

## Rearrangement Reactions of Bicyclic Systems. Part I. Synthesis of a Model Compound Related to Flavothebaone Trimethyl Ether. The Abnormal Ultraviolet Absorption Spectrum of Flavothebaone and its Trimethyl Ether

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3,6-Dimethoxybenzenediazonium-2-carboxylate decomposed to 3,6-dimethoxybenzyne (8), which reacted with veratrole to form 1,5,8-trimethoxy-1,4-etheno-2-tetralone (9) in 40% yield. Reduction, and acid-catalysed rearrangement of the resulting *exo*-alcohol (10), afforded 5,9-dihydro-1,4-dimethoxy-5,9-methanobenzocyclohepten-6-one (7). The u.v. spectrum of compound (7) is entirely analogous to that of flavothebaone trimethyl ether (3).

THEBAINEHYDROQUINONE (1) rearranges<sup>1</sup> to flavothebaone<sup>2</sup> in the presence of strong acids. The u.v. spectrum of flavothebaone reveals an unexpected maximum at 346 nm ( $\log \epsilon$  3.56), also observed in that of the trimethyl ether (3) at 337 nm ( $\log \epsilon$  3.49). These bands were assigned to the  $\pi \rightarrow \pi^*$  transition in the  $\alpha\beta$ -unsaturated ketone chromophore, the long wavelength of the transition being due to homoconjugation with the oxygenated aryl residue as indicated in structure (2).<sup>2a</sup> In the absence of appropriate model compounds the spectrum of flavothebaone was regarded as a problem *per se*. Approaches to the synthesis of a suitable model have been reported<sup>3</sup> but, as far as we are aware,<sup>4</sup> these have not been completely successful. In a previous study<sup>5</sup> we established that 5,6,7,8-tetrafluoro-1-methoxy-2-*exo-p*-tolylsulphonyloxy-1,4-ethenotetralin (4) could be rearranged quantitatively to the compound (5). The analogous compound (7) would constitute a suitable model for u.v. spectral studies.

We now report a synthesis of compound (7). Electronic effects on arynes are largely inductive in origin.<sup>6</sup> It is well established<sup>7</sup> that the presence of electron-withdrawing substituents, particularly in the 3- and 6-positions, in benzyne enables Diels-Alder reactions to be carried out in high yields with arenes. In our synthesis we required 2-amino-3,6-dimethoxybenzoic acid from which we could prepare 3,6-dimethoxybenzenediazonium-2-carboxylate as a precursor for 3,6-dimethoxybenzyne (8). 3,6-Dimethoxy-2-nitrobenzamide<sup>8</sup> is a hindered amide which we converted into 3,6-dimethoxy-2-nitrobenzoic acid in 88% yield by treatment of a solution in concentrated sulphuric acid with an excess of sodium nitrite.<sup>9</sup> The nitro-group was reduced in 80% yield by use of hydrazine in the presence of palladium-carbon.<sup>10</sup>

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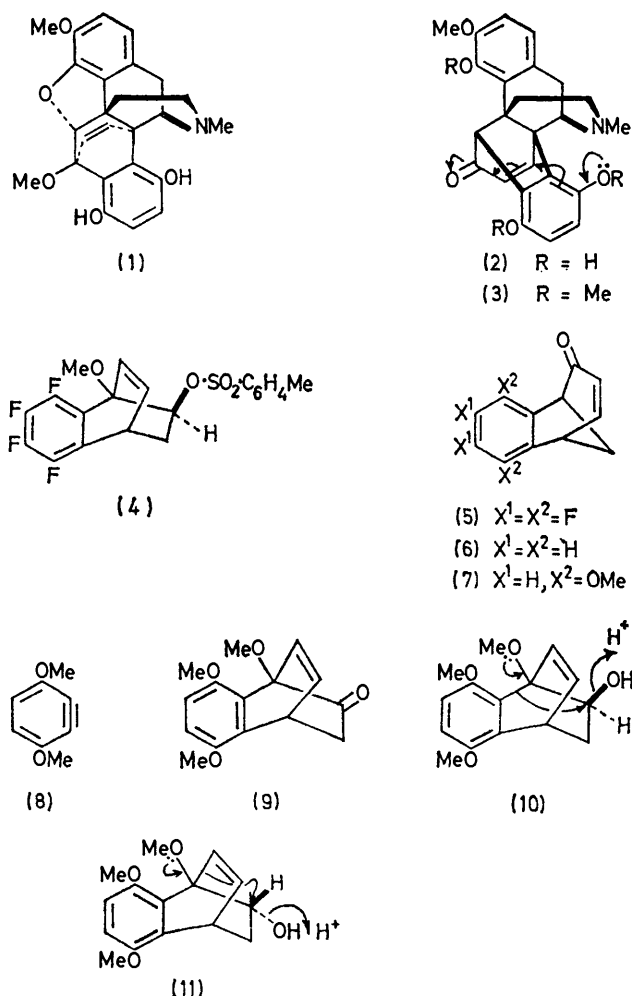
<sup>1</sup> C. Schöpf, K. von Gottberg, and W. Petri, *Annalen*, 1938, 536, 216.

