.99 (2 H, s, OCH_2O), and 6.44 (1 H, s, ArH). On hydrolysis with aqueous methanolic sodium hydroxide at room temperature this compound afforded the phenol (**34**).

Methyl 6-*Benzyl*-4-*hydroxy*-7-*methoxy*-1,3-*benzodioxol*-5-*ylacetate* (**32**).—The ester (**31**) (400 mg) was heated under reflux for 1 h with sodium methoxide [from sodium (400 mg)] in anhydrous methanol (40 ml) under dry nitrogen. The solution was acidified with dilute hydrochloric acid and isolation with ethyl acetate gave a crude product which was subjected to radial chromatography with 20% ethyl acetate–light petroleum as eluant. This gave the phenol (**32**) (306 mg, 89%) as a thick oil; *m*/*z* 330 (M^+); δ_H($CDCl_3$, 80 MHz) 3.57 (5 H, s, CH_2CO_2Me), 3.79 (3 H, s, OMe), 4.03 (2 H, s, $ArCH_2Ph$), 5.97 (2 H, s, OCH_2O), 6.39 (1 H, s, D_2O-exchangeable OH), and 7.03—7.20 (5 H, m, Ph); δ_C($CDCl_3$, 20.1 Hz) 31.9 and 32.7 (each t, CH_2CO_2Me or $ArCH_2Ph$), 52.5 (q, CO_2Me), 60.3 (q, *Me*), 101.8 (t, C-2), 116.3 and 125.4 (each s, ArC), 126.0, 128.2, and 128.5 (each d, 5 × PhCH), 135.9, 136.8, 137.2, 138.2, and 140.8 (each s, 4 × ArC and 1 × PhC), and 173.9 (s, CO); $\nu_{max.}$(film) 3 340 (br, OH), 1 715 (C=O), 1 620, and 1 480 cm^{-1}. On methylation with iodomethane and potassium carbonate in *N*,*N*-dimethylformamide at room temperature this phenol afforded *methyl* 6-*benzyl*-4,7-*dimethoxy*-1,3-*benzodioxol*-5-*ylacetate* (**33**) as a thick oil (Found: C, 66.35; H, 5.8%; M^+, 344. $C_{19}H_{20}O_6$ requires C, 66.25; H, 5.85%; *M*, 344); δ_H ($CDCl_3$, 80 MHz) 3.55 (5 H, s, CH_2CO_2Me), 3.79 and 3.90 (each 3 H, s, OMe), 3.97 (2 H, s, $ArCH_2Ph$), 5.95 (2 H, s, OCH_2O), and 7.01—7.21 (5 H, m, Ph); δ_C($CDCl_3$, 75.5 MHz) 31.9 and 32.0 (each t, CH_2CO_2Me or $ArCH_2Ph$), 51.8 (q, CO_2Me), 59.8 and 60.0 (each q, O*Me*), 101.24 (t, C-2), 119.6 and 125.4 (each s, ArC), 125.7, 128.0, and 128.2 (each d, 5 × PhCH), 137.0, 137.4, 137.7, 138.2, and 140.4 (each s, 4 × ArC and 1 × PhC), and 172.2 (CO); $\nu_{max.}$(film) 1 740 (C=O), 1 615, 1 450, 1 345, and 1 055 cm^{-1}.

Methyl 4-*Hydroxy*-7-*methoxy*-1,3-*benzodioxol*-5-*ylacetate* (**34**).—The benzyl ether (**29**) (770 mg) in ethyl acetate (20 ml) containing concentrated hydrochloric acid (2 drops) was stirred under an atmosphere of hydrogen with palladized charcoal (10%, 150 mg) until absorption ceased. Work-up gave the phenol (**34**) (554 mg, 99%), which formed plates (from dichloromethane–light petroleum), m.p. and mixed m.p. 89—89.5 °C.

Methyl 4-*Isopropoxy*-7-*methoxy*-1,3-*benzodioxol*-5-*ylacetate* (**35**).—The foregoing phenol (**34**) (300 mg) was stirred in anhydrous *N*,*N*-dimethylformamide (5 ml) with potassium carbonate (252 mg) and 2-bromopropane (221 mg) at 70 °C (bath) under dry nitrogen for 2 h. The mixture was poured into water and isolation with ethyl acetate gave a crude product which was filtered through a plug of alumina with 10% ethyl acetate–light petroleum as eluant. This afforded the *acetate* (**35**) (298 mg, 85%) as an oil, b.p. 140—150 °C at 0.01 mmHg (Kugelrohr) (Found: C, 59.75; H, 6.35%; M^+, 282. $C_{14}H_{18}O_6$ requires C, 59.55; H, 6.45%; *M*, 282); δ_H($CDCl_3$, 80 MHz) 1.26 (6 H, d, $CHMe_2$), 3.56 (2 H, s, CH_2CO_2Me), 3.69 (3 H, s, CO_2Me), 3.85 (3 H, s, OMe), 4.60 (1 H, septet, $CHMe_2$), 5.93 (2 H, s, OCH_2O), and 6.39 (1 H, s, ArH).

