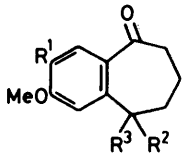
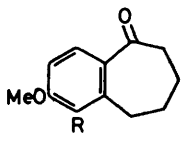
Synthesis of Structural Analogues of 6,7,8,9-Tetrahydro-3-hydroxy-2-methoxybenzocyclohepten-5-one

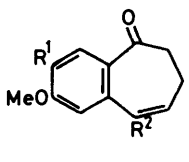
By **Philip D. Carpenter, Venkateswarlu Peesapati,** and **George R. Proctor,*** Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow G1 1XL

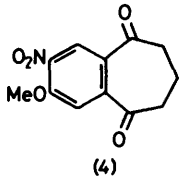
6,7,8,9-Tetrahydro-2-methoxy-3-nitrobenzocyclohepten-5-one has been made, separated from an isomer, and converted into several bromo-compounds, two of which were further studied. 2,3,4,5-Tetrahydro-7-hydroxy-8-methoxy-1-benzazepin-5-one has been obtained in several steps from methyl 4,5-dimethoxyanthranilate for which an improved synthesis has been developed. Preparations of 6-hydroxy-7-methoxynaphthalen-1(2*H*)-one and 7-hydroxy-6-methoxynaphthalen-1(2*H*)-one have been reinvestigated and an unequivocal synthesis of the latter is presented.

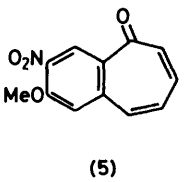
FOR the reasons outlined in the previous paper,[1] we have been interested in making molecules whose structures resembled the title compound (1; R^1 = OH, R^2 = R^3 = H). First we studied the effect of replacing the hydroxy-group with a nitro- or amino-group: this was achieved *via* the 2-methoxybenzocycloheptenone [2] (1; R^1 = R^2 = R^3 = H) now made in improved yield from the corresponding *m*-methoxyphenylpentanoic acid by treatment with polyphosphoric acid at 45 °C. Nitration with copper(II) nitrate in acetic anhydride furnished a mixture of compounds (1; R^1 = NO_2, R^2 = R^3 = H)

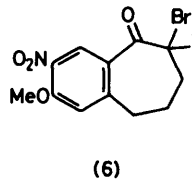

(1)

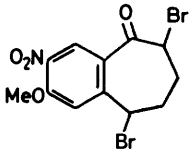

(2)

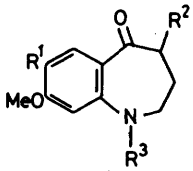

(3)


(4)


(5)


(6)


(7)


(8)

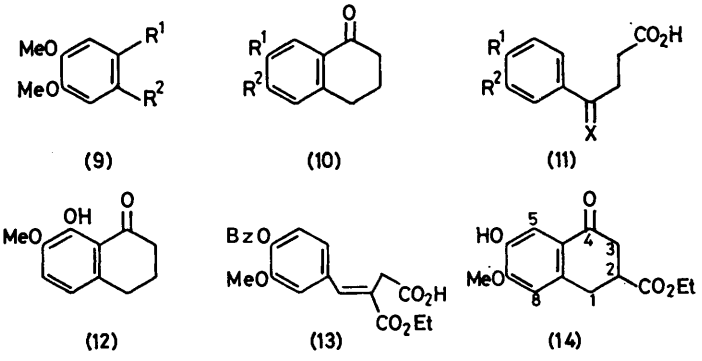
and (2; R = NO_2) which were separated by column chromatography and identified by n.m.r. spectroscopy, in particular by the multiplicity of the downfield proton signal due to 4-H (see Experimental section). Reduction of the nitro-compound (1; R^1 = NO_2, R^2 = R^3 = H) gave the amine (1; R^1 = NH_2, R^2 = R^3 = H) while demethylation of (1; R = NO_2, R^2 = R^3 = H) and (2; R = NO_2) gave the corresponding phenolic nitro-ketones. When the nitro-ketone (1; R^1 = NO_2, R^2 = R^3 = H) was treated with *N*-bromosuccinimide, substitution took place at C-9 yielding the bromide (1; R^1 = NO_2, R^2 = Br, R^2 = H) or dibromide (1; R^1 = NO_2, R^2 = R^3 = Br) depending on the proportion of reagent employed. Dehydrobromination of the 9-monobromide with collidine gave the expected enone (3; R^1 = NO_2, R^2 = H) whilst with either 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), or triethylamine a complex mixture was obtained. In the latter case two products were isolated, they were the bromo-enone (3; R^1 = NO_2, R^2 = Br) and a dione [presumably (4)] by analogy with work on benzocycloheptenone.[2] The same two products were more cleanly obtained, along with a small amount of the benzotropone (5), by reaction of the dibromide (1; R^1 = NO_2, R^2 = R^3 = Br) with silver acetate followed by hydrolysis. Formulation of these compounds as shown was supported by the fact that bromination of the nitro-ketone (1; R^1 = NO_2, R^2 = R^3 = H) with bromine (2 mol. equiv.) in chloroform yielded a different dibromo-compound (6); further, bromination of the monobromide (1; R^1 = NO_2, R^2 = Br, R^3 = H) with bromine in chloroform gave yet a further dibromide (7). This confirmatory work was necessary since there are reports [3,4] of NBS reactions which tended to introduce a second bromine atom into benzocycloalkanones at a position α to the carbonyl group rather than in the benzylic position and geminal with the first bromine atom.

