5,9-Methanobenzoannulenamines. Part 1. Improved Synthesis of 11-Amino-5,9-methanobenzo[8]annulenes

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Reaction of 1-(3,4-dihydronapthalen-2-yl)pyrrolidine with acrylaldehyde gave an epimeric mixture of 8-hydroxy-5,6,7,8,9,10-hexahydro-5,9-methanobenzo[8]annulen-11-ones which was used for the synthesis of several 11-amino derivatives.

As part of our work to evaluate the pharmacological properties of conformationally restrained arylalkylamines, in particular phenylethyl- and phenylpropyl-amines, we embarked on the synthesis and biological evaluation of amino-substituted 5,9-methanobenzo[8]annulenamines (Fig. 1). We describe here part of this work pertaining to the synthesis of 11-amino-5,9-methanobenzo[8]annulenes.

At the outset of this study only one, very low yielding synthesis of the 11-amino-5,9-methanobenzo[8]annulenamines **1a–c** had been described,[1] involving reaction of the β-tetralone enamine **2a** with acrylaldehyde and conversion of the resultant mixture of pyrrolidine isomers **5a** and **6a**, *via* the ketone **10a**, into the amines **1a**. Since no biological data had been published for these compounds we decided to reinvestigate this synthesis in order to provide sufficient material for pharmacological evaluation and also to establish a chemical synthesis to the other skeletal amine isomers as indicated in Fig. 1.

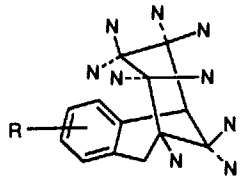
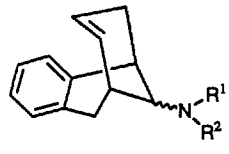
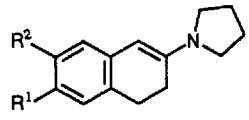


Fig. 1



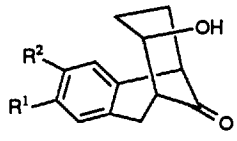
1

a; $R^1 = R^2 = H$
b; $R^1 = H$, $R^2 = Me$
c; $R^1 = R^2 = Me$



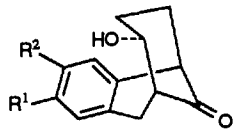
2

a; $R^1 = R^2 = H$
b; $R^1 = Cl$, $R^2 = H$
c; $R^1 = R^2 = Cl$



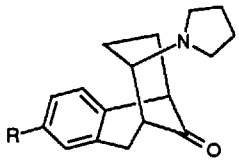
3

a; $R^1 = R^2 = H$
b; $R^1 = Cl$, $R^2 = H$
c; $R^1 = R^2 = Cl$



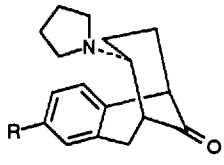
4

a; $R^1 = R^2 = H$
b; $R^1 = Cl$, $R^2 = H$
c; $R^1 = R^2 = Cl$



5

a; R = H
b; R = Cl



6

a; R = H
b; R = Cl

Results and Discussion

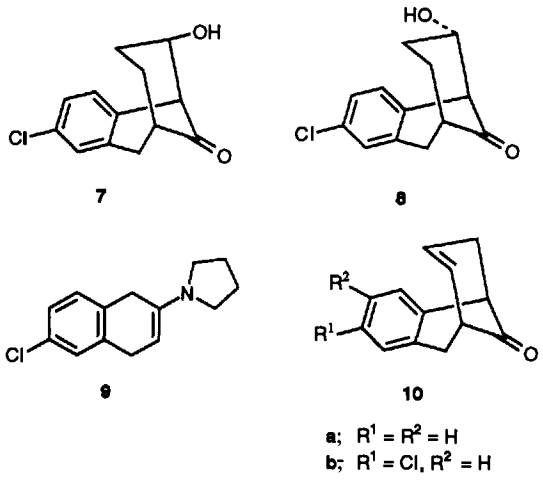
We were surprised, however, to find that reaction of the tetralone enamine **2a** with acrylaldehyde gave, in 90% yield, a 4:1 mixture of the 8-*exo* and 8-*endo*-keto alcohols **3a** and **4a**, respectively, and not a mixture of the 8-pyrrolidines **5a** and **6a** as previously reported[1] although not isolated. Crystallisation of the neutral portion of the reaction product gave the 8-*exo*-alcohol **3a**, the 8-*endo*-alcohol **4a** being obtained from the mother liquors by chromatograhy. The basic portion of the reaction product consisted of a mixture of the 8-pyrrolidino compounds **5a** and **6a**, the former of which was isolated by crystallisation.

On further investigation of this reaction, we found that 5% aq. tetrahydrofuran (THF) was the most convenient reaction solvent which maximised the formation of the ketol products **3** and **4**, and under these conditions this reaction was successfully reproduced on a 10 kg scale. The use of anhydrous THF as solvent in this reaction resulted in the formation of a much greater amount of the pyrrolidino products **5** and **6**, the expected products[2] from the reaction of cyclohexanone enamines with acrylaldehyde, but the ketols still remained the major part of the reaction mixture.