Methyl 7-*Isopropoxy*-4-*methoxy*-5-(1-*oxopropyl*)-1,3-*benzodioxol*-6-*ylacetate* (**36**).—Propionylation of the acetate (**35**) (88 mg) in a similar manner to that described for the synthesis of compound (**27**) gave a crude product which was purified by radial chromatography with 20% ethyl acetate–light petroleum as eluant. This afforded the *ketone* (**36**) (94 mg, 89%) as a pale yellow oil, b.p. 135—140 °C at 0.01 mmHg (Kugelrohr) (Found: C, 60.55; H, 6.55%; M^+, 338. $C_{17}H_{22}O_7$ requires C, 60.35; H, 6.55%; *M*, 338); δ_H($CDCl_3$, 80 MHz) 1.11 (3 H, t, CH_2Me), 1.24 (6 H, d, $CHMe_2$), 2.79 (2 H, q, CH_2Me), 3.58 (2 H, s, CH_2CO_2Me), 3.66 (3 H, s, CO_2Me), 3.91 (3 H, s, OMe), 4.62 (1 H, septet, $CHMe_2$), and 5.95 (2 H, s, OCH_2O).

6-*Hydroxy*-4-*isopropoxy*-9-*methoxy*-7-*methylnaphtho*[2,3-d]-1,3-*dioxole*-5,8-*dione* (**38**).—Ring-closure and oxidation of the ketone (**36**) (266 mg) in a manner similar to that described above for the synthesis of the quinone (**15**) gave, after chromatography of the crude product over silica gel with 30% ethyl acetate–light petroleum as eluant, the *quinone* (**38**) as feathery yellow needles (132 mg, 58%), m.p. 133—135 °C (from dichloromethane–light petroleum) (Found: C, 59.75; H, 5.3%; M^+, 320. $C_{16}H_{16}O_7$ requires C, 60.0; H, 5.05%; *M*, 320); δ_H($CDCl_3$, 80 MHz) 1.38 (6 H, d, $CHMe_2$), 2.01 (3 H, s, Me), 3.98 (3 H, s, OMe), 4.68 (1 H, septet, $CHMe_2$), 6.13 (2 H, s, OCH_2O), and 7.48 (1 H, s, D_2O-exchangeable OH); $\nu_{max.}$(KBr) 3 350, 1 640 (C=O), and 1 568 cm^{-1}; $\lambda_{max.}$(MeOH) 216, 270, 318, and 388 nm (ε 17 400, 16 600, 7 800, and 2 000, respectively).

6,9-*Dihydroxy*-4-*isoproproxy*-7-*methylnaphtho*[2,3-d]-1,3-*dioxole*-5,8-*dione* (**39**).—Boron trichloride (220 mg) in dichloromethane (0.2 ml) was added at −78 °C to a stirred solution of the foregoing quinone (**38**) (100 mg) in dichloromethane (5 ml). The solution was stirred at −78 °C for 10 min and then quenched with water. Isolation with ethyl acetate gave a crude product which was subjected to radial chromatography with 25% ethyl acetate–light petroleum as eluant. A band of higher R_F yielded the *quinone* (**39**) (25 mg, 26%) which formed orange needles (from dichloromethane–light petroleum), m.p. 207—208 °C (Found: C, 59.15, H, 4.55%; M^+, 306. $C_{15}H_{14}O_7$ requires C, 58.85; H, 4.6%; *M*, 306); δ_H($CDCl_3$, 80 MHz) 1.38 (6 H, d, $CHMe_2$), 2.02 (3 H, s, Me), 4.70 (1 H, septet, $CHMe_2$), 6.17 (2 H, s, OCH_2O), and 7.85 (1 H, s, D_2O-exchangeable OH); $\nu_{max.}$(KBr) 3 315, 1 621 (C=O), and 1 320 cm^{-1}; $\lambda_{max.}$(MeOH)

227, 266, 332, and 434 nm (ε 15 100, 13 500, 6 000, and 3 000, respectively).