In principle, replacement of C-9 in the title compound with an NH group gives a tetrahydro-1-benzazepin-5-one (8; R^1 = OH, R^2 = R^3 = H) of, hitherto, unknown substitution pattern. Synthesis was achieved by application of published procedures [5] to methyl 4,5-dimethoxyanthranilate (9; R^1 = CO_2Me, R^2 = NH_2). For moderate-scale preparations of the latter, modifications were required for methods in the literature.† Thus veratraldehyde was nitrated in the dark to give 4,5-dimethoxy-2-nitrobenzaldehyde [6] (9; R^1 = CHO, R^2 = NO_2) which, without isolation, was oxidised in the same vessel using nitric acid at a higher temperature to yield 4,5-dimethoxy-2-nitrobenzoic acid [7] (9; R^1 = CO_2H, R^2 = NO_2) in moderate yield. The acid chloride was conveniently converted into the ester (9; R^1 = CO_2Me, R^2 = NO_2) by reaction with methanol; catalytic hydrogenation then yielded the desired amino-ester [8] (9; R^1 = CO_2Me, R^2 = NH_2). Thence by published [5] procedures, *via* the oxo-ester (8; R^1 = OMe, R^2 = CO_2Et, R^3 = tosyl), the ketone (8, R^1 = OMe, R^2 = H, R^3 = tosyl) was obtained and detosylated by sulphuric acid in acetic acid [9] at 20 °C to give the amino-ketone (8; R^1 = OMe, R^2 =

† We thank Dr. M. D. Scott (G. D. Searle Co.) for very helpful collaboration.

R^3 = H) in 89% yield. Demethylation to (8, R^1 = OH, R^2 = R^3 = H) was troublesome; it was finally achieved in low yield by treatment of the amino-ketone (8; R^1 = OMe, R^2 = R^3 = H) with a mixture of sulphuric and acetic acids at 90 °C or by 40% hydrogen bromide in acetic acid. The position of demethylation was deduced from n.m.r. studies of the aminophenol (8; R^1 = OH, R^2 = R^3 = H), its *ON*-diacetate and the dimethoxy-compounds (8; R^1 = OMe, R^2 = H, R^3 = H, Ac, and tosyl) (see Experimental section), in particular from the changes of chemical shift for 6-H seen in this series of compounds.

The last structural modification to the title compound was a reduction in ring size. The relevant hydroxy-methoxytetralone (10; R^1 = OH, R^2 = OMe) had been



previously obtained along with the isomer (10; R^1 = OMe, R^2 = OH) by partial demethylation of the dimethoxytetralone (10; R^1 = R^2 = OMe) and the isomers were separated by preparative layer chromatography.[10] For larger scale work we sought an alternative approach. Contrary to a previous report,[11] we found that partial demethylation of the dimethoxybenzoylpropionic acid (11; R^1 = R^2 = OMe, X = O) gave both the possible monomethoxy-isomers. Consequently, subsequent reduction of the carbonyl group gave a mixture of the phenylbutanoic acids (11; R^1 = OH, R^2 = OMe, X = H_2) and (13; R^1 = OMe, R^2 = OH, X = H_2) which on cyclisation with 95% H_2SO_4 yielded three ketones separated by preparative layer chromatography. They were respectively (12) (2%), (10; R^1 = OMe, R^2 = OH) (58%), and (10; R^1 = OH; R^2 = OMe) (40%); the two major isomers correspond with those reported in the literature.[10] While their structures were not in serious doubt, it was desirable to obtain confirmation and a more fruitful source of pure ketone (10; R^1 = OH, R^2 = OMe). This was done as follows. 4-Benzyloxy-3-methoxybenzaldehyde [12] was subjected to the Stobbé condensation with diethyl succinate using potassium t-butoxide in t-butyl alcohol [13] to give the half ester (13) which was hydrogenated and then cyclised with polyphosphoric acid to give the tetralone ester (14). The latter was hydrolysed and decarboxylated to yield the hydroxymethoxytetralone (10; R^1 = OH, R^2 = OMe) identical to one of the isomers described above and corresponding in melting point with the previously formulated material.[10]

Although an unequivocal synthesis of the hydroxy-methoxybenzoylpropanoic acid (11; R^1 = OH, R^2 = OMe, X = O) was initiated from benzylvanillic acid [14] *via* the oxazolone route,[15] the yield of corresponding nitrile was poor and its hydrolysis was not examined.

EXPERIMENTAL

6,7,8,9-*Tetrahydro*-2-*methoxybenzocyclohepten*-5-*one* (1; R^1 = R^2 = R^3 = H).—5-(3-Methoxyphenyl)pentanoic acid [2] (160 g) and polyphosphoric acid (2 kg) were stirred together for 24 h at 40—45 °C. The usual work up gave the *product* (130 g) m.p. 62 °C.