In a similar manner as described above for the enamine **2a**, treatment of the enamine **2b**, prepared from 6-chloro-β-tetralone,[3] with acrylaldehyde but with 5% aq. THF as solvent gave predominantly a mixture of ketols **3b** and **4b** along with a small amount of the pyrrolidines **5b** and **6b**. Both pairs of isomers were separated by chromatography.

Careful examination of the neutral mother liquors of this reaction revealed (GLC) another epimeric pair of isomers, which were assigned as the ketols **7** and **8**. This pair of isomers was not isolated but their structures were confirmed by an independent synthesis of one of the isomers (see below). Although the enamine **2b** showed no evidence (NMR) of the epimeric structure **9**, deuteriation experiments indicated that the 1 and 3 protons were exchanged. The formation of the epimeric ketols **7** and **8** could thus be accounted for by the addition of acrylaldehyde to an equilibrium mixture of the enamines **2b** and **9**.

The configurations of the ketol and pyrrolidine products were readily assigned by NMR spectroscopy which showed



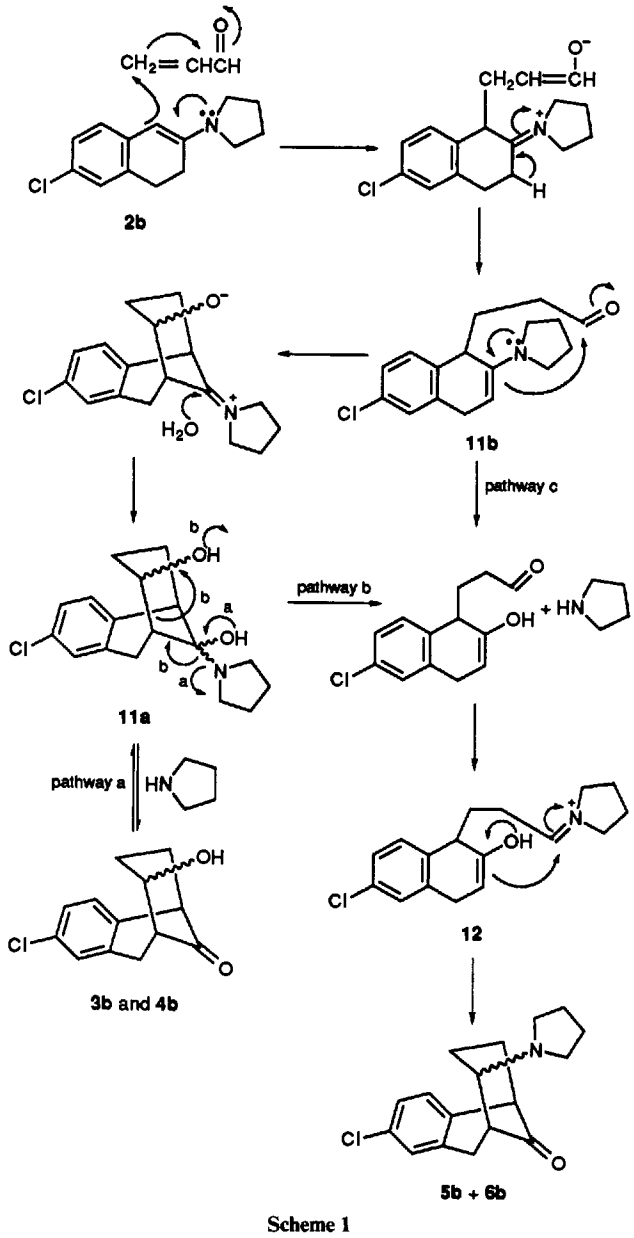
typical broad and narrow multiplets for their 8-axial and 8-equatorial protons, respectively.

Although the mechanism of the reaction of acrylaldehyde with β-tetralone enamines leading to the ketol products **3** and **4** can be readily envisaged as outlined in Scheme 1 (pathway a from structure **11a**) the mechanism for the formation of the pyrrolidines **5** and **6** is less straightforward and has never been properly elucidated. The diol **11a** is probably a key intermediate in the process since treatment of either ketol **3b** or **4b** with pyrrolidine rapidly gives rise to a mixture of the pyrrolidino compounds **5b** and **6b** presumably *via* the intermediate **11a**. Loss of pyrrolidine from diol **11a** by reverse-aldol reaction (pathway b), followed by formation of the imine product **12** and recyclisation could be expected to give the pyrrolidine products **5b** and **6b**. Alternatively, the initial addition product **11b** could be converted into the imine **12** as shown (pathway c) prior to cyclisation to the mixture of pyrrolidines **5b** and **6b**. It is apparent that an excess of water favours formation of the ketols, whilst more anhydrous conditions or an excess of pyrrolidine promotes pathway b or c and formation of the pyrrolidines.

