Some Aspects of the Chemistry of 6,7,8,9-Tetrahydro-3-hydroxy-2-methoxybenzocycloheptan-5-one

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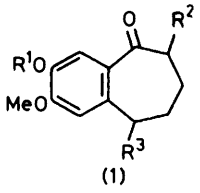
6,7,8,9-Tetrahydro-3-hydroxy-2-methoxybenzocyclohepten-5-one has been converted into several bromo-derivatives, acetals, and esters, and into 3-hydroxy-2-methoxybenzocyclohepten-5-one; further, its reduction with $LiAlH_4$ has been compared with that of 6,7-dihydro-3-hydroxy-2-methoxybenzocyclohepten-5-one. A synthesis of 6,7-dihydro-3-hydroxy-8-hydroxycarbonyl-2-methoxybenzocyclohepten-5-one has been developed. Synthesis of 6,7,8,9-tetrahydro-4-methoxy-10*H*-cyclohepta[*e*]benzofuran-10-ones, 9-hydroxy-5,6-dihydro-8-methoxy-4*H*-benzo[6,7]cyclohept[1,2-*c*]pyrazole, 5,6-dihydro-9-hydroxy-8-methoxy-4*H*-benzo[3,4]cyclohept-[1,2-*d*]isoxazole, and 10-hydroxy-6,7-dihydro-9-methoxybenzo[5,6]cyclohept[1,2-*b*]indole are described.

DURING routine anti-tumour screening,[1] the title compound (1; $R^1 = R^2 = R^3 = H$) showed some activity in murine P388 tests, so a programme of structural modification was undertaken. Since most of the products were biologically inactive, we now report on their chemistry in this and the following paper.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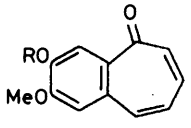
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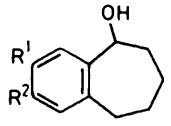
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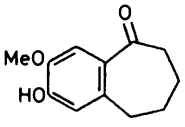
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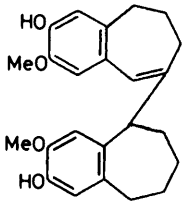
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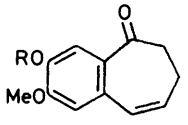
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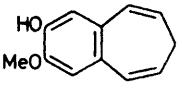
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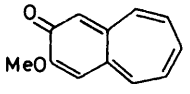
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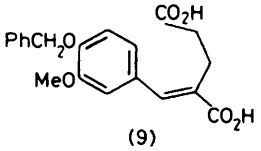
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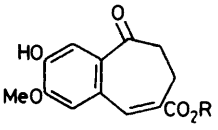
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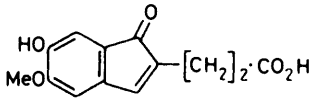
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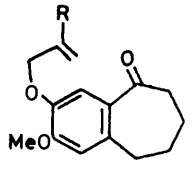
In the first place, several hitherto [2] unknown but straightforward substituted derivatives of the title compound were made by conventional procedures; these included hexanoyl esters [*e.g.* (1; $R^1 = n\text{-}C_6H_{13}CO$, $R^2 = R^3 = H$)], bromo-compounds (1; $R^1 = Ac$, $R^2 = Br$, Br_2; $R^3 = H$ and Br), and acetals; details are recorded in the Experimental section. Although the 6-bromo-ketone (1; $R^1 = Ac$, $R^2 = Br$, $R^3 = H$) was remarkably resistant to basic reagents, the dibromo-ketone (1; $R^1 = Ac$, $R^2 = Br_2$, $R^3 = H$) reacted with lithium chloride in DMF [3] to yield the corresponding benzotropone (2; R = Ac) and thence the hydroxymethoxybenzotropone (2; R = H).

The title compound (1; $R^1 = R^2 = R^3 = H$) behaved normally on oximation and on reduction with lithium aluminium hydride at 0 °C gave the expected hydroxy-compound (3; $R^1 = OH$, $R^2 = OMe$) which is in contrast to some related compounds which sometimes gave dimeric products albeit at higher temperatures. For comparison the isomeric hydroxymethoxy-ketone [2] (4) was treated with lithium aluminium hydride in tetrahydrofuran (THF) at 0 °C; this proved to be a capricious reaction which sometimes yielded the hydroxy-compound (3; $R^1 = OMe$, $R^2 = OH$), sometimes a dimeric product [4]

($C_{24}H_{28}O_4$) [possibly (5)] and sometimes both of these. On the other hand, reduction of the hydroxy-ketone (6; R = H) yielded a mixture of hydroxymethoxytropilidenes ($C_{34}H_{12}O_2$) (7) and isomers which gave, slowly when set aside or rapidly with DDQ, the red 3-methoxybenzocycloheptenone-2-one (8) identical with authentic [2] material.