<sup>2</sup> (a) J. Meinwald and G. A. Wiley, *J. Amer. Chem. Soc.*, 1957, 79, 2569; (b) K. W. Bentley, J. Dominguez, and J. P. Ringe, *J. Org. Chem.*, 1957, 22, 418.

<sup>3</sup> J. Meinwald and G. A. Wiley, *J. Amer. Chem. Soc.*, 1958, 80, 3667.

<sup>4</sup> See for example N. Filipescu and D. S. C. Chang, *J. Amer. Chem. Soc.*, 1972, 94, 5990.

The aprotic diazotisation of 2-amino-3,6-dimethoxybenzoic acid in the presence of furan gave the expected



aryne adduct<sup>8</sup> in 80% yield. As anticipated the presence of the methoxy-groups increases the electrophilicity

<sup>5</sup> H. Heaney and S. V. Ley, *Chem. Comm.*, 1971, 224.

<sup>6</sup> R. W. Hoffmann, 'Dehydrobenzene and Cycloalkynes,' Academic Press, New York, 1967.

<sup>7</sup> H. Heaney, *Fortschr. Chem. Forsch.*, 1970, 16 (1), 35.

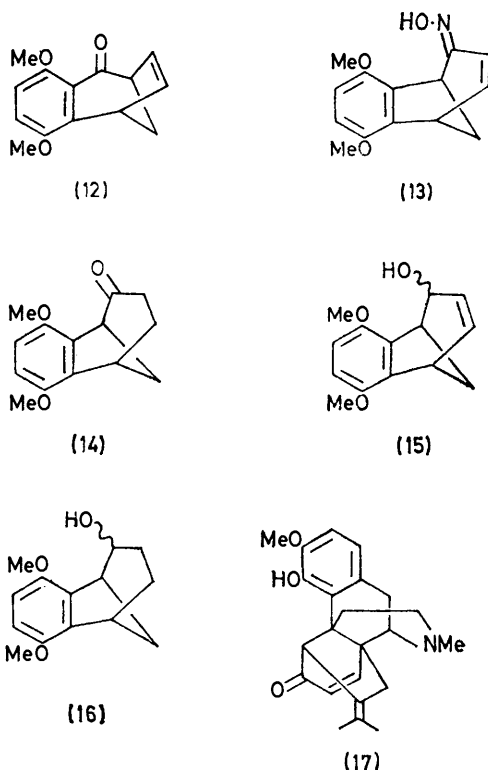
<sup>8</sup> C. W. Rees and D. E. West, *J. Chem. Soc. (C)*, 1970, 583.

<sup>9</sup> J. J. Sudborough, *J. Chem. Soc.*, 1895, 67, 601.

<sup>10</sup> M. J. S. Dewar and T. Mole, *J. Chem. Soc.*, 1956, 2556.

of the aryne (8) as compared with benzyne. The decomposition of 3,6-dimethoxybenzenediazonium-2-carboxylate in the presence of veratrole gave, after hydrolysis, 1,5,8-trimethoxy-1,4-etheno-2-tetralone (9) in 40% yield. This result may be compared with that obtained in the reaction of tetrafluorobenzyne with veratrole.<sup>11</sup> Reduction of the ketone (9) with lithium aluminium hydride gave an epimeric mixture of alcohols (10) and (11). The mixture of alcohols was separated only with considerable difficulty by multiple-elution t.l.c. The stereochemistry of the individual components was established by <sup>1</sup>H n.m.r. spectroscopy; in particular the methine proton at position 2 resonates at higher field in the case of the *exo*-alcohol (10).