Reaction of ketols **3a** and **3b** and **4a** and **4b**, either as single epimers, or as a mixture of epimers, with toluene-*p*-sulfonyl chloride followed by treatment of the tosyl derivatives with Li_2CO_3–dimethylacetamide (DMA) gave good yields of the enones **10a** and **10b**, the former having an IR spectrum similar to that previously reported.[1]

The enones **10a** and **10b** were converted into the amines **13**, **14**, **17** and **18** by several methods. Reaction of the ketone **10b** with formic acid and formamide (Leuckart reaction) gave a 1 : 1 mixture of the 11-*anti* and 11-*syn** amides **13d** and **14d** along with 30% of a mixture of bis-amines **15**.

The products were separated by chromatography and the formamides **13d** and **14d** were converted by either base hydrolysis or reduction using lithium aluminium hydride into the primary amines **13a** and **14a** or the methylamines **13b** and **14b**, respectively. A more effective way of preparing the 11-*anti*-primary amine **13a** was by reduction, using sodium boranuide, of the imine **16a** prepared *in situ* from the ketone **10b** and liquid ammonia in ethanol. In this way a 4:1 mixture of the 11-*anti*- and 11-*syn*-amine **13a** and **14a** were obtained in 90% yield, from which the *anti*-amine **13a** could be obtained directly by crystallisation from the mixture of the hydrochloride salts. The remaining products from the sodium boranuide reaction consisted of the corresponding alcohols. In a similar manner



Scheme 1

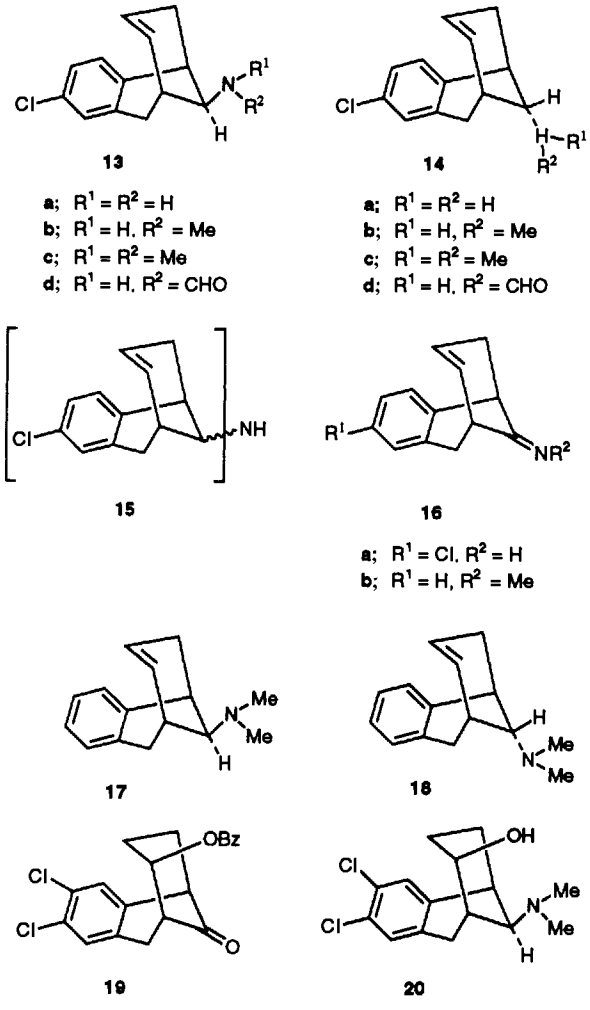
reaction of the ketone **10b** with methylamine followed by reduction of the resultant imine **16b** using sodium boranuide gave a 4 : 1 mixture of the 11-*anti*- and 11-*syn*-methylamine, **13b** and **14b**.

The dimethylamines were obtained by Eschweiler–Clark[4] alkylation of either the primary or methyl amines, or by direct treatment of the enone **10a** with dimethylformamide (DMF) and formic acid which gave an equal mixture of the 11-*anti*- and 11-*syn*-dimethylamines **17** and **18** (epimers of **1c**). Separation of this mixture was readily achieved by crystallisation, initially of the hydrochloride salt, to give the pure 11-*anti*-dimethylamine **17**, followed by crystallisation of the fumarate salt of the mother liquors to give the pure 11-*syn*-dimethylamine **18**.

Direct amination of the ketols **3** and **4** was not possible because the compounds were unstable to the reaction conditions. However, benzoylation of the dichloro ketol **3c** prepared in a similar manner to that described above from the enamine **2c**[3] gave the benzoate **19**, which on treatment with DMF and formic acid gave predominantly, after hydrolysis, the 11-*anti*-dimethylamino-8-*exo*-alcohol **20**.

The configurational assignments of the amines were based on the small downfield shift, seen in the NMR spectra, of the 11-

* The terms '*syn*' and '*anti*' refer to the relative configurations of the 11-substituent and the aromatic ring.