To obtain derivatives of the title compound substituted at C-8, it is convenient to follow the example of House and his co-workers [5] and to cyclise the diacid (9) with polyphosphoric acid to the oxo-acid (10; R = H). The diacid (9) was made by condensation of benzylvanillin and diethyl glutarate in presence of potassium t-butoxide, followed by hydrolysis. The structure of the oxo-acid (10; R = H) is confirmed in particular by i.r. spectroscopy ($\nu_{max.}$ 1 655 cm^{-1}) and by comparing the ^{13}C n.m.r. spectrum of the ethyl ester (10; R = Et) with that of the related compound (6; R = H). Thus the alternative isomeric oxoindenecarboxylic acid formulation (11) is excluded.

The title compound can conveniently be used for the annelation of several heterocyclic systems. The *O*-allyl ethers (12; R = H or Cl) undergo Claisen rearrangement to the 4-allyl compounds (13; R = H or Cl) which can be converted by PPA treatment into the furano-compounds (14; R = H or Me), in the former case the intermediate was first ozonised. The hydroxymethylene ketone (15) proved to be a fruitful intermediate for conversion into a number of fused heterocyclic compounds including the pyrazoles [16; R^1 = H or $PhCH_2$, R^2 = H, Ph, *p*-$NO_2C_6H_4$ or 2,4-$(NO_2)_2C_6H_3$] which are formulated thus by analogy with literature precedents.[6] The isoxazoles (17; R = H or $PhCH_2$) were obtained by



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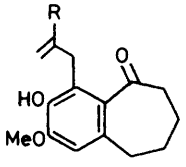

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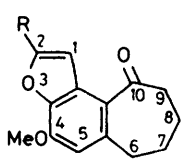

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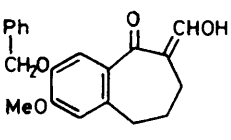

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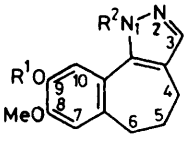

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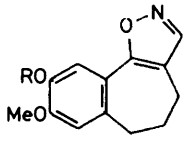

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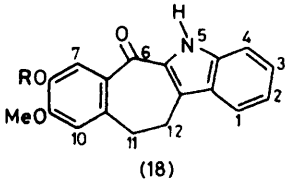

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reaction of compound (15) with hydroxylamine hydrochloride in acetic acid; use of pyridine as solvent for this reaction gave the same products and not the alternative isoxazole isomers as has been reported in some other cases.[6,7] Finally, application of the Japp–Klingemann reaction [8] to compound (15) was successful and the phenyl hydrazone thus obtained was cyclised to the indolo-derivatives (18; R = H and $PhCH_2$). Interestingly the i.r. carbonyl stretching frequency for these compounds was very low ($\nu_{max.}$ 1 610—1 615 cm^{-1}) presumably because of hydrogen bonding with the indole NH group: there are precedents for this phenomenon.[9]

The bromo-ketones (1; R^1 = Ac, R^2 = Br, R^3 = H) and (1; R = Ac, R^2 = H, R^3 = Br) showed antitumour activity in tissue cultures,[1] in contrast to all other products which showed no significant activity.

EXPERIMENTAL

3-Acetoxy-9-bromo-6,7,8,9-tetrahydro-2-methoxybenzocyclohepten-5-one (1; R^1 = Ac, R^2 = H, R^3 = Br).—3-Acetoxy-6,7,8,9-tetrahydro-2-methoxybenzocyclohepten-5-one (1; R^1 = Ac, R^2 = R^3 = H) [2] (6.6 g), *N*-bromosuccinimide (4.8 g), and carbon tetrachloride (150 ml) were refluxed together for 6 h over a 150-W bulb. After filtration and concentration of the solvent, recrystallisation of the residue from ether–light petroleum (b.p. 40—60 °C) gave needles, m.p. 128—129 °C (82%) (Found: C, 51.35; H, 4.65; Br, 24.55. $C_{14}H_{15}BrO_4$ requires C, 51.35; H, 4.6; Br, 24.45%). Heating of this compound with collidine gave 3-acetoxy-6,7-dihydro-2-methoxybenzocyclohepten-5-one (6; R = Ac), m.p. 86—87 °C.[2]

6,7-Dihydro-3-hydroxy-2-methoxybenzocyclohepten-5-one (6; R = H).— 3-Acetoxy-6,7-dihydro-2-methoxybenzocyclohepten-5-one (6; R = Ac) was stirred at 20 °C with alcoholic aqueous sodium hydroxide (8%, excess) for 24 h. The phenolic product was obtained in the usual way and crystallised from dichloromethane–light petroleum (b.p. 60—80 °C) as needles (68%), m.p. 89 °C (Found: C, 70.3; H, 5.75. $C_{12}H_{12}O_3$ requires C, 70.55; H, 5.9%); the ^{13}C n.m.r. spectrum showed 12 peaks: 200.7, 150.3, 144.6, 131.5, 131.15, 130.6, 129.7, 116.1, 113.4, 55.9, 42.3, and 23.2 p.p.m.