In view of the difficulty of separating the alcohols (10) and (11) we carried out preparative scale acid-catalysed rearrangements on the epimeric mixture using a mixture of trifluoroacetic and sulphuric acids, and separated the products (7) and (12). That the alcohols (10) and (11) underwent the expected stereospecific rearrangements to (7) and (12), respectively, was shown by small-scale rearrangements of the separate alcohols, using analytical t.l.c. and i.r. spectroscopy to identify the products.



The u.v. spectra of the model compound (7) and a number of derivatives (13)—(16) are recorded in the Table and in Figures 1 and 2. The close similarity between the spectra of the compounds (7) and (13) and flavothebaonetrimeethyl ether (3) and the corresponding oxime<sup>2b</sup> shows that the original aromatic ring of the

<sup>11</sup> B. Hankinson and H. Heaney, *Tetrahedron Letters*, 1970, 1335.

U.v. spectra of compound (7) (a) in ethanol and (b) in cyclohexane [ $\lambda_{\max}$ /nm (log  $\epsilon$ )]

(a) 220 (4.11), 230 (3.91), 240 (3.63), 250 (3.28), 260 (3.19), 270 (3.16), 280 (3.00), 290 (3.00), 300 (3.13), 310 (3.30), 320 (3.37), 330 (3.35), 340 (3.28), 350 (3.19), 360 (3.18), and 380 (2.75).  
(b) 230 (4.12), 240 (3.37), 250 (3.06), 260 (2.96), 270 (2.84), 280 (2.69), 290 (2.98), 300 (3.26), 315 (3.45), 320 (3.43), 330 (3.29), 340 (2.98), 350 (2.63), 356 (2.69), 366 (2.47), 372 (2.51), and 380 (2.29).

alkaloid makes little, if any, contribution to the abnormal spectrum. The spectra of the saturated ketone (14), the unsaturated alcohol (15), and the saturated alcohol

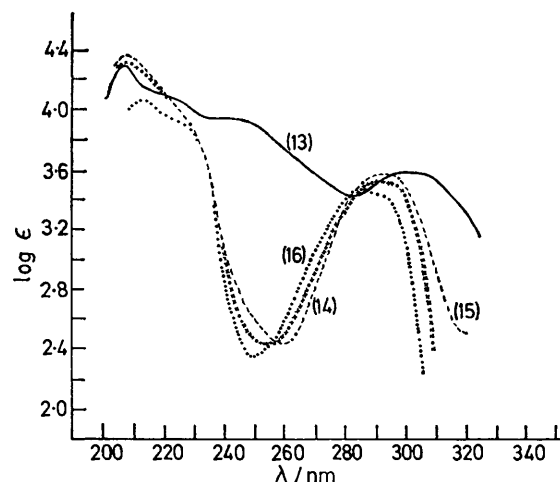


FIGURE 1 U.v. spectra of compounds (13)—(16)

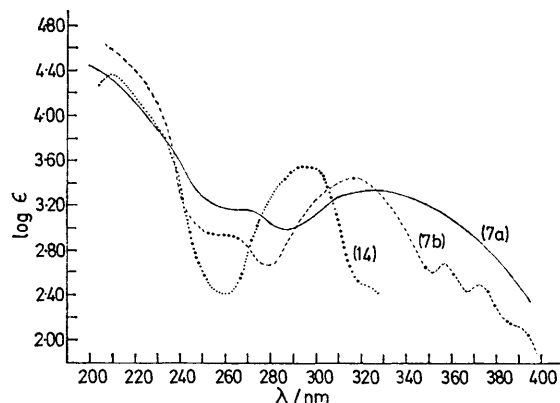


FIGURE 2 U.v. spectra of compounds (7) [(a) in ethanol, (b) in cyclohexane] and (14) (in cyclohexane)