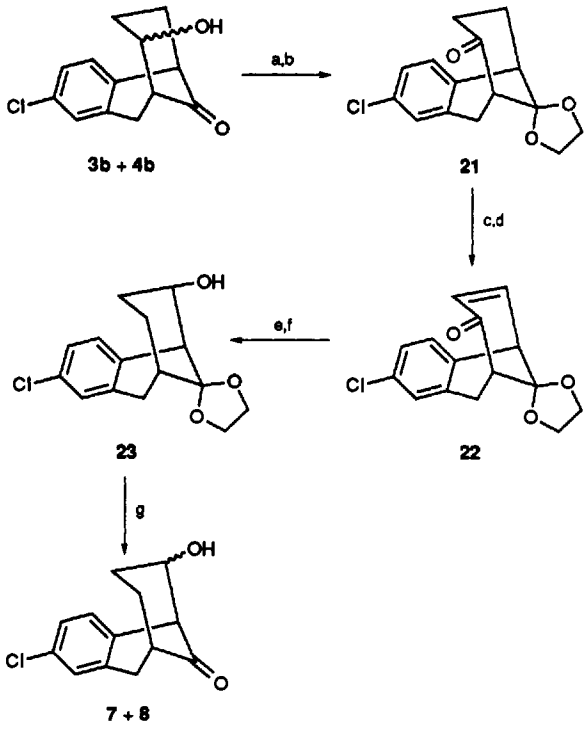
anti-N-methyl or -N,N-dimethyl signals compared with the corresponding signals of the 11-*syn* isomers, an observation which can be attributed to the shielding effect of the aromatic ring on the N-methyl groups of the *syn* isomers.[1]

Conversion of a mixture of ketols **3b** and **4b** into the epimeric pair of isomers **7** and **8** was carried out as shown in Scheme 2. Ketalisation of the ketol mixture followed by Jones oxidation gave the saturated ketone **21** (Scheme 2), which was converted by standard means into the αβ-unsaturated ketone **22**. Epoxidation of enone **22** followed by treatment of the resultant epoxide with hydrazine[5] gave the 6-*exo*-alcohol **23** which, on hydrolysis, gave a mixture of ketols **7** and **8** from which the pure *endo*-isomer **8** was isolated by chromatography.

Pharmacological and Clinical Results.—The 11-amino-5,9-methanobenzo[8]annulenes demonstrated a variety of pharmacological effects. The primary amine **13a**, Org 6582, is a potent *in vivo* selective 5-HT (serotonin) re-uptake inhibitor[6] having activity in animal models predictive of clinical antidepressant activity. In a limited clinical trial the compound behaved as an effective antidepressant.[7]

Both the 11-*syn*- and 11-*anti*-dimethylamines **17** and **18**, Org 6401 and Org 6370, are potent anticonvulsant agents[8] as demonstrated in pre-clinical electroconvulsant shock tests. The latter compound, Org 6370, was evaluated in clinical trials and was shown to give good protection against seizures, particularly in patients refractory to other anticonvulsant medication.[9]

The dimethylamine **20**, Org 6837, is a potent anti-obesity agent which, in preclinical tests in rats, caused an excess of



Scheme 2 *Reagents:* a, $HOCH_2CH_2OH$, H^+; b, CrO_3, acetone; c, Br_2, CH_2Cl_2; d, $LiCO_3$, LiBr, DMA; e, H_2O_2, NaOH; f, aq. NH_2NH_2; g, NaOH

weight loss over that which could be expected by a reduction in food intake alone.[10]

Experimental

M.p.s were taken with a Kofler micro hot-stage apparatus and are uncorrected. IR spectra were determined with a Perkin-Elmer 457 spectrometer. UV spectra were recorded with a Pye Unicam SP 800 spectrometer. NMR spectra were recorded for samples in deuteriochloroform solutions (except where stated) at 60 MHz with a Perkin-Elmer R12B, at 100 MHz with a Varian Associates XL-100A-12FT, and at 200 MHz with a Bruker W.P. 200 spectrometer, and only salient features of the spectra are recorded. *J* Values are given in Hz. Preparative HPLC was carried out on a Waters Associates Prep. LC/System 500 machine using columns packed with silica gel. Gas-liquid chromatograms were obtained using 3% OV-17 or OV-1 Chromosorb W-HP 100–120 mesh on 6 ft columns or by using SE-30 fused silica on 25 m capillary columns. Ether refers to diethyl ether throughout and extracts were washed with water and dried over anhydrous sodium sulfate before evaporation under reduced pressure. Light petroleum refers to the fraction with distillation range 40–60 °C

All chiral compounds are racemic mixtures.