Reduction of 6,7-Dihydro-3-hydroxy-2-methoxybenzocyclohepten-5-one (6; R = H).—The title compound (1 g), lithium aluminium hydride (0.9 g), and tetrahydrofuran (40 ml) were stirred together for 6 h under N_2 at 20 °C. After the usual work-up and chromatography on neutral alumina, a mixture (0.5 g) of isomers (t.l.c. and n.m.r.) was obtained, m.p. 100—102 °C (light petroleum) (Found: C, 74.9; H, 6.65%; M^+, 188.0828. $C_{12}H_{12}O_2$ requires C, 74.85; H, 6.35%; *M*, 188.0837). After being set aside for 3 years, these crystals were pink and t.l.c. showed the presence of 3-methoxybenzocyclohepten-2-one (8); [2] reaction of the compound with DDQ in dichloromethane caused very rapid conversion into the red enone (8),[2] m.p. 143—144 °C.

Dimethyl Acetal of 3-Acetoxy-6,7,8,9-tetrahydro-2-methoxybenzocyclohepten-5-one (1; R^1 = Ac; R^2 = R^3 = H).—Treatment of the ketone (2 g), methyl orthoformate (2.66 ml), toluene-*p*-sulphonic acid (0.08 g), and dry methanol (50 ml) at reflux for 3 h, gave the product (1.95 g) as needles, m.p. 96—98 °C (from benzene) (Found: C, 65.25; H, 7.4. $C_{16}H_{22}O_3$ requires C, 65.3; H, 7.5%), τ 2.6 (1 H, s, 4-H), 3,35 (1 H, s, 1-H), 6.2 (3 H, s, OMe), 6.95 [6 H, s, $(OMe)_2$], 7.2 (2 H, m, 9-H), 7.76 (3 H, s, OAc), and 8.15 (6 H, m, 6-, 7-, and 8-H). The *diethyl acetal* was made similarly and had m.p. 98—100 °C (Found: C, 66.1; H, 8.05. $C_{18}H_{26}O_5$ requires C, 66.15; H, 8.05%).

3-Acetoxy-6-bromo-6,7,8,9-tetrahydro-2-methoxybenzocyclohepten-5-one (1; R^1 = Ac, R^2 = Br, R^3 = H).—3-

Acetoxy-6,7,8,9-tetrahydro-2-methoxybenzocyclohepten-5-one (1; R^1 = Ac, R^2 = R^3 = H) (1.3 g), phenyltrimethylammonium tribromide (1 g), and THF (25 ml) were stirred together for 4 h, and then concentrated to give a product which recrystallised from dichloromethane–light petroleum (b.p. 60—80°) as needles, m.p. 128—130 °C (1.3 g) (Found: C, 51.35; H, 4.65; Br, 24.55. $C_{14}H_{15}BrO_4$ requires C, 51.35; H, 4.6; Br, 24.45%). Treatment of the starting material with bromine in chloroform yielded the same product which was unaffected by treatment with collidine at 125 °C for 8 h.

Oxime of 6,7,8,9-*Tetrahydro*-3-*hydroxy*-2-*methoxybenzocyclohepten*-5-*one* (1; R^1 = R^2 = R^3 = H).—This was obtained using hydroxylamine hydrochloride in refluxing ethanol and had m.p. 189—192 °C (Found: C, 64.95; H, 6.35; N, 6.75. $C_{12}H_{15}NO_3$ requires C, 65.15; H, 6.7; N, 6.35%).

6,7,8,9-*Tetrahydro*-3,5-*dihydroxy*-2-*methoxybenzocycloheptene* (3; R^1 = OH, R^2 = OMe).—The hydroxy-ketone (1; R^1 = R^2 = R^3 = H) (3.0 g), lithium aluminium hydride (0.9 g), and dry THF (100 ml) were stirred together at 0 °C for 6 h and 20 °C for 18 h. The usual work-up [4] gave the product which recrystallised from benzene–ethyl acetate as needles, m.p. 131—133 °C (2.8 g) (Found: 68.8; H, 7.8%; M^+, 208.1075. $C_{12}H_{16}O_3$ requires C, 69.3; H, 7.75%; *M*, 208.1099).

Reduction of 6,7,8,9-*Tetrahydro*-2-*hydroxy*-3-*methoxybenzocyclohepten*-5-*one* (4).—(*a*) The hydroxy-ketone (3.5 g),[2] lithium aluminium hydride (0.9 g), and dry THF (100 ml) were stirred at 0 °C for 5 h and at 20 °C for 18 h. The usual work-up gave 6,7,8,9-*tetrahydro*-2,5-*dihydroxy*-3-*methoxybenzocycloheptene* (3; R^1 = OMe, R^2 = OH)(3.25 g), m.p. 138—141 °C (dichloromethane) (Found: C, 69.65; H, 7.75%; M^+, 208.1096. $C_{12}H_{16}O_3$ requires C, 69.3; H, 7.75%; *M*, 208.1099). Heating of this material with toluene *p*-sulphonic acid in benzene yielded 6,7-*dihydro*-3-*hydroxy*-2-*methoxybenzocycloheptene*, m.p. 104 °C (from light petroleum) (Found C, 76.0, H, 7.3%; M^+, 190.0996. $C_{12}H_{14}O_2$ requires C, 75.85; H, 7.45%; *M*, 190.0994). Catalytic hydrogenation of the latter gave 6,7,8,9-*tetrahydro*-3-*hydroxy*-2-*methoxybenzocycloheptene*, m.p. 108 °C (lit.,[10] 110 °C) identical to that previously obtained.