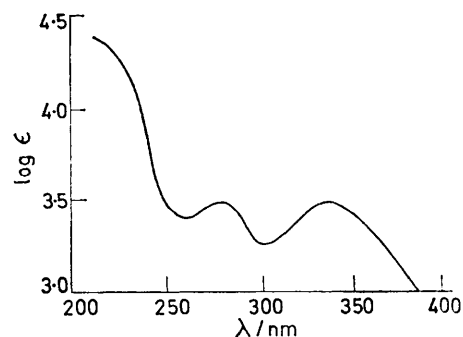


FIGURE 3 U.v. spectrum of flavothebaone trimethyl ether

(16) are clearly similar and are typical of simple 2,3-dialkylquinol dimethyl ethers.<sup>3,4</sup> The u.v. spectra of other analogues of the compound (7), for example (5) and (6), show only very low intensity maxima in the region 225–250 nm ( $\log \epsilon$  ca. 2.3). The ketone (17)<sup>12</sup> similarly shows low intensity absorption in the region 225–250 nm [ $\lambda_{\text{max}}$ , 335 ( $\log \epsilon$  2.71)]. The high extinction coefficient of the compound (7), as compared with those observed for the compounds (5), (6), and (17) is due to the presence of the methoxy-groups.

It thus appears that the abnormal spectrum of flavo-thebaone trimethyl ether is, as originally suggested,<sup>2a</sup> due to homoconjugation of the alkoxybenzene ring with the enone function. Weak interactions between the *p*-dimethoxybenzene unit and the formally nonconjugated  $\pi$  chromophore in the compounds (14) and (15) result in a bathochromic shift of ca. 10 nm in the u.v. spectra relative to that of the compound (16). Interactions of this type have been noted previously in related systems.<sup>4,13</sup>

#### EXPERIMENTAL

I.r. spectra were determined for potassium bromide discs using a Perkin-Elmer 257 grating spectrophotometer. U.v. spectra were determined with a Unicam SP 8000 spectrophotometer. <sup>1</sup>H N.m.r. spectra were determined at 100 MHz for solutions in deuteriochloroform (tetramethylsilane as internal standard) at the P.C.M.U. Mass spectra were determined with an A.E.I. MS 12 spectrometer and accurate mass measurements at the P.C.M.U.

Light petroleum refers to that fraction having b.p. 60–80°, unless otherwise stated. M.p.s were determined using a Kofler hot-stage apparatus. T.l.c. was carried out using silica (Merck PF<sub>254</sub>).

**3,6-Dimethoxy-2-nitrobenzoic Acid.**—3,6-Dimethoxy-2-nitrobenzamide<sup>8</sup> (25 g) was dissolved in sulphuric acid (750 g, 90%) and cooled to 0°. Sodium nitrite (8.0 g) in water (15 ml) was added rapidly below the surface of the acid and the mixture was stirred and allowed to warm to room temperature during 1 h. The treatment with sodium nitrite was repeated twice (total sodium nitrite 24.0 g). The mixture was then heated at 60° on a water-bath until gas evolution ceased, and then added to ice (ca. 2 kg). The precipitate was removed, washed with water, dried, and recrystallised from aqueous ethanol to afford 3,6-dimethoxy-2-nitrobenzoic acid (22 g, 88%), m.p. 192–194° (Found: C, 47.7; H, 4.1; N, 6.4. C<sub>9</sub>H<sub>9</sub>NO<sub>6</sub> requires C, 47.6; H, 4.0; N, 6.2%),  $\nu_{\text{max}}$ , 1735, 1700, 1540, and 1365 cm<sup>-1</sup>.

**2-Amino-3,6-dimethoxybenzoic Acid.**—3,6-Dimethoxy-2-nitrobenzoic acid (21 g) was dissolved in hot ethanol (300 ml) and palladium-carbon (400 mg, 10%) was added. Hydrazine hydrate (30.5 ml) was added during 0.5 h and the mixture was heated under reflux for 3 h, cooled, and filtered. The filtrate was evaporated to a small volume and cooled, and gave 2-amino-3,6-dimethoxybenzoic acid (14.5 g, 80%), m.p. 96–97° (from ethanol) (Found: C, 55.0; H, 5.7; N, 7.0. C<sub>9</sub>H<sub>11</sub>NO<sub>4</sub> requires C, 54.8; H, 5.6; N, 7.1%),  $\nu_{\text{max}}$ , 3460, 3340, 3300br, and 1700 cm<sup>-1</sup>.