6,7,8,9-*Tetrahydro*-2-*methoxy*-3-*nitrobenzocyclohepten*-5-*one* (1; R^1 = NO_2, R^2 = R^3 = H).—6,7,8,9-Tetrahydro-2-methoxybenzocyclohepten-5-one (30.25 g) and cupric nitrate trihydrate (40 g) were swirled together in acetic anhydride (200 ml) until an exothermic reaction commenced. After cooling, the mixture was stirred for 1 h and poured onto ice when the solid was filtered off. After drying, ether extraction left almost pure *product* which crystallised from benzene–ether as pale yellow needles (14.46 g), m.p. 150—151 °C (Found: C, 61.15; H, 5.85; $C_{12}H_{13}NO_4$ requires C, 61.35; H, 5.6%), $\nu_{max.}$ (Nujol) 1 660 (C=O) and 1 519 (NO_2) cm^{-1}; τ 1.76 (1 H, s, 4-H), 3.12 (1 H, s, 1-H), 6.0 (3 H, s, OMe), 7.0 (2 H, t, J = 6 Hz, 9-H), 7.26 (2 H, t, J = 6 Hz, 6-H), and 7.9—8.35 (4 H, m, 7- and 8-H). The material from the ether extract was chromatographed on silica gel; elution with benzene gave first 6,7,8,9-*tetrahydro*-2-*methoxy*-1-*nitrobenzocyclohepten*-5-*one* (2; R = NO_2) (9.6 g), m.p. 127—128 °C (Found C, 61.45; H, 5.75. $C_{12}H_{13}NO_4$ requires C, 61.35; H, 5.6%), $\nu_{max.}$ (Nujol) 1 670 (C=O) and 1 527 (NO_2) cm^{-1}; τ 2.21 (1 H, d, J = 9 Hz, 4-H), 3.06 (1 H, d, J = 9 Hz, 3-H), 6.09 (3 H, s, OMe), 7.1—7.4 (4 H, m, 7- and 8-H), and 8.0—8.3 (4 H, m, 7- and 8-H). Further elution yielded additional product (2.64 g).

6,7,8,9-*Tetrahydro*-2-*hydroxy*-3-*nitrobenzocyclohepten*-5-*one* [*the Phenol from* (1; R^1 = NO_2, R^2 = R^3 = H)].—6,7,8,9-Tetrahydro-2-methoxy-3-nitrobenzocyclohepten-5-one (1; R^1 = NO_2, R^2 = R^3 = H) (5.0 g), anhydrous aluminium bromide (12.5 g), and dry benzene (200 ml) were refluxed together for 3 h and worked up in the usual way. After chromatography on silica gel (elution with 10% $CHCl_3$ in benzene) the *product* (2.2 g) crystallised from benzene–ether as plates, m.p. 113—114 °C (Found: C, 60.05; H, 5.05, N, 6.15. $C_{11}H_{11}NO_4$ requires C, 59.8; H, 5.0; N, 6.35%), $\nu_{max.}$ (Nujol) 3 255 (OH), 1 665 (C=O), and 1 525 (NO_2) cm^{-1}; τ −0.79 (1 H, s, exchangeable OH), 1.49 (1 H, s, 4-H), 3.04 (1 H, s, 1-H), 7.04 (2 H, t, J = 6 Hz, 9-H), 7.27 (2 H, t, J = 6 Hz, 6-H), and 7.9—8.4 (4 H, m, 7 and 8-H). The O-*acetate* was obtained by reaction of this phenol with acetic anhydride

in pyridine and had m.p. 110—111 °C (from ether–benzene) (Found: C, 59.3; H, 5.05; N, 5.31. $C_{13}H_{16}NO_5$ requires C, 59.35; H, 5.0; N, 5.3%), $\nu_{max.}$ (Nujol) 1 765 (OAc), 1 670 (C=O), and 1 520 (NO_2) cm^{-1}; τ 1.64 (1 H, s, 4-H), 2.98 (1 H, s, 1-H), 7.03 (2 H, t, J = 6 Hz, 9-H), 7.26 (2 H, t, J = 6 Hz, 6-H), 7.64 (3 H, s, OAc), and 8.0—8.3 (4 H, m, 7- and 8-H).

6,7,8,9-*Tetrahydro*-2-*hydroxy*-1-*nitrobenzocyclohepten*-5-*one* [*the Phenol from* (2; R = NO_2)].—6,7,8,9-Tetrahydro-2-methoxy-1-nitrobenzocyclohepten-5-one (2; R = NO_2) (10 g), anhydrous aluminium bromide (30.5 g), and dry benzene were refluxed together for 3 h and worked up as usual. The *product* crystallised from benzene as grey needles (2.36 g), m.p. 189—190 °C (Found: C, 59.9; H, 5.15; N, 6.15. $C_{11}H_{11}NO_4$ requires C, 59.8; H, 5.0; N, 6.35%), $\nu_{max.}$ (Nujol) 3 100 (OH), 1 650 (C=O), and 1 530 cm^{-1} (NO_2); τ 0.6 (1 H, s, exchangeable, OH), 2.24 (1 H, d, J = 9 Hz, 4-H), 2.98 (1 H, d, J = 9 Hz, 3-H), 7.03 (2 H, t, J = 6 Hz, 9-H), 7.32 (2 H, t, J = 6 Hz, 6-H), and 7.8—8.5 (4 H, m, 7- and 8-H).

3-*Amino*-6,7,8,9-*tetrahydro*-2-*methoxybenzocyclohepten*-5-*one* (1; R^1 = NH_2, R^2 = R^3 = H).—6,7,8,9-Tetrahydro-2-methoxy-3-nitrobenzocyclohepten-5-one (1; R^1 = NO_2, R^2 = R^3 = H) (5.8 g) was hydrogenated in ethanol (150 ml) over platinum oxide (250 mg). The *product* crystallised from carbon tetrachloride as fawn microcrystals, m.p. 126—129 °C (Found: C, 69.9; H, 7.3; N, 6.35. $C_{12}H_{15}NO_2$ requires C, 70.3; H, 7.4; N, 6.8%), $\nu_{max.}$ (Nujol) 3 465, 3 375 (NH), and 1 655 (C=O) cm^{-1}; τ 2.8 (1 H, s, 4-H), 3.43 (1 H, s, 1-H), 6.13 (3 H, s, OMe), 6.33 (2 H, s, exchangeable, NH_2), 7.1—7.4 (4 H, m, 6- and 9-H), and 8.1—8.4 (4 H, m, 7- and 8-H). The N-*acetate* was obtained by reaction of this amine with acetic anhydride in pyridine, when crystallised from carbon tetrachloride it had m.p. 152 °C (Found: C, 67.55; H, 6.8; N, 5.45. $C_{14}H_{17}NO_3$ requires C, 68.1; H, 6.95, N, 5.65%), $\nu_{max.}$ (Nujol) 3 420 (NH), 1 685 (CONH), and 1 660 (aryl CO) cm^{-1}; τ 1.4 (1 H, s, 4-H), 2.4br (1 H, exchangeable, NH), 3.35 (1 H, s, 1-H), 6.1 (3 H, s, OMe), 7.1—7.55 (4 H, m, 6- and 9-H), 7.85 (3 H, s, CH_3CO), and 8.1—8.4 (4 H, m, 7- and 8-H).