(*b*) Repetition of the experiment but allowing the temperature to rise above 0 °C during the first hour, led to isolation of crystalline material, m.p. 158—159 °C (Found: C, 75.4; H, 7.35%; M^+ 380.2005. $C_{24}H_{28}O_4$ requires C, 75.75, H, 7.4%; *M*, 380.1987), τ 3.30 (1 H, s, aryl), 3.32 (1 H, s, aryl), 3.35 (1 H, s, aryl), 3.46 (1 H, s, aryl), 3.9 (1 H, s, olefinic), 4.5 (1 H, s, OH, exchangeable), 4.6 (1 H, s, OH, exchangeable), 6.2 (3 H, s, OMe), 6.25 (3 H, s, OMe), 6.5 (1 H, m, C*H*), 7.2—7.5 (4 H, m, CH_2), and 7.75—8.5 (10 H, m, CH_2).

3-*n*-*Hexanoyl*-6,7,8,9-*tetrahydro*-2-*methoxybenzocyclohepten*-5-*one* (1; R^1 = n-$C_6H_{13}CO$, R^2 = R^3 = H).—The hydroxy-ketone (1; R^1 = R^2 = R^3 = H) (3 g), n-hexanoyl chloride (5 g), anhydrous potassium carbonate (15 g), and dry acetone were refluxed together for 4 h. The crude product was chromatographed on silica gel and crystallised from light petroleum (b.p. 60—80°) to give prisms, m.p. 65—67 °C (3.2 g) (Found: C, 70.9; H 7.95. $C_{18}H_{24}O_4$ requires C, 71.05; H, 7.9%).

9-*Bromo*-3-*n*-*hexanoyl*-6,7,8,9-*tetrahydro*-2-*methoxybenzocyclohepten*-5-*one* (1; R^1 = n-$C_6H_{13}CO$; R^2 = H, R^3 = Br).—The previous ester (2 g), *N*-bromosuccinimide (1.4 g), and carbon tetrachloride (100 ml) were refluxed together as above. The usual work-up gave the *product* (90%), m.p. 126—128 °C (Found: C, 56.3; H, 6.0; Br, 20.65. $C_{18}H_{23}BrO_4$ requires C, 56.45; H, 6.05; Br, 20.85%).

3-*n*-*Hexanoyl*-6,7-*dihydro*-2-*methoxybenzocyclohepten*-5-*one* (6; R = n-$C_6H_{13}CO$).—The previous bromo-ketone (2.5 g) and collidine (20 ml) were held at 120 °C for 3 h. The usual work-up gave a liquid, b.p. 200 °C/0.3 mmHg (2 g) (Found: C, 71.35; H, 7.2. $C_{18}H_{22}O_4$ requires C, 71.55; H, 7.35%).

3-*Acetoxy*-6,6-*dibromo*-6,7,8,9-*tetrahydro*-2-*methoxybenzocyclohepten*-5-*one* (1; R^1 = Ac; R^2 = Br_2, R^3 = H).—Bromine (4 g) in carbon tetrachloride (5 ml) was added dropwise to a stirred solution of the acetoxy-ketone (1; R = Ac; R^2 = R^3 = H) (2.25 g) in carbon tetrachloride (25 ml) during 3 h. After being washed with aqueous sodium hydrogen carbonate solution, the solvent was removed and the product recrystallised from ethanol to yield a solid, m.p. 164—166 °C (3.3 g) (Found: C, 41.95; H, 3.45. $C_{14}H_{14}Br_2O_4$ requires C, 41.45; H, 3.45%), $\nu_{max.}$ (KBr) 1 755 (Ac) and 1 660 (C=O) cm^{-1}; τ 2.9 (1 H, s, 4-H), 3.4 (1 H, s, 1-H), 6.2 (3 H, s, OMe), 7.1—7.4 (4 H, m, 7 and 9-H), 7.7 (3 H, s, OAc), and 7.8—8.1 (2 H, m, 8-H).