**1,4-Epoxy-1,4-dihydro-5,8-dimethoxynaphthalene.**—A solution of 2-amino-3,6-dimethoxybenzoic acid (1.0 g) in aceto-

nitrile (10 ml) was added concurrently with a solution of pentyl nitrite (0.6 g) in acetonitrile (10 ml) to a solution of furan (10 ml) in acetonitrile (40 ml) which was kept at 60°. The mixture was kept at 60° for 1 h, the solvents were removed under reduced pressure, and the residue was placed on a column of silica (50 g). Elution with dichloromethane-benzene (1:1) gave 1,4-epoxy-1,4-dihydro-5,8-dimethoxynaphthalene (800 mg, 80%), m.p. 85.5–87° (lit.,<sup>8</sup> 86–87°).

**1,5,8-Trimethoxy-1,4-etheno-2-tetralone.**—Pentyl nitrite (7.5 ml) was added to a solution of 2-amino-3,6-dimethoxybenzoic acid (5.4 g, 0.02 mol) and trichloroacetic acid (50 mg) in ether (30 ml) and tetrahydrofuran (30 ml) and the mixture was stirred at room temperature for 2 h. The supernatant liquid was poured off the dark red solid, which was washed with 1,2-dichloroethane (3 × 10 ml), slurried in 1,2-dichloroethane (10 ml), added to preheated veratrole (200 g) at 60° and kept at this temperature for 3 h. Ether (300 ml) was added to the cooled solution, which was washed with 2M-hydrochloric acid (100 ml), 2M-sodium hydroxide (4 × 100 ml), and water (2 × 100 ml), dried (MgSO<sub>4</sub>), and evaporated to leave a dark oil. Preparative layer chromatography [10 × 1 m × 20 cm, 0.75 mm thickness; eluant ether-light petroleum (b.p. 40–60°), 9:1] gave 1,5,8-trimethoxy-1,4-etheno-2-tetralone (2.75 g, 40%) (9), m.p. 64–66° (from light petroleum) (Found: C, 69.7; H, 6.4%; M<sup>+</sup>, 260. C<sub>15</sub>H<sub>16</sub>O<sub>4</sub> requires C, 69.35; H, 6.15%; M, 260),  $\nu_{\text{max}}$ , 3005, 2940, 2840, and 1743 cm<sup>-1</sup>;  $\lambda_{\text{max}}$  (EtOH) 305 (log  $\epsilon$  3.51) and 297 (3.56) nm;  $\tau$  3.25 (4H, m), 5.35 (1H, m), 6.2 (3H, s), 6.22 (3H, s), 6.25 (3H, s), and 7.92 (2H, octet, |J| ca. 18 and 3 Hz), *m/e* 260.1045 (M<sup>+</sup>; C<sub>15</sub>H<sub>16</sub>O<sub>4</sub> requires 260.1049) and 218.0938 (M<sup>+</sup> - 42; C<sub>13</sub>H<sub>14</sub>O<sub>3</sub> requires 218.0943).

**Reduction of 1,5,8-Trimethoxy-1,4-etheno-2-tetralone.**—The ketone (9) (500 mg) in ether (10 ml) was added to a suspension of lithium aluminium hydride (250 mg) in ether (15 ml) and the mixture was stirred at room temperature for 0.25 h. 2M-Sulphuric acid (25 ml) was then added slowly and the ether layer was separated and washed with water (2 × 5 ml). The aqueous acid layer was extracted with chloroform (2 × 10 ml) and the combined organic layers were dried (MgSO<sub>4</sub>) and evaporated to afford an epimeric mixture of alcohols (472 mg, 94%).