Methyl 4-Methoxy-5-(1-oxopropyl)-7-propionyloxy-1,3-benzodioxol-6-ylacetate (**37**).—The phenol (**34**) (270 mg) in propionic acid (1.7 ml) was stirred at 0 °C during the dropwise addition of trifluoroacetic anhydride (3.5 ml). The solution was stirred at room temperature for 7 days and work-up gave a crude product which was purified by radial chromatography with 20% ethyl acetate–light petroleum as eluant. The major band afforded the *ketone* (**37**) (247 mg, 63%) which formed needles (from light petroleum), m.p. 82–83.5 °C (Found: C, 58.15; H, 5.65%; M^+, 352. $C_{17}H_{20}O_8$ requires C, 57.95; H, 5.7%; *M*, 352); δ_H($CDCl_3$, 300 MHz) 1.14 (3 H, t, $COCH_2Me$), 1.26 (3 H, t, $OCOCH_2Me$), 2.60 (2 H, q, $COCH_2Me$), 2.82 (2 H, q, $OCOCH_2Me$), 3.47 (2 H, s, CH_2CO_2Me), 3.64 (3 H, s, CO_2Me), 3.98 (3 H, s, OMe), and 6.01 (2 H, s, OCH_2O).

4,6-*Dihydroxy-9-methoxy-7-methylnaphtho*[2,3-d]-1,3-*dioxole-5,8-dione* (**5**).—Ring-closure and oxidation of the ketone (**37**) (120 mg) in a manner similar to that described for the synthesis of compound (**15**) gave, after chromatography of the crude product over silica gel, the *quinone* (**5**) (90 mg, 67%), as orange needles (from acetone–light petroleum), m.p. 223–226 °C (Found: C, 56.2, H, 3.6. $C_{13}H_{10}O_7$ requires C, 56.1; H, 3.6%); *m/z* (35 eV) 278 (100%, M^+), 263 (16), 260 (25), 235 (15), 232 (30), 204 (35), 203 (17), 176 (29), 149 (19), and 121 (20); δ_H($CDCl_3$, 80 MHz) 2.05 (3 H, s, Me), 3.98 (3 H, s, OMe), 6.20 (2 H, s, OCH_2O), and 7.04 and 11.64 (each 1 H, s, D_2O-exchangeable OH); $\nu_{max.}$(KBr) 3 380, 1 660 (C=O), 1 626 (C=O), and 1 380 cm^{-1}; $\lambda_{max.}$(MeOH) 225, 268, 330, and 424 mm (ε 19 500, 20 900, 9 100, and 4 300, respectively).

Methyl 4-Hydroxy-7-methoxy-5-(1-oxopropyl)-1,3-benzodioxol-6-ylacetate (**40**).—Boron trichloride (235 mg) in dichloromethane (0.5 ml) was added at −10 °C to a stirred solution of the ketone (**27**) (309 mg) in dichloromethane (5 ml). Work-up in the usual way after 5 min at −10 °C gave a crude product which crystallized from dichloromethane–light petroleum as plates (268 mg, 91%) of the *ketone* (**40**), m.p. 96—96.5 °C (Found: C, 56.5; H, 5.4%; M^+, 296. $C_{14}H_{16}O_7$ requires C, 56.75; H, 5.45%; *M*, 296); δ_H($CDCl_3$, 80 MHz) 1.17 (3 H, t, $COCH_2Me$, 2.84 (2 H, q, $COCH_2Me$), 3.73 (3 H, s, CO_2Me), 3.79 (2 H, s, CH_2CO_2Me), 3.88 (3 H, s, OMe), 6.05 (2 H, s, OCH_2O), and 9.08 (1 H, s, D_2O-exchangeable OH).

4,7-*Dihydroxy-9-methoxy-6-methylnaphtho*[2,3-d]-1,3-*dioxole-5,8-dione* (*Nepenthone-A*) (**6**).—Ring-closure and oxidation of the foregoing ketone (**40**) (200 mg) in a manner similar to that described for the synthesis of compound (**15**) gave, after chromatography of the crude product over silica gel with 50% ethyl acetate–light petroleum as eluant, the *nepenthone-A* (**6**) (58 mg, 31%) as orange needles (from acetone), m.p. and mixed m.p. 255–261 °C decomp. with shrinkage from 249 °C (lit.,[1] 255—260 °C decomp. with shrinkage from 245 °C) (Found: C, 56.1; H, 3.55%. $C_{13}H_{10}O_7$ requires C, 56.1; H, 3.6%); *m/z* 278 (100%, M^+), 249 (17), 232 (15), 176 (15), and 149 (13); δ_H(CD_3SOCD_3, 80 MHz) 1.86 (3 H, s, Me), 3.88 (3 H, s, OMe), 6.25 (2 H, s, OCH_2O), and 13.34 (1 H, s, OH); $\nu_{max.}$(KBr) 3 310, 1 645 (C=O), 1 615, and 1 310 cm^{-1}; $\lambda_{max.}$(MeOH) 228, 266, 332, and 430 nm (ε 19 100, 17 800, 8 100, and 4 500).*

It was identical with an authentic sample (i.r., mass, and electronic spectra, mixed m.p., and R_F values on t.l.c. in three different solvent systems).

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* The electronic spectrum recorded by Cannon *et al.*,[1] appears to be in error since the spectrum recorded by us for the authentic material was identical with that recorded for the synthetic quinone.

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