3-*Acetoxy*-2-*methoxybenzocyclohepten*-5-*one* (2; R = Ac).—The dibromide (2 g) from above, anhydrous lithium chloride (0.8 g), and dry DMF (40 ml) were refluxed together under nitrogen for 3 h. The usual work-up [3] gave the *product* (0.9 g) from benzene as needles, m.p. 79—80 °C (Found: C, 69.15; H, 4.9 $C_{14}H_{12}O_4$ requires C, 68.9; H, 4.95%), $\nu_{max.}$ (KBr) 1 760 (Ac) and 1 640 (C=O) cm^{-1}, τ 2—3.5 (6 H, m, aryl + olefinic), 6.2 (3 H, s, OMe), and 7.75 (3 H, s, Ac).

3-*Hydroxy*-2-*methoxybenzocyclohepten*-5-*one* (2; R = H).—The acetate (0.25 g) from above was treated with alcoholic aqueous sodium hydroxide (8%, excess) at 80 °C for 30 min. and worked up as usual to give colourless solid, m.p. 220 °C (0.17 g from ethanol) (Found: C, 71.55; H, 5.1. $C_{12}H_{10}O_3$ requires C, 71.35; H, 5.0%), $\nu_{max.}$ (KBr) 3 250 (OH) and 1 640 (C=O) cm^{-1}; τ (CF_3CO_2H) 2.05—2.85 (6 H, m, aryl + olefinic), and 6.0 (3 H, s, OMe).

Reaction of Diethyl Glutarate with Benzylvanillin.[5]—Diethyl glutarate (30 g), benzylvanillin (38.6 g), and t-butyl alcohol (150 ml) were added dropwise to the solution obtained by dissolution of potassium (12 g) in t-butyl alcohol (200 ml). After 16 h, the reaction mixture was worked up as usual to give a gum which was stirred for 18 h with aqueous sodium hydroxide (8%, 600 ml). Extraction of the acidic material and crystallisation from ethyl acetate yielded the diacid (9) as a powder (30 g), m.p. 208—210 °C (Found: C, 67.0; H, 5.55. $C_{20}H_{20}O_6$ requires C, 67.4; H, 5.65%), $\nu_{max.}$ (KBr) 1 675br (CO_2H) and 1 585 cm^{-1} (C=C).

6,7-*Dihydro*-3-*hydroxy*-8-*hydroxycarbonyl*-2-*methoxybenzocyclohepten*-5-*one* (10; R = H).—The diacid (2 g) from above and polyphosphoric acid (100 g) were stirred together at 90 °C for 1 h. The usual work-up followed by chromatography on silica (elution with 2% methanol in chloroform) gave (from ethyl acetate) a powder (700 mg), m.p. 245 °C (Found: C, 62.4; H, 4.75%; M^+ 248.0930. $C_{13}H_{12}O_5$ requires C, 62.9; H, 4.85%; *M*, 248.0950), $\nu_{max.}$ (KBr) 3 400br (OH), 1 724 (CO_2H), 1 655 (C=O), and 1 600 cm^{-1} (C=C). The *ethyl ester* was obtained using H_2SO_4 in ethanol and had m.p. 135 °C (Found: C, 65.5; H, 5.75. $C_{15}H_{16}O_5$ requires C, 65.25; H, 5.85%); the ^{13}C n.m.r. spectrum showed 15 peaks: 199.2, 167.5, 150.0, 139.4 (2), 132.75, 131.05, 128.3, 116.7, 115.0, 61.2, 56.1, 41.9, 21.7, and 14.3 p.p.m.

3-*Allyloxy*-6,7,8,9-*tetrahydro*-2-*methoxybenzocyclohepten*-5-*one* (12; R = H).—The hydroxy-ketone (1; R^1 = R^2 = R^3 = H) (4 g), allyl bromide (4 ml), anhydrous potassium

carbonate (20 g), and dry acetone (100 ml) were refluxed together for 6 h. The usual work-up gave the *product* (4.5 g) as prisms (from light petroleum), m.p. 46—47 °C, (Found: C, 73.55; H, 7.4. $C_{15}H_{18}O_3$ requires C, 73.25; H, 7.35%), $\nu_{max.}$ (KBr) 1 655 (C=O) cm^{-1}; τ 2.8 (1 H, s, aryl), 3.5 (1 H, s, aryl), 4.15 (1 H, dd, C*H*=), 4.7—4.95 (2 H, m, =CH_2), 5.5 (2 H, d, OCH_2), 6.2 (3 H, s, OMe), 7.15—7.45 (4 H, m, H-6 + H-9), and 8.15—8.35 (4 H, m, H-7 + H-8).

4-*Allyl*-6,7,8,9-*tetrahydro*-3-*hydroxy*-2-*methoxybenzocyclohepten*-5-*one* (13; R = H).—The previous *o*-allyl ether (12; R = H) (1 g) was held at 200 °C *in vacuo* (1 mmHg) for 3 h. After cooling, the solid crystallised from benzene as prisms (0.95 g), m.p. 140—141 °C (Found: C, 73.2; H, 7.5. $C_{15}H_{18}O_3$ requires C, 73.25; H, 7.35%), $\nu_{max.}$ (KBr) 3 300 (OH) and 1 650 (C=O) cm^{-1}, τ 3.65 (1 H, s, aryl), 4.25 (1 H, m, C*H*=CH_2), 4.45 (1 H, s, exchangeable OH), 5.16 (2 H, d, CH_2=CH), 6.2 (3 H, s, OMe), 6.55 (2 H, d, CH_2CH=CH_2), 7.3—7.6 (4 H, m, H-6 + H-9), and 8.2—8.45 (4 H, m, H-7 + H-8).