9-*Bromo*-6,7,8,9-*tetrahydro*-2-*methoxy*-3-*nitrobenzocyclohepten*-5-*one* (1; R^1 = NO_2, R^2 = Br, R^3 = H).—The nitro-ketone (1; R^1 = NO_2, R^2 = R^3 = H) (0.67 g), *N*-bromosuccinimide (0.54 g), benzoyl peroxide (10 mg), and dry carbon tetrachloride (50 ml) were refluxed over a 150-W lamp for 3 h. The usual work-up gave the *product* as prisms (from ether), m.p. 128—129 °C (Found: C, 46.1; H, 3.8; Br, 25.3; N, 4.5. $C_{12}H_{12}BrNO_4$ requires C, 45.9; H, 3.85; N, 4.45; Br, 25.45%), τ 1.88 (1 H, s, 4-H), 2.9 (1 H, s, 1-H), 4.5 (1H, t, 9-H), 6.0 (3 H, s, OMe), and 6.8—8.0 (6 H, m, 6-, 7- and 8-H).

9,9-*Dibromo*-6,7,8,9-*tetrahydro*-2-*methoxy*-3-*nitrobenzocyclohepten*-5-*one* (1; R^1 = NO_2, R^2 = R^3 = Br).—The nitro-ketone (1; R^1 = NO_2, R^2 = R^3 = H) (3.05 g) and *N*-bromosuccinimide (5.63 g) were heated together in carbon tetrachloride (200 ml) as above. The *product* (2.5 g) crystallised from ether and had m.p. 117—121 °C (Found: C, 37.05; H, 2.85; N, 4.3. $C_{12}H_{11}Br_2NO_4$ requires C, 36.7; H, 2.8; N, 3.6%), τ 2.02 (1 H, s, 4-H), 2.08 (1 H, s, 1-H), 5.9 (3 H, s, OMe), 6.85 and 7.12 (4 H, 2 t, 6- and 8-H), and 7.7—7.95 (2 H, m, 7-H).

6,6-*Dibromo*-6,7,8,9-*tetrahydro*-2-*methoxy*-3-*nitrobenzocyclohepten*-5-*one* (6).—The nitro-ketone (1; R^1 = NO_2, R^2 = R^3 = H) (2.35), bromine (1 ml), and chloroform (100 ml) were left together for 1 day at 20 °C. The usual work-up provided *product* (3.5 g, from dichloromethane–light petroleum), m.p. 154—156 °C (Found: C, 36.35; H, 2.8; Br, 40.25; N, 3.85. $C_{12}H_{11}Br_2NO_4$ requires C, 36.65; H, 2.8; Br, 40.65; N, 3.55%), $\nu_{max.}$ (Nujol) 1 695 (C=O) cm^{-1}; τ 2.1 (1 H, s, 4-H), 3.15 (1 H, s, 1-H), 6.02 (3 H, s, OMe), 7.0—7.3 (4 H, m, 7- and 9-H), and 7.75—8.02 (2 H, m, 8-H).

6,6-*Dibromo*-6,7,8,9-*tetrahydro*-2-*methoxy*-1-*nitrobenzocyclohepten*-5-*one* [*the* 6,6-*Dibromo-derivative of* (2; R = NO_2)].— 6,7,8,9-Tetrahydro-2-methoxy-1-nitrobenzocyclohepten-5-one (2; R = NO_2) (2.35 g) was brominated as in the previous paragraph and gave *prisms* (3.3 g, from dichloromethane–light petroleum), m.p. 182 °C (Found: C, 36.85; H, 2.85; Br, 40.2; N, 3.7. $C_{12}H_{11}Br_2NO_4$ requires C, 36.65; H, 2.8; Br, 40.65; N, 3.55%), $\nu_{max.}$ (Nujol) 1 700 cm^{-1}; τ 2.53 (1 H, d, J = 9 Hz, 4-H), 3.12 (1 H, d, J = 9 Hz, 3-H), 6.1 (3 H, s, OMe), 7.2—7.45 (4 H, m, 7- and 9-H), and 7.85—8.12 (2 H, m, 8-H).

6,7-*Dihydro*-2-*methoxy*-3-*nitrobenzocyclohepten*-5-*one* (3; R^1 = NO_2, R^2 = H).—9-Bromo-6,7,8,9-tetrahydro-2-methoxy-3-nitrobenzocyclohepten-5-one (1; R^1 = NO_2, R^2 = Br, R^3 = H) (4.8 g) and collidine (100 ml) were heated at 170 °C for 45 min. The usual work-up followed by chromatography on silica gel yielded the *product* (434 mg) which recrystallised from light petroleum (b.p. 60—80 °C) and had m.p. 145—147 °C (Found: C, 61.85; H, 4.95; N, 5.75%; M^+, 233.0691. $C_{12}H_{11}NO_4$ requires C, 61.85; H, 4.75; N, 6.0%; M, 233.0688), $\nu_{max.}$ (Nujol) 1 660 (sh, C=O) and 1 672 cm^{-1} (m, C=C); τ 1.5 (1 H, s, 4-H), 3.15 (1 H, s, 1-H), 3.50 and 3.52 (2 H, 2 d, 8- and 9-H), 6.0 (3 H, s, OMe), and 7.0—7.6 (4 H, m, 6- and 7-H).