Reaction of 1-(3,4-*Dihydronaphthalen*-2-*yl*)*pyrrolidine* **2a** *with Acrylaldehyde.*—The enamine **2a**[3] (100 g) was added over a period of 15 min to a stirred solution of acrylaldehyde (55 cm^3) in dichloromethane (1 dm^3) at −40 °C and the temperature was allowed to rise slowly to 0 °C over a period of 2 h. Water (100 cm^3) and dil. hydrochloric acid were added to the solution and the product was extracted with ether. The extract was washed, dried, and evaporated to give an oil (90 g), which cyrstallised from ether to give (5α,8α,9α)-8-*hydroxy*-5,6,7,8,9,10-*hexahydro*-5,9-*methanobenzo*[8]*annulen*-11-*one* **3a** (76 g), m.p. 151–152 °C; ν_{max}(KCl)/cm^{-1} 3470 (OH) and 1710 (C=O); δ(100 MHz) 1.75 (3 H, m) and 2.5 (1 H, m, together CH_2CH_2), 2.68 (1 H, s, OH), 2.8 (1 H, m, 9-H), 2.16 (1 H, d, *J* 17, 10β-H), 3.46 (1 H, dd, *J* 17

and 7, 10α-H), 3.5 (1 H, narrow, m, 5-H), 4.36 (1 H, narrow m, $W_{\frac{1}{2}}$ 7 Hz, 8β-H) and 7.2 (4 H, m, ArH) (Found: C, 77.4; H, 6.9. $C_{13}H_{14}O_2$ requires C, 77.2; H, 7.0%).

Chromatography of a portion (20%) of the mother liquors on silica gel gave (5α,8β,9α)-8-*hydroxy*-5,6,7,8,9,10-*hexahydro*-5,9-*methanobenzo*[8]*annulen*-11-*one* **4a** (1.5 g), m.p. 114–118 °C; ν_{max}(KCl)/cm^{-1} 3470 (OH) and 1710 (C=O); δ(100 MHz) 2.8 (4 H, m, CH_2CH_2), 2.16 (1 H, d, OH), 2.95 (1 H, m, 9-H), 2.13 (1 H, dd, *J* 19 and 7, 10α-H) 2.42 (1 H, narrow m, 5-H), 2.72 (1 H, d, *J* 19, 10β-H), 4.05 (1 H, m, $W_{\frac{1}{2}}$ 20 Hz, 8α-axial H) and 7.0 (1 H, m) and 7.2 (3 H, m, together ArH) (Found: C, 77.5; H, 7.1).

The above acidic aqueous layer was basified and the product was extracted with ether to give, on evaporation, a gum (20 g), which was dissolved in ether and the solution was filtered through a column of silica gel. The eluent was evaporated to a low volume, and allowed to crystallize, to give (5α,8α,9α)-8-*pyrrolidino*-5,6,7,8,9,10-*hexahydro*-5,9-*methanobenzo*[8]*annulen*-11-*one* **5a** (1.8 g), m.p. 109–110 °C; ν_{max}(KCl)/cm^{-1} 1700 (C=O); δ(100 MHz) ~ 1.8 (8 H, m), ~ 2.5 (5 H, m), 2.95 (1 H, m, 5-H), 3.05 (1 H, dd, part of AB, *J* 17 and 8, 10α-H), 3.34 (1 H, m, $W_{\frac{1}{2}}$ 8 Hz, 8-equatorial-H), 3.83 (1 H, d, part of AB, *J* 17, 10β-H), and 7.0 and 7.18 (1 H and 2 H, m, ArH) (Found: C, 80.25; H, 8.45; N, 5.56. $C_{17}H_{21}NO$ requires C, 80.0; H, 8.3; N, 5.5%).

(5α,9α)-5,6,9,10-*Tetrahydro*-5,9-*methanobenzo*[8]*annulen*-11-*one* **10a**.—Toluene-*p*-sulfonyl chloride (88 g) was added in portions to a stirred solution of the hydroxy ketone **3a** (75 g) in dry pyridine (150 cm^3) and the solution was stirred at 35 °C for 48 h. Water was added slowly and the precipitate (130 g) was collected, washed and dried *in vacuo* at 70 °C. Lithium carbonate (130 g) and lithium bromide (27 g) were added to a solution of this precipitate in DMA (1.25 dm^3) and the mixture was heated under reflux for 2 h, cooled, poured into water, and the product was extracted into ether. The extract was washed, dried and evaporated to give an oil, which was distilled under high vacuum, to yield the ketone **10a** (52 g), b.p. 144 °C/4 mmHg; m.p. 38–51 °C (from ether) (lit.,[1] b.p. 125–135 °C/1 mmHg); ν_{max}(CH_2Cl_2)/cm^{-1} 1750 and 1730 (C=O, split peak) (lit.,[1] ν_{max}(film)/cm^{-1} 1705); δ(60 MHz) 2.3–3.5 (several ms), 5.65 (CH=CH) and 7.12 (4 H, m, ArH) (Found: C, 84.5; H, 6.8. Calc. for $C_{13}H_{13}O_2$: C, 84.75; H, 6.6%).