A portion of the mixture (100 mg) was separated by preparative layer chromatography (1 × 1 m × 20 cm × 0.75 mm) [elution (×6) with benzene-chloroform (1:4)] and gave an upper band of 1,2,3,4-tetrahydro-1,5,8-trimethoxy-1,4-ethenonaphthalen-2-exo-ol (10) (31 mg), m.p. 191–192° (from methanol) (Found: C, 68.8; H, 7.0%; M<sup>+</sup>, 262. C<sub>15</sub>H<sub>18</sub>O<sub>4</sub> requires C, 68.7; H, 6.85%; M, 262),  $\nu_{\text{max}}$ , 3518 cm<sup>-1</sup>;  $\lambda_{\text{max}}$  (EtOH) 300 (log  $\epsilon$  3.44) and 290 (3.54) nm;  $\tau$  3.25–3.45 (4H, m), 5.6–5.8 (1H, m), 6.06 (1H, dd, |J| ca. 12 and 3 Hz), 6.18 (3H, s), 6.24 (3H, s), 6.25 (3H, s), 7.3 (1H, m, exchangeable), 8.1 (1H, m), and 8.7 (1H, dt |J| ca. 12 and 3 Hz).

A lower band contained 1,2,3,4-tetrahydro-1,5,8-trimethoxy-1,4-ethenonaphthalen-2-endo-ol (11) (44 mg), m.p. 186° (from methanol) (Found: C, 68.8; H, 6.9%; M<sup>+</sup>, 262),  $\nu_{\text{max}}$ , 3520 cm<sup>-1</sup>;  $\lambda_{\text{max}}$  (EtOH) 300 (log  $\epsilon$  3.36) and 290 (3.52) nm;  $\tau$  3.28 (2H, s), 3.44 (2H, m), 5.68 (1H, m), 5.95 (1H, dd, |J| ca. 12 and 3 Hz), 6.18 (3H, s), 6.22 (3H, s), 6.30 (3H, s), 7.72 (1H, m, exchangeable), 7.9 (1H, octet), and 8.96 (dt, |J| ca. 12 and 3 Hz).

<sup>12</sup> K. W. Bentley, D. G. Hardy, and B. Meek, *J. Amer. Chem. Soc.*, 1967, **89**, 3293.

<sup>13</sup> See for example R. C. Cookson and N. S. Wariyar, *J. Chem. Soc.*, 1956, 2302.

*Rearrangement of an Epimeric Mixture of the Alcohols (10) and (11).*—A mixture of the alcohols (300 mg) was dissolved in a mixture of trifluoroacetic acid (2 ml) and sulphuric acid (2 ml) and stirred at room temperature for 0.5 h before being added to ice (25 g). The products were extracted with ether (5 × 10 ml) and the extracts were each washed with sodium hydrogen carbonate and water and were then combined and dried (MgSO<sub>4</sub>). Evaporation gave an oil (269 mg), which was separated by preparative layer chromatography [eluant ether–light petroleum (b.p. 40–60°), 4:1] and gave an upper band of 5,8-dimethoxy-2,4-etheno-1-tetralone (12) (130 mg), m.p. 83–84° (from ether), (Found: C, 73.1; H, 6.4%; *M*<sup>+</sup>, 230. C<sub>14</sub>H<sub>14</sub>O<sub>3</sub> requires C, 73.05; H, 6.1%; *M*, 230),  $\nu_{\max}$  1687 cm<sup>-1</sup>;  $\lambda_{\max}$  (cyclohexane) 350 (log  $\epsilon$  3.56), 340 (3.62), 263 (3.35), and 216 (4.27) nm;  $\tau$  3.15 (2H, q, |*J*| 9.5 Hz), 3.64 (2H, octet  $\Delta\delta$  48 Hz), 5.78 (1H, m), 6.18 (3H, s), 6.21 (3H, s), 6.62 (1H, m), and 7.48 (2H, m).

The lower band contained 5,9-dihydro-1,4-dimethoxy-5,9-methanobenzocyclohepten-6-one (7) (74 mg), m.p. 140–141° (from methanol) (Found: C, 73.2; H, 6.2%; *M*<sup>+</sup>, 230),  $\nu_{\max}$  1680 cm<sup>-1</sup>;  $\tau$  2.54 (1H, q, |*J*| ca. 10 and 6 Hz), 3.38 (2H, s), 4.55 (1H, q, |*J*| ca. 10 and 2 Hz), 5.94 (1H, m), 6.15 (1H, m), 6.22 (6H, s), and 7.32 (2H, m).