Reaction of 9,9-*Dibromo*-6,7,8,9-*tetrahydro*-2-*methoxy*-3-*nitrobenzocyclohepten*-5-*one* (1; R^1 = NO_2, R^2 = R^3 = Br) *with Silver Acetate*.—The title compound (3.4 g), silver acetate (3.1 g), and acetic acid (50 ml) were refluxed together for 2 h. After addition of water (50 ml), refluxing was continued for a further 30 min. After the usual work-up, the crude product (2.4 g) was chromatographed on silica gel: elution with benzene gave 3 bands. The first band comprised 9-*bromo*-6,7-*dihydro*-2-*methoxy*-3-*nitrobenzocyclohepten*-5-*one* (3; R = Br) (850 mg), m.p. 147—149 °C (Found: C, 45.7; H, 3.2; N, 4.75. $C_{12}H_{10}BrNO_4$ requires C, 45.2; H, 3.2; N, 4.5%), τ 1.75 (1 H, s, 4-H), 2.56 (1 H, s, 1-H), 3.0 (1 H, t, 8-H), 5.93 (3 H, s, OMe), 7.0—7.2 (2 H, m, 6-H), and 7.5—7.72 (2 H, m, 7-H). The second band (150 mg) was 2-*methoxy*-3-*nitrobenzocyclohepten*-5-*one* (5), m.p. 235 °C (decomp.) (Found: C, 62.35; H, 4.0; N, 5.9%; M^+, 231.0525. $C_{12}H_9NO_4$ requires C, 62.4; H, 3.95; N, 6.05%; M, 231.0532), $\nu_{max.}$ (Nujol) 1 618 (C=O) cm^{-1}; τ 1.32 (1 H, s, 4-H), 2.92 (1 H, s, 1-H), 2.9—3.4 (4 H, m, vinylic), and 6.05 (3 H, s, OMe). The third band (850 mg) comprised 6,7,8,9-*tetrahydro*-2-*methoxy*-3-*nitrobenzocycloheptene*-5,9-*dione* (4), m.p. 137 °C (Found: C, 57.75; H, 4.25; N, 5.8. $C_{12}H_{11}NO_5$ requires C, 57.9; H, 4.45; N, 5.65%), $\nu_{max.}$ (Nujol) 1 700 and 1 688 (C=O) cm^{-1}; τ 1.72 (1 H, s, 4-H), 2.62 (1 H, s, 1-H), 5.95 (3 H, s, OMe), 7.0—7.25 (4 H, m, 6- and 8-H), and 7.75—8.05 (2 H, m, 7-H).

6,9-*Dibromo*-6,7,8,9-*tetrahydro*-2-*methoxy*-3-*nitrobenzocyclohepten*-5-*one* (7).—9-Bromo-6,7,8,9-tetrahydro-2-methoxy-3-nitrobenzocyclohepten-5-one (1; R^1 = NO_2, R^2 = Br, R^3 = H) (1.2 g) and bromine (0.19 ml) were left together in chloroform (60 ml) at 20 °C for 24 h. The usual work-up gave the *product* (1.1 g), m.p. 165 °C (from dichloromethane–light petroleum) (Found: C, 36.4; H, 2.8; Br, 40.8; N, 3.55. $C_{12}H_{11}Br_2NO_4$ requires C, 36.65; H, 2.8; Br, 40.65; N, 3.55%), $\nu_{max.}$ (Nujol) 1 682 (C=O) cm^{-1}; τ 2.05 (1 H, s, 4-H), 3.1 (1 H, s, 1-H), 4.6—4.7 (1 H, m, 6-H), 5.02—5.15 (1 H, m, 9-H), 6.03 (3 H, s, OMe), and 6.9—7.85 (4 H, m, 7- and 8-H).

4,5-*Dimethoxy*-2-*nitrobenzoic Acid* [7] (9; $R^1 = CO_2H$, $R^2 = NO_2$).—Veratraldehyde (70 g) was nitrated as described in the literature [6] except that concentrated nitric acid (300 ml) was used and after the first reaction was conducted at >20 °C, the reaction vessel (foil covered) was kept at 35—40 °C for 6 h and cooled. The acidic material (61 g) was the desired material, m.p. 187—190 °C (lit.,[7] 189—191°). The yellow neutral material (18 g) was 3,4-dinitroveratrole, m.p. 129 °C (Found: C, 42.6; H, 3.6; N, 12.0. Calc. for $C_8H_8N_2O_6$: C, 42.15; H, 3.55; N, 12.3%), τ 2.68 (2 H, s, aryl), and 6.0 (6 H, s, OMe). The latter increased in proportion with increases of time or temperature.

Methyl 2-*Nitro*-4,5-*dimethoxybenzoate* (9; $R^1 = CO_2Me$, $R^2 = NO_2$).—The above acid (89 g) and phosphorus pentachloride (90 g) were stirred and heated together at 90 °C for 1.5 h. After removal of phosphoryl chloride *in vacuo*, the reaction mixture was cooled (ice) while dry methanol (excess) was added with stirring. The usual work-up gave the *product* (86 g), m.p. 141—145 °C (lit.,[7] 144—145°), $\nu_{max.}$ (Nujol) 1 725 cm^{-1} (ester).