Reaction of 1-(6-*Chloro*-3,4-*dihydronaphthalen*-2-*yl*)*pyrrolidine* **2b** *with Acrylaldehyde*.—Acrylaldehyde (258 cm^3) was added to a stirred solution of the enamine **2b**[3] (570 g) in 95% aq. THF (2.85 dm^3) at −10 °C, while the temperature of the reaction mixture was kept below 25 °C. The mixture was stirred at 25 °C for 2 h, dil. hydrochloric acid was added slowly (to pH 1, using Duotest pH paper range 1–12), and the product was extracted with ether. The extract was washed, dried and evaporated to give an oil (570 g) (TLC, two main spots in ratio ~ 1:1); GLC ($SiMe_3$ derivative) t_R 1.25 (2.3%), 1.31 (37%) and 1.45 (47%). A portion of this mixture (4 g) was dissolved in toluene and chromatographed on silica gel. Elution with toluene–ethyl acetate (9:1) gave a small amount of an oily material, which was discarded. Elution with toluene–ethyl acetate (2:1) gave (5α,8β,9α)-2-*chloro*-8-*hydroxy*-5,6,7,8,9,10-*hexahydro*-5,9-*methanobenzo*[8]*annulen*-11-*one* **4b** (1.5 g), m.p. 116 °C; ν_{max}(KCl)/cm^{-1} 3470 (OH) and 1710 (C=O); δ(200 MHz) 1.5 and 1.9 (4 H, m, CH_2CH_2), 1.62 (1 H, s, OH), 2.9 (1 H, m, 9-H), 3.10 (1 H, 1, *J* 7.5 and 18.5, 10α-H), 3.40 (1 H, br s, 5-H), 3.7 (1 H, d, *J* 18.5, 10β-H), 4.05 (1 H, ddd, *J* 5, 5.5 and 12, 8α-axial-H), 6.95 and 7.2 (3 H, m, ArH). (In decoupling experiments 9-H decouples with both 8-H and 10α-H) (Found: C, 65.9; H, 5.8; Cl, 15.0. $C_{13}H_{13}ClO_2$ requires C, 66.0; H, 5.5; Cl, 15.0%).

Further elution gave (5α,8α,9α)-2-chloro-8-hydroxy-5,6,7,8,9,10-hexahydro-5,9-methanobenzo[8]annulen-11-one **3b** (1.1 g), m.p. 127–128 °C; ν_{max}(KCl)/cm^{-1} 3470 (OH) and 1710 (C=O); δ(200 MHz) 2.32 (1 H, s, OH), 2.51 (1 H, m, 9-H), 2.75 (3 H, m, 6-H_2 and 7β-H), 3.13 (1 H, d, *J* 18, 10β-H), 3.38 (1 H, dd, *J* 8 and 18, 10α-H), 3.8 (1 H, m, 8β-H) and 6.92 and 7.17 (3 H, m, ArH). (In decoupling experiments 9-H decouples with both 8β-H and 10α-H) (Found: C, 66.1; H, 5.5; Cl, 14.5. $C_{13}H_{13}ClO_2$ requires C, 66.0; H, 5.5; Cl, 15.0%). Other minor products present in the mixture could not be isolated.

The above acidic aqueous layer was basified and the product was extracted into ether. The extract was washed, dried, and evaporated to give an oil (100 g). Chromatography of a portion of this product on alumina gave, on elution with toluene–ethyl acetate (9:1), a mixture of the *exo*- and *endo*-pyrrolidino compounds **5b** and **6b**. Crystallisation of this mixture from ether gave the *endo*-isomer, (5α,8α,9α)-2-*chloro*-8-*pyrrolidino*-5,6,7,8,9,10-*hexahydro*-5,9-*methanobenzo*[8]*annulen*-11-*one* **6b**, m.p. 142–150 °C; ν_{max}(KCl)/cm^{-1} 1700 (C=O); δ(100 MHz) 2.94 (1 H, narrow m, 9-H), 3.15 [1 H, d, (part of q), *J* 7, 10α-H] 3.4 (1 H, narrow m, 5-H) and 3.80 (1 H, d, *J* 17, 10β-H) (Found: C, 70.5; H, 6.95; N, 5.0; Cl, 12.6. $C_{17}H_{20}ClNO$ requires C, 70.4; H, 6.95; N, 4.85; Cl, 12.25%). Fractional crystallisation of the mother liquors gave (5α,8α,9α)-2-*chloro*-8-*pyrrolidino*-5,6,7,8,9,10-*hexahydro*-5,9-*methanobenzo*[8]*annulen*-11-*one* **5b**, m.p. 137–139 °C; ν_{max}(KCl)/cm^{-1} 1700 (C=O); δ(100 MHz) 2.98 (1 H, m, 9-H), 3.17 (1 H, d, *J* 18, 10β-H), 3.40 (1 H, m, 5-H) and 3.41 (1 H, dd, *J* 18 and 8, 10α-H) (Found: 70.8; H, 7.10; Cl, 12.6; N, 4.74%.)

Reaction of 1-(6-*Chloro*-3,4-*dihydronaphthalen*-2-*yl*)*pyrrolidine* **2b** *with Acrylaldehyde in Dry THF*.—Acrylaldehyde (2.5 cm^3) was added to a stirred solution of the enamine **2b**[3] (5 g) in THF (10 cm^3) (dried over molecular sieves type 4A) at 17 °C, while the temperature of the reaction mixture was kept below 25 °C, and the mixture was stirred at 25 °C for 3 h before being worked up as described above to give a neutral portion (3.6 g) consisting of a mixture of ketols **3b** (52%) and **4b** (40%) (GLC SE30 at 230 °C, capillary column) and a basic portion (3.0 g) consisting of a mixture of the pyrrolidino products **5b** (82%) and **6b** (11%) (GLC SE30 at 230 °C, capillary column).