6,7,8,9-*Tetrahydro*-4-*methoxy*-10H-*cyclohepta*[e]*benzofuran*-10-*one* (14; R = H).—The previous *C*-allyl compound (13; R = H; 0.5 g) in dichloromethane at —40 °C was treated with a stream of ozone for 6 h. The crude product obtained as usual was stirred with polyphosphoric acid (10 g) at 95 °C for 45 min and poured into ice. After extraction and chromatography on alumina, elution (ethyl acetate–benzene) gave the product (150 mg), m.p. 92—94 °C (from benzene) (Found: C, 73.35; H, 6.6%; M^+ 230.0922. $C_{14}H_{14}O_3$ requires C, 73.1; H, 6.2%; *M*, 230.0943), $\nu_{max.}$ (KBr) 1 660 cm^{-1} (C=O); τ 2.38 (1 H, d, *J* = 3 Hz, H-1), 3.65 (1 H, d, *J* = 3 Hz, H-2), 3.4 (1 H, s, 5-H), 6.0 (3 H, s, OMe), 6.8—7.4 (4 H, m, 6-H + 9-H), and 8.0—8.7 (4 H, m, 7-H + 8-H).

3-(2-*Chloroallyloxy*)-6,7,8,9-*tetrahydro*-2-*methoxybenzocyclohepten*-5-*one* (12; R = Cl).—The hydroxy-ketone (1; R^1 = R^2 = R^3 = H) (5 g), 2,3-dichloropropene (10 ml), potassium iodide (2 g), anhydrous potassium carbonate (20 g), and dry acetone (200 ml) were refluxed together for 10 h. The usual work-up gave the product (6.2 g) (from benzene–light petroleum) having m.p. 58—59 °C (Found: C, 64.2; H, 6.2; Cl, 12.5. $C_{15}H_{17}ClO_3$ requires C, 64.3; H, 6.1; Cl, 12.65%), τ 2.9 (1 H, s, aryl), 3.45 (1 H, s, aryl), 4.52 and 4.7 (2 H, 2 d, *J* = 2 Hz, CCl=CH_2), 5.45 (2 H, s, OCH_2), 6.17 (3 H, s, OMe), 7.1—7.45 (4 H, m, 6-H + 9-H), and 8.1—8.4 (4 H, m, 7-H + 8-H).

4-(2-*Chloroallyl*)-6,7,8,9-*tetrahydro*-3-*hydroxy*-2-*methoxybenzocyclohepten*-5-*one* (13; R = Cl).—The above chloroallyl ether (2.5 g) was kept in *NN*-dimethylaniline (4 ml) at 205 °C for 3 h under N_2. The usual work-up yielded the *product* (2.4 g) (from benzene–light petroleum), m.p. 130—131 °C (Found: C, 64.3; H, 6.15; Cl, 12.65%; M^+, 280.0865. $C_{15}H_{17}ClO_3$ requires C, 64.3, H, 6.1; Cl, 12.65%; *M*, 280.0866); $\nu_{max.}$ (KBr) 3 350—3 200 (OH) and 1 670 (C=O) cm^{-1}; τ 3.6 (1 H, s, aryl), 4.4 (1 H, s, exchangeable OH), 4.95 and 5.06 (2 H, 2 d, *J* = 2 Hz, CCl=CH_2), 6.18 (2 H, s, CH_2CCl=), 6.2 (3 H, s, OMe), 7.3—7.6 (4 H, m, 6-H + 9-H), and 8.2—8.45 (4 H, m, 7-H + 8-H).

6,7,8,9-*Tetrahydro*-4-*methoxy*-2-*methyl*-10H-*cyclohepta*[e]*benzofuran*-10-*one* (14; R = Me).—The above *C*-chloroallyl compound (0.3 g) was stirred in polyphosphoric acid for 45 min at 100 °C. The usual work-up followed by preparative t.l.c. [SiO_2/chloroform–benzene(7 : 3)] gave the *product* (100 mg), m.p. 78—80 °C (Found: C, 73.3; H, 7.0%; M^+, 244.1104. $C_{15}H_{16}O_3$ requires C, 73.7; H, 6.6%; *M*, 244.1099), $\nu_{max.}$ (KBr) 1 655 (C=O) cm^{-1}; τ 3.18 (1 H, s, H-1), 3.6 (1 H, s, 5-H), 6.05 (3 H, s, OMe), 7.05—7.4 (4 H, m, 6-H + 9-H), 7.6 (3 H, s, Me), and 8.1—8.4 (4 H, m, 7-H + 8-H).