Methyl 2-*Amino*-4,5-*dimethoxybenzoate* (9; $R^1 = CO_2Me$, $R^2 = NH_2$).—The nitro-ester (86 g) from above was hydrogenated in methanol (1 l) using platinum oxide (3 g). After the uptake of hydrogen (26.5 l) ceased, the usual work-up gave product (83.5 g) sufficiently pure for most purposes. Recrystallisation from methanol gave material, m.p. 130 °C (lit.,[8] 133 °C), $\nu_{max.}$ (KCl) 3 450 (NH), 3 350 (NH), and 1 775 (ester) cm^{-1}; τ 2.72 (1 H, s, 6-H), 3.88 (1 H, s, 3-H), 4.4br (2 H, exchangeable, NH_2), 6.20 (6 H, s, OMe), and 6.22 (3 H, s, ester). The N-*tosyl derivative* had m.p. 128 °C (from MeOH) (Found: C, 55.8; H, 5.15; N, 4.05. $C_{17}H_{19}NO_6S$ requires C, 55.85; H, 5.25, N, 3.85%), $\nu_{max.}$ (Nujol) 3 400br (NH) and 1 665 (C=O) cm^{-1}; τ −0.45 (1 H, exchangeable, NH), 2.35 (2 H, d, J = 9 Hz, aryl adjacent to SO_2), 2.72 (2 H, s, 3- and 6-H), 2.83 (2 H, d, J = 9 Hz, aryl adjacent to Me), 6.1 (3 H, s, ester), 6.2 (6 H, s, OMe), and 7.68 (3 H, s, Me).

Ethyl N-p-*Tolylsulphonyl*-4-(4,5-*dimethoxy*-2-*methoxycarbonylanilino*)*butyrate* [9; $R^1 = CO_2Me$, R^2 = N-tosyl $(CH_2)_3CO_2Et$].—Methyl 2-(*N*-*p*-tolylsulphonylamino-4,5-dimethoxybenzoate (9; $R^1 = CO_2Me$, R^2 = NHtosyl) (36.5 g) and anhydrous potassium carbonate (21.7 g) were vigorously stirred at 140 °C while ethyl γ-bromobutyrate [5] (30 g) was added over 0.5 h. After a further 20 h at 130 °C the reaction was worked up [5] to give the *product* (56 g) pure enough for cyclisation. Chromatography on silica gel and recrystallisation from methanol gave colourless needles, m.p. 78—79 °C (Found: C, 57.9; H, 5.9; N, 3.05. $C_{23}H_{29}NO_8S$ requires C, 57.6; H, 6.1; N, 2.9%), $\nu_{max.}$ (KCl) 1 722 (ester) and 1 690sh cm^{-1} (aryl ester); τ 2.4—2.85 (6 H, m, aryl), 5.9 (2 H, q, CH_2CH_3), 6.08 (3 H, s, CO_2Me), 6.25 (3 H, s, OMe), 6.3 (3 H, s, OMe), 6.2—6.35 (2 H, m, CH_2), 7.5—7.7 (2 H, m, CH_2), 7.59 (3 H, s, Me), 7.9—8.28 (2 H, m, CH_2), and 8.78 (3 H, t, CH_3CH_2).

4-*Ethoxycarbonyl*-7,8-*dimethoxy*-1,2,3,4-*tetrahydro*-1-*tolyl*-p-*sulphonyl*-1-*benzazepin*-5-*one* (8; R^1 = OMe, $R^2 = CO_2Me$, R^3 = tosyl).—The foregoing ester (20 g) was cyclised using potassium t-butoxide (from 7.8 g potassium) in toluene as previously described.[16] The usual work-up gave product (16.4 g) which could be conveniently used. Purification by chromatography on silica gel and crystallisation from methanol gave material, m.p. 140 °C (Found: C, 59.3; H, 5.85; N, 3.35. $C_{22}H_{25}NO_7S$ requires C, 59.05; H, 5.65; N, 3.15%), $\nu_{max.}$ (KCl) 1 645 (ester), 1 620 (C=O), and 1 600 (C=C) cm^{-1}; τ −2.2 (1 H, s, exchangeable, enolic H), 2.55—3.12 (6 H, m, aryl), 5.92 (2 H, q, CH_2CH_3), 5.8—6.1 (2 H, m, CH_2), 6.08 (3 H, s, OMe), 6.13 (3 H, s, OMe), 7.65 (3 H, s, Me), 7.58—7.85 (2 H, m, CH_2), and 8.72 (3 H, t, CH_3CH_2). In some batches the corresponding methyl ester was present as impurity (up to 30%), detectable by n.m.r. absorptions at τ −1.9 (s, exchangeable) and 6.32 (s, CO_2Me).

6,7,8,9-*Tetrahydro*-7,8-*dimethoxy*-1-p-*tolylsulphonyl*-1-*benzazepin*-5-*one* (8; R^1 = OMe, R^2 = H, R^3 = tosyl).—The previously described β-oxo-ester mixture (50 g), acetic acid (300 ml), ethanol (100 ml), water (50 ml), and concentrated hydrochloric acid (50 ml) were refluxed together for 48 h. Work-up as usual followed by chromatography on alumina (benzene elution) and recrystallisation from ethanol yielded prisms, m.p. 144 °C (Found: C, 61.1; H, 5.8; N, 3.8. $C_{19}H_{21}NO_5S$ requires C, 60.85; H, 5.65; N, 3.75%), $\nu_{max.}$ 1 680 (C=O) cm^{-1}; τ 2.35—3.05 (6 H, m, aryl), 6.1 (3 H, s, OMe), 6.15 (3 H, s, OMe), 6.0—6.3 (2 H, m, CH_2), 7.58 (3 H, s, Me), 7.5—7.8 (2 H, m, CH_2), and 7.9—8.22 (2 H, CH_2).