Reaction of (5α,8α,9α)-2-*Chloro*-8-*hydroxy*-5,6,7,8,9,10-*hexahydro*-5,9-*methanobenzo*[8]*annulen*-11-*one* **3b** *with Pyrrolidine*.—Pyrrolidine (2 cm^3) was added to a solution of the ketol **3b** in dichloromethane (5 cm^3), and the solution was stored at room temperature for 3 h before being evaporated to give a mixture of the pyrrolidino compounds **5b** and **6b**, which was separated as described in the above procedure.

In a similar manner reaction of the 8-*endo* ketol isomer **4b** with pyrrolidine also gave the same mixture of the two pyrrolidino compounds.

2-*Chloro*-5,6,9,10-*tetrahydro*-8,9-*methanobenzo*[8]*annulen*-11-*one* **10b**.—Toluene-*p*-sulfonyl chloride (130 g) was added in portions to a solution of a mixture of the ketols **3b** and **4b** (107 g) in dry pyridine (226 cm^3) at 12 °C. The temperature of the reaction mixture was raised to 40 °C and was held at that level for 48 h. The reaction mixture was then cooled, water was added carefully to destroy the excess of toluene-*p*-sulfonyl chloride, the solution was poured into water, and the product was extracted with dichloromethane. The extract was washed, dried, and evaporated to give a mixture of tosyl esters (150 g), which was dissolved in DMA (1.5 dm^3). Li_2CO_3 (150 g) and LiBr (30 g) were added to this solution and the mixture was heated under reflux for 2 h. The solution was cooled, poured into water, and the product was extracted with ether. The extract was washed, dried and evaporated to give an oil (64 g), which crystallised on storage. Recrystallisation from ether gave the *ketone* **10b**, m.p. 74–78 °C; ν_{max}(KCl)/cm^{-1} 1730 (C=O); δ(60 Hz) 5.65 (2 H, m, CH=CH) and 7.1 (3 H, m, ArH)

(Found: C, 71.3; H, 5.0; Cl, 16.2. $C_{13}H_{11}ClO$ requires C, 71.2; H, 5.1; Cl, 16.0%).

Reaction of 2-*Chloro*-5,6,9,10-*tetrahydro*-5,9-*methanobenzo*-[8]*annulen*-11-*one* **10b** *with Formic Acid and Formamide*.—The ketone **10b** (38 g) was dissolved in a mixture of formamide (56 cm^3) and formic acid (28 cm^3), and the solution was heated under reflux for 2 h, cooled, and poured into water. The product was extracted with dichloromethane and the extract was washed, dried and evaporated to give a gum (40 g), which was dissolved in toluene and chromatographed on alumina (1 kg). Elution with toluene–light petroleum gave mixtures of the bis-amines **15** (10.2 g).

Elution with toluene gave a product (12.5 g), which was crystallised from dichloromethane–ether to give (5α,9α,11R*)-2-*chloro*-N-*formyl*-5,6,9,10-*tetrahydro*-5,9-*methanobenzo*[8]-*annulen*-11-*amine* **14d** (11.6 g), m.p. 152–153 °C; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3430 (NH) and 1690 (C=O); δ(60 MHz) 4.35 (1 H, m, 11-H) and 8.0 (1 H, s, CHO) (Found: C, 67.8; H, 5.6; Cl, 14.2; N, 5.6. $C_{14}H_{14}ClNO$ requires C, 67.9; H, 5.7; Cl, 14.3; N, 5.65%).

Elution with ethyl acetate gave a product (14.6 g), which was recrystallised from dichloromethane to give (5α,9α,11S*)-2-*chloro*-N-*formyl*-5,6,9,10-*tetrahydro*-5,9-*methanobenzo*[8]-*annulen*-11-*amine* **13d** (13.3 g), m.p. 135–137 °C; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3430 (NH) and 1690 (C=O); δ(60 MHz) 4.35 (1 H, m, 11-H) and 8.22 (1 H, s, CHO) (Found: C, 67.8; H, 5.7; Cl, 14.4; N, 5.65%).

(5α,9α,11S*)-2-*Chloro*-N-*methyl*-5,6,9,10-*tetrahydro*-5,9-*methanobenzo*[8]*annulen*-11-*amine Hydrochloride* **13b**.—A suspension of lithium aluminium hydride (925 mg) in dry THF (21 cm^3) was added dropwise to a solution of the 11-*anti* formamide **13d** (3.5 g) in 1,4-dioxane (5 cm^3), and the resultant mixture was stirred at room temperature for 5 h. Water (1 cm^3), aq. sodium hydroxide (0.9 cm^3; 4 mol dm^{-3}) and water (2.5 cm^3) were then added successively to the mixture and the inorganic salts were filtered off. The filtrate was concentrated, diluted with water, and the product was extracted into ether. The extract was washed, dried, and evaporated to give the free base **13b** as an oil (3.5 g), which was dissolved in ether, and an ethereal solution of dry HCl was added. The precipitate was collected, and crystallised from methanol–ether to give the *amine* **13b** as the *hydrochloride*, m.p. 220 °C; δ(60 MHz; free base) 1.52 (1 H, s, NH) and 2.48 (3 H, s, NMe) (Found: C, 62.5; H, 6.1; Cl, 26.0; N, 5.3. $C_{14}H_{17}Cl_2N$ requires C, 62.2; H, 6.3; Cl, 26.25; N, 5.2%).