3-*Benzyloxy*-6,7,8,9-*tetrahydro*-2-*methoxybenzocyclohepten*-5-*one* (1; R^1 = $PhCH_2$, R^2 = R^3 = H).—The hydroxy-ketone (1; R^1 = R^2 = R^3 = H) (12 g), benzyl chloride (12 ml), anhydrous potassium carbonate (20 g), and dry acetone (200 ml) were refluxed together for 6 h. The usual work-up followed by recrystallisation from benzene–light petroleum (b.p. 60—80 °C) gave the *product* (12.5 g) as needles, m.p. 66—86 °C (Found: C, 76.45; H, 6.75. $C_{19}H_{20}O_3$ requires C, 76.85; H, 6.8%).

3-*Benzyloxy*-6,7,8,9-*tetrahydro*-6-*hydroxymethylene*-2-*methoxybenzocyclohepten*-5-*one* (15).—A solution of the above benzyloxy-ketone (5.4 g), ethyl formate (5.2 ml), and dry toluene (80 ml) was cooled to 0 °C and added to a suspension of sodium methoxide (from 3.8 g of sodium) in toluene (50 ml) at 0 °C. After 2 h at 0 °C and 24 h at 20 °C, the product was obtained by extraction with sodium hydroxide (10%, aqueous) and acidification. Recrystallisation from ether–light petroleum (b.p. 40—60 °C) gave pale brown needles (4.3 g), m.p. 74—75 °C (Found: C, 73.9; H, 6.1. $C_{20}H_{20}O_4$ requires C, 74.15; H, 6.2%), $\nu_{max.}$ (KBr) 1 635 (C=O) and 1 605 (C=C) cm^{-1}; τ —4.8br (1 H, exchangeable, OH), 2.25 (1 H, d, collapsing to s with D_2O, vinylic), 2.7—3 (6 H, m, 5 aryl + 4-H), 3.46 (1 H, s, 1-H), 5.0 (2 H, s, CH_2Ph), 6.2 (3 H, s, OMe), 7.38—7.55 (2 H, m, 9-H), and 7.95—8.25 (4 H, m, 7-H + 8-H).

9-*Benzyloxy*-5,6-*dihydro*-8-*methoxy*-4H-*benzo*[6,7]*cyclohept*[1,2-c]*pyrazole* (16; R^1 = $PhCH_2$, R^2 = H).—The hydroxymethylene ketone (15; 0.45 g), hydrazine hydrate (0.65 ml; 99%), and methanol (25 ml) were stirred together for 2 h at 20 °C. The usual work-up provided crystals (0.35 g), m.p. 114—115 °C (from ethanol) (Found: C, 74.6; H, 6.2; N, 8.5%; M^+, 320.1521. $C_{20}H_{20}N_2O_2$ requires C, 75.05; H, 6.3; N, 8.75%; *M*, 320.1525), $\nu_{max.}$ (KBr) 3 165 (NH) cm^{-1}; τ —0.3br (1 H, exchangeable, NH), 2.8—3.1 (7 H, m, aryl + 3-H + 10-H), 3.53 (1 H, s, 7-H), 5.3 (2 H, s, CH_2Ph), 6.3 (3 H, s, OMe), 7.3—7.55 (4 H, m, 4-H + 6-H), and 8.0—8.3 (2 H, m, 5-H). Treatment of this product with acetic acid containing concentrated hydrochloric acid (1%) gave the corresponding 5,6-dihydro-9-hydroxy-8-methoxy-4*H*-benzo[6,7]cyclohept[1,2-*c*]pyrazole (16; R^1 = R^2 = H), m.p. 186—187° (Found: C, 67.75; H, 6.1; N, 12.15. $C_{13}H_{14}N_2O_2$ requires C, 67.9; H, 6.15; N, 12.15%).

In similar fashion were made the following:

Structure (16)			Found				Required			
R^1	R^2	M.p. (°C)	C(%)	H(%)	N(%)	*M*	C(%)	H(%)	N(%)	*M*
$PhCH_2$	Ph	150 *	74.95	6.25	6.9	396.1826	74.45	6.35	6.75	396.1838
H	Ph	235	74.0	5.95	9.0		74.5	5.95	9.15	
$PhCH_2$	*p*-$NO_2C_6H_4$	195—197 *	67.8	5.4	8.65	441.1698	68.05	5.5	9.1	441.1688
H	*p*-$NO_2C_6H_4$	198	64.6	4.9	11.65		64.9	4.85	11.4	
$PhCH_2$	2,4-di$NO_2C_6H_3$	162—163	63.9	4.75	11.15		64.25	4.55	11.5	
H	2,4-di$NO_2C_6H_3$	185—187	57.2	4.3	13.8	396.1082	57.5	4.05	14.1	396.1070