6,7,8,9-*Tetrahydro*-7,8-*dimethoxy*-1-*benzazepin*-5-*one* (8; R^1 = OMe, $R^2 = R^3$ = H).—The tosyl ketone (8; R^1 = OMe, R^2 = H, R^3 = tosyl) (5 g) was stirred at 50 °C with 40% sulphuric acid in acetic acid (40 ml) [9] for 3 h. Work-up of the basic fraction gave the *product* (2.6 g, 89%), m.p. 98—99 °C (from benzene–light petroleum) (Found: C, 64.55; H, 6.95; N, 6.4. $C_{12}H_{15}NO_3$ requires C, 64.2; H, 6.85; N, 6.35%), $\nu_{max.}$ (KBr) 3 335 (NH) and 1 645 (C=O) cm^{-1}; τ 2.72 (1 H, s, 6-H), 3.76 (1 H, s, 9-H), 5.45 (1 H, br, exchangeable, NH), 6.16 (3 H, s, OMe), 6.18 (3 H, s, OMe), 6.8 (2 H, t, 4-H), 7.2 (2 H, t, 2-H), and 7.9 (2 H, m, 3-H). The N-*acetate* had, m.p. 118—120° (from benzene–ether) (Found: C, 64.4; H, 6.65; N, 5.3. $C_{14}H_{17}NO_4$ requires C, 63.95; H, 6.5; N, 5.35%), $\nu_{max.}$ (Nujol) 1 655sh (COAr) and 1 640 ($NCOCH_3$) cm^{-1}; τ 2.72 (1 H, s, 6-H), 3.4 (1 H, s, 9-H), 6.1 (6 H, s, OMe), 6.8—8.3, (6 H, m, CH_2), and 8.06 (3 H, s, CH_3CO).

6,7,8,9-*Tetrahydro*-7-*hydroxy*-8-*methoxy*-1-*benzazepin*-5-*one* (8; R^1 = OH, $R^2 = R^3$ = H).—7,8-Dimethoxy-6,7,8,9-tetrahydro-1-*p*-tolylsulphonyl-1-benzazepin-5-one (8; R^1 = OMe, R^2 = H, R^3 = tosyl) (13.5 g) and concentrated sulphuric acid were stirred together at 50 °C for 24 h. Work-up of the basic fraction as usual and removal of phenolic basic material with 10% sodium hydroxide solution gave a mixture from which the product (350 mg) was obtained by repeated preparative t.l.c. (silica gel/40% benzene–ether). It had b.p. 190 °C/0.05 mmHg (Found: C, 63.95; H, 6.35; N, 6.6%; M^+, 207.0901. $C_{11}H_{13}NO_3$ requires C, 63.8; H, 6.35; N, 6.75%; M, 207.0895). The ON-*diacetate* had m.p. 183.5—184.5 °C (Found: C, 62.25; H, 6.05; N, 4.75. $C_{15}H_{17}NO_5$ requires C, 61.9; H, 5.9; N, 4.8%), $\nu_{max.}$ (Nujol) 1 760 (CH_3COO), 1 655sh (ArC=O), and 1 640 cm^{-1} (CH_3CON); τ 2.4 (1 H, s, 6-H), 3.23 (1 H, s, 9-H), 6.12 (3 H, s, OMe), 7.2—8.3 (6 H, m, CH_2), 7.7 (3 H, s, OAc), and 8.0 (3 H, s, $NCOCH_3$).

Demethylation of β-(3,4-*Dimethoxybenzoyl*)*propionic acid*.[11]—β-(3,4-Dimethoxybenzoyl)propionic acid (25.4 g) was treated with hydriodic acid (55%) as described.[11] A portion of the crude product (0.5 g) was purified by preparative t.l.c. (silica gel/20% ethanol–chloroform). The faster-moving band gave β-(3-*hydroxy*-4-*methoxybenzoyl*)*propionic acid* (0.32 g), m.p. 146—147 °C (Found: C, 58.9; H, 5.4. $C_{11}H_{12}O_5$ requires C, 59.0; H, 5.4%), $\nu_{max.}$ (KBr) 3 450 (OH), 1 700 (COOH), and 1 670 (ArCO) cm^{-1}. The slower-moving band gave β-(4-*hydroxy*-3-*methoxybenzoyl*)*propionic acid* (0.17 g), m.p. 175—176 °C (lit.,[11] m.p. 177 °C).