A sample (5 mg) of the *endo*-alcohol (11) was shown to give only the tetralone (12) on rearrangement; similarly the *exo*-alcohol gave only the  $\alpha\beta$ -unsaturated ketone (7).

*Reduction of the Ketone (7) with Lithium Aluminium Hydride.*—The ketone (50 mg) in ether was added to an excess of lithium aluminium hydride in ether and gave, after normal work-up, 6,9-dihydro-1,4-dimethoxy-5,9-methano-5H-benzocyclohepten-6-ol (15) (42 mg), m.p. 103–104° (from light petroleum) (Found: C, 72.6; H, 7.1%; *M*<sup>+</sup>, 232. C<sub>14</sub>H<sub>16</sub>O<sub>3</sub> requires C, 72.4; H, 6.9%; *M*, 232),  $\nu_{\max}$  3460 cm<sup>-1</sup>;  $\lambda_{\max}$  (cyclohexane) 298 (log  $\epsilon$  3.50) and 290

(3.52) nm;  $\tau$  3.36 (2H, m), 3.70 (1H, m), 4.78 (1H, dt, |*J*| ca. 10 and 2 Hz), 5.45 (1H, m), 6.15 (1H, m), 6.22 (3H, s), 6.24 (3H, s), 6.58 (1H, m), 7.75 (2H, m), and 8.20 (1H, m, exchangeable).

*Reductions of the Ketone (7).*—Reduction in ethanolic solution at atmospheric pressure with hydrogen in the presence of palladium–carbon gave 5,7,8,9-tetrahydro-1,4-dimethoxy-5,9-methanobenzocyclohepten-6-one (14) (100%), m.p. 103–103.5° (from methanol) (Found: C, 72.6; H, 7.1%; *M*<sup>+</sup>, 232. C<sub>14</sub>H<sub>16</sub>O<sub>3</sub> requires C, 72.4; H, 6.9%; *M*, 232),  $\nu_{\max}$  1720 cm<sup>-1</sup>;  $\lambda_{\max}$  (cyclohexane) 292 (log  $\epsilon$  3.56) nm;  $\tau$  3.32 (2H, q, |*J*| ca. 9 Hz), 6.16 (1H, m), 6.20 (3H, s), 6.26 (3H, s), 6.45 (1H, m), 7.40 (1H, m), and 7.90 (5H, m).

Reduction of the ketone (14) with lithium aluminium hydride gave 6,7,8,9-tetrahydro-1,4-dimethoxy-5,9-methano-5H-benzocyclohepten-6-ol (16) (100%), m.p. 87–88° (from light petroleum) (Found: C, 72.4; H, 7.9%; *M*<sup>+</sup>, 234.1256. C<sub>14</sub>H<sub>18</sub>O<sub>3</sub> requires C, 71.8; H, 7.7%; *M*, 234.1256),  $\nu_{\max}$  3500 cm<sup>-1</sup>;  $\lambda_{\max}$  (EtOH) 286 (log  $\epsilon$  3.47) nm;  $\tau$  3.34 (2H, m), 6.22 (3H, s), 6.23 (3H, s), 6.55 (1H, m), 6.70 (1H, m), 7.80 (1H, m), 8.24 (1H, m, exchangeable), and 8.45 (6H, m).

*Reaction of the Ketone (7) with Hydroxylamine.*—Reaction in solution in pyridine gave the *oxime* (13) (75%), m.p. 188–190° (from light petroleum) (Found: C, 68.8; H, 6.4; N, 5.7%; *M*<sup>+</sup>, 245. C<sub>14</sub>H<sub>15</sub>NO<sub>3</sub> requires C, 68.55; H, 6.1; N, 5.7%; *M*, 245),  $\nu_{\max}$  3200 cm<sup>-1</sup>;  $\lambda_{\max}$  (EtOH) 303 (log  $\epsilon$  3.60), 245 (3.95), and 215 (4.15) nm;  $\tau$  3.36 (2H, m), 3.45 (1H, m), 4.28 (1H, m), 5.00 (1H, m), 5.90 (1H, m), 6.20 (3H, s), 6.22 (3H, s), 6.30 (1H, m), and 7.65 (2H, m).

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