* +H_2O

9-*Benzyloxy*-5,6-*dihydro*-8-*methoxy*-4H-*benzo*[3,4]*cyclohept*[1,2-d]*isoxazole* (17; R = $PhCH_2$).—The hydroxymethylene ketone (15; 0.25 g), hydroxylamine hydrochloride (0.05 g), and acetic acid (6 ml) were refluxed together for 6 h. The usual work-up gave material which was separated by preparative t.l.c. on silica using benzene–ethyl acetate (50 : 50). The first band yielded the desired product (0.15 g) (from benzene), m.p. 160 °C (Found: C, 75.1; H, 6.0; N, 4.15%; M^+, 321.1360. $C_{20}H_{19}NO_3$ requires C, 74.85; H, 5.95; N, 4.35%; *M*, 321.1365), τ 2.12 (1 H, s, 3-H), 2.62 (1 H, s, 10-H), 2.8 (5 H, m, aryl), 3.49 (1 H, s, 7-H), 4.96 (2 H, s, CH_2Ph), 6.22 (3 H, s, OMe), and 7.19—8.25 [6 H, m, $(CH_2)_3$]. The second band gave 5,6-*dihydro*-9-*hydroxy*-8-*methoxy*-4H-*benzo*[3,4]*cyclohept*[1,2-d]*isoxazole* (17; R = H) (0.05 g) from benzene–ethyl acetate as prisms, m.p. 208—210 °C (Found: C, 67.65; H, 5.65; N, 5.85%; M^+, 231.0899. $C_{13}H_{13}NO_3$ requires C, 67.6; H, 5.65; N, 6.05%; *M*, 231.0895), $\nu_{max.}$ (KBr) 3 410 (OH) cm^{-1}; τ 1.98 (1 H, s, 3-H), 2.65 (1 H, s, 10-H), 3.45 (1 H, s, 7-H), 4.5br (1 H, s, exchangeable, OH), 6.16 (3 H, s, OMe), and 7.12—8.1 [6 H, m, $(CH_2)_3$].

The latter compound was also obtained by hydrolysis of the former using concentrated hydrochloric acid in acetic acid.

3-*Benzyloxy*-6,7,8,9-*tetrahydro*-2-*methoxybenzocycloheptene*-5,6-*dione* 6-*Monophenylhydrazone*.—A solution of benzenediazonium chloride (from 0.9 g aniline) was added during 20 min at 0 °C to a stirred mixture of hydroxymethylene ketone (15, 3.3 g), sodium acetate (2 g), methanol (40 ml), water (7 ml), and benzene (15 ml). The precipitated solid was washed with water and recrystallised from ethanol to give needles (2.75 g), m.p. 130—132 °C (Found: C, 74.9; H, 6.1; N, 6.9. $C_{25}H_{24}N_2O_3$ requires C, 75.0; H, 6.0; N, 7.0%), τ 2.6—2.95 (11 H, m, aryl), 3.48 (1 H, s, 1-H), 4.96 (2 H, s, CH_2Ph), 5.5br (1 H, exchangeable, NH), 6.2 (3 H, s, OMe), and 7.25—8.1 [6 H, m, $(CH_2)_3$].

8-*Benzyloxy*-11,12-*dihydro*-9-*methoxybenzo*[5,6]*cyclohept*-[1,2-b]*indole* (18; R = $PhCH_2$).—The foregoing phenylhydrazone (1 g), acetic acid (8 ml), and concentrated hydrochloric acid (0.9 ml) were refluxed together for 2.5 h. Work-up in the usual fashion gave a yellow solid (0.875 g) consisting of two substances (t.l.c.). Preparative t.l.c. on silica (elution with benzene–ethyl acetate) gave the *product* (240 mg) as faster-moving component, m.p. 190—191 °C (Found: C, 78.75; H, 5.4; N, 3.6. $C_{25}H_{21}NO_3$ requires C, 78.3; H, 5.4; N, 3.6%), $\nu_{max.}$ (KBr) 3 300 (NH) and 1 610 (C=O) cm^{-1}; τ 0.9br (1 H, NH), 2.4 (1 H, s, 7-H), 2.65—2.95 (9 H, m, aryl), 3.4 (1 H, s, 10-H), 4.92 (2 H, s, CH_2Ph), 6.12 (3 H, s, OMe), and 6.9 (4 H, s, 11-H + 12-H). The slower-moving component (0.55 g) had m.p. 220—221 °C (ethanol) (Found: C, 73.6; H, 5.3; N, 4.4%; M^+, 293.1045. $C_{18}H_{15}NO_3$ requires C, 73.7; H, 5.1; N, 4.8%; *M*, 293.1052), $\nu_{max.}$ (KBr) 3 600br (OH), 3 300 (NH), and 1 615 (C=O) cm^{-1}, τ 0.95br (1 H, NH), 2.42 (1 H, s, 7-H), 2.45—3.5 (4 H, m, aryl), 3.4 (1 H, s, 10-H), 4.5br (1 H, exchangeable, OH), 6.15 (3 H, s, OMe), and 6.9 (4 H, s, 11-H + 12-H). It was the debenzylated analogue.

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