The remainder (20 g) of the crude product of demethylation was refluxed with amalgamated zinc (40 g), water (37 ml), concentrated hydrochloric acid (88 ml), and toluene (50 ml) for 40 h. The usual work-up gave a mixture (12.5 g); a portion (12 g) was added to 95% sulphuric acid (55 ml) and kept at 100 °C for 45 min. The crude product (7.8 g) was separated by preparative t.l.c. (silica gel/20% ethyl acetate–benzene). The first band (200 mg) was *3,4-dihydro-8-hydroxy-7-methoxynaphthalen-1(2H)-one* (12), m.p. 73—74 °C (Found: C, 68.65; H, 6.45%; M^+, 192.0782. $C_{11}H_{12}O_3$ requires C, 68.8; H, 6.3%; *M*, 192.0786), $\nu_{max.}$ (KBr) 1 630 (C=O) cm^{-1}; τ −2.6 (1 H, s, exchangeable, OH), 3.15 and 3.5 (2 H, 2 d, J = 9 Hz, 5- and 6-H), 6.24 (3 H, s, OMe), 7.15—7.5 (4 H, 2 t, H-2 and H-4), and 7.85—8.15 (2 H, m, H-3); violet $FeCl_3$ test. The second band (4 g) was *3,4-dihydro-6-hydroxy-7-methoxynaphthalen-1(2H)-one* (10; R^1 = OMe, R^2 = OH), m.p. 123—124 °C (lit.,[11] m.p. 117—119 °C), green $FeCl_3$ colour. The third band (3 g) was *3,4-dihydro-7-hydroxy-6-methoxynaphthalen-1(2H)-one* (10; R^1 = OH, R^2 = OMe), m.p. 148—151 °C (lit.,[10] m.p. 148—152 °C), no $FeCl_3$ colour. The O-*acetate* from *4-dihydro-6-hydroxy-7-methoxynaphthalen-1(2H)-one* had m.p. 79—80 °C (from benzene) (Found: C, 66.7; H, 6.1. $C_{13}H_{14}O_4$ requires C, 66.75; H, 6.05%), $\nu_{max.}$ (KBr) 1 765 (CH_3COO) and 1 675 cm^{-1} (Ar*C*=*O*); τ 2.56 (1 H, s, 8-H), 3.25 (1 H, s, 5-H), 6.24 (3 H, s, OMe), 7.2 (2 H, t, 2-H), 7.45 (2 H, t, 4-H), 7.75 (3 H, s, CH_3CO), and 7.8—8.05 (2 H, m, 3-H). The *O-acetate* from *3,4-dihydro-8-hydroxy-7-methoxynaphthalen-1(2H)-one* (14) had m.p. 126—128 °C (from benzene–light petroleum) (Found: C, 66.6; H, 6.15. $C_{13}H_{14}O_4$ requires C, 66.75; H, 6.05%), $\nu_{max.}$ (KBr) 1 765 (CH_3COO) and 1 670 (ArC=O) cm^{-1}; τ 2.54 (1 H, s, 8-H), 3.45 (1 H, s, 5-H), 6.25 (3 H, s, OMe), 7.2 (2 H, t, 2-H), 7.51 (2 H, t, 4-H), 7.8 (3 H, s, CH_3CO), and 7.85—8.1 (2 H, m, 3-H).

Ethyl 1,2,3,4-Tetrahydro-6-hydroxy-7-methoxy-4-oxo-2-naphthoate (14).—Using published[13] procedures from benzylvanillin *via* the half-ester (13), the product gave prisms m.p. 145—146 °C (from benzene–ethyl acetate) (Found: C, 63.65; H, 6.0%; M^+, 264.0920. $C_{14}H_{16}O_5$ requires C, 63.7; H, 6.1%; *M*, 264.0953), $\nu_{max.}$ (KBr) 3 405 (OH), 1 725 (ester), and 1 660 (C=O) cm^{-1}; τ 2.62 (1 H, s, 5-H), 3.45 (1 H, s, 8-H), 4.35br (1 H, exchangeable OH), 5.88 (2 H, q, CH_2CH_3), 6.13 (3 H, s, OMe), 6.9—7.3 (5 H, m, 1-, 2-, and 3-H), and 8.8 (3 H, t, CH_3CH_2). When this material was hydrolysed (10% NaOH–H_2O, 2 h) and the acidic product then refluxed in quinoline containing copper powder for 3 h, the product was 3,4-dihydro-7-hydroxy-6-methoxynaphthalen-1(2*H*)-one, mixed m.p. 150—151 °C.

We thank the Cancer Campaign for a fellowship and Dr. S. A. Mahmud, Mrs. L. Rees, and Mrs I. M. Bell for technical assistance.

[7/2164 *Received*, 9*th December*, 1977]

REFERENCES

[1] Preceding paper.
[2] A. M. Khan, G. R. Proctor, and L. Rees, *J. Chem Soc.* (*C*), 1966, 990.
[3] E. W. Collington and G. Jones, *J. Chem. Soc.* (*C*), 1969, 2656.
[4] M. Suzuki, H. Hart, E. Dunkelblum, and W. Li, *J. Amer. Chem. Soc.*, 1977, **99**, 5083.
[5] I. McCall, G. R. Proctor, and L. Purdie, *J. Chem. Soc.* (*C*), 1970, 1126.
[6] C. A. Fetscher, Org. Synth. Coll. Vol. **4**, 1963, 735.
[7] ' Dictionary of Organic Compounds,' 4th edn., 1965, **2**, 1132.
[8] ' Dictionary of Organic Compounds,' 4th edn., 1965, **1**, 120.
[9] P. D. Carpenter and M. Lennon, *Chem. Comm.*, 1973, 664.
[10] G. Grethe, V. Toome, H. L. Lee, M. Uskokovic, and A. Brossi, *J. Org. Chem.*, 1968, **33**, 504.
[11] F. Zymalkowski and J. Aelberg, *Arch. Pharm.*, 1966, **299**, 545.
[12] R. A. Anker, A. H. Cook, and I. M. Heilbron, *J. Chem. Soc.*, 1945, 917.
[13] M. Lehrer and R. Stevenson, *J.C.S. Perkin I*, 1974, 1165.
[14] T. Heap and R. Robinson, *J. Chem. Soc.*, 1926, 2336.
[15] G. Steglich and P. Gruber, *Angew. Chem.*, 1971, **10**, 655.
[16] A. Cromarty, G. R. Proctor, and M. Shabbir, *J.C.S. Perkin I*, 1972, 2012.