In a similar manner, reduction of the 11-*syn* formamide **14d** gave (5α,9α,11R*)-2-*chloro*-N-*methyl*-5,6,9,10-*tetrahydro*-5,9-*methanobenzo*[8]*annulen*-11-*amine hydrochloride* **14b**, m.p. 225 °C; δ(60 MHz; free base) 1.22 (1 H, s, NH) and 2.40 (3 H, s, NMe) (Found: C, 62.5; H, 6.45; Cl, 26.3; N, 5.0%).

(5α,9α,11S*)-2-*Chloro*-5,6,9,10-*tetrahydro*-5,9-*methanobenzo*[8]*annulen*-11-*amine Hydrochloride* **13a**.—Aq. potassium hydroxide (4.6 cm^3; 10 mol dm^{-3}) was added to a solution of the 11-*anti* formamide **13d** (4.6 g) in EtOH (46 cm^3), and the solution was boiled under reflux for 4 h. Water was added to the cooled solution and the product was extracted with ether. The extract was washed, dried, and evaporated to give a gum (4 g), which was dissolved in ether and treated with a saturated solution of dry HCl in ether. The precipitate was collected, and recrystallised from methanol–ether to give the *amine* **13a** as the *hydrochloride salt*, m.p. > 360 °C; δ(60 MHz; free base) 1.5 (2 H, s, NH_2) (Found: C, 60.65; H, 5.85; Cl, 27.95; N, 5.5. $C_{13}H_{15}Cl_2N$ requires C, 60.95; H, 5.9; Cl, 27.7; N, 5.5%).

In a similar manner, hydrolysis of the *syn* amide **14d** gave (5α,9α,11R*)-2-*chloro*-5,6,9,10-*tetrahydro*-5,9-*methanobenzo*[8]*annulen*-11-*amine hydrochloride* **14a**, m.p. ~250 °C (decomp.); δ(60 MHz; free base) 1.25 (2 H, br s, NH_2) (Found: 60.9; H, 5.9; Cl, 27.7; N, 5.4%).

(5α,9α,11S*)-2-*Chloro*-N,N-*dimethyl*-5,6,9,10-*tetrahydro*-5,9-*methanobenzo*[8]*annulen*-11-*amine Hydrochloride* **13c**.—A solution of the *anti* amine **13a** (1 g) in a mixture of formic acid (2.4 cm^3) and formalin (1.7 cm^3) was heated at 90–100 °C for 1 h. The solution was cooled and dil. aq. potassium hydroxide was added. The product was extracted with ether and the extract was washed, dried, and evaporated to give the free base **13c** as an oil, which was converted, as described above, into the *hydrochloride salt*, m.p. 205 °C (decomp.); δ(60 MHz; free base) 2.33 (6 H, s, NMe_2) and 3.2 (1 H, m, 11-H) (Found: C, 63.1; H, 6.7; Cl, 24.75; N, 5.05. $C_{15}H_{19}Cl_2N$ requires C, 63.4; H, 6.7; Cl, 24.95; N, 4.97%).

In a similar manner, the alkylation of *syn* amine **14a** gave (5α,9α,11R*)-2-*chloro*-N,N-*dimethyl*-5,6,9,10-*tetrahydro*-5,9-*methanobenzo*[8]*annulen*-11-*amine hydrochloride* **14c**, m.p. 200 °C (decomp.); δ(60 MHz; free base) 2.23 (6 H, s, NMe_2) and 3.25 (1 H, m, 11-H) (Found: C, 63.1; H, 6.7; Cl, 24.4; N, 5.0%).

Reaction of (5α,9α)-2-*Chloro*-5,6,9,10-*tetrahydro*-5,9-*methanobenzo*[8]*annulen*-11-*one* **10b** *with Ammonia/Sodium Boranuide*.—A solution of liquid ammonia (20 cm^3) in ethanol (20 cm^3) was added to a solution of the enone **10b** (20 g) in ethanol (100 cm^3), and the reaction flask was closed and kept at room temperature for 48 h. Sodium boranuide (10 g) was then added in portions to the stirred solution, while the temperature of the reaction mixture was kept below 20 °C by using external cooling, and the mixture was stirred for a further 2 h. Dil. hydrochloric acid was added cautiously to the solution, and the mixture was diluted with water and extracted with ether. The extract contained mainly a mixture of alcohols. The aqueous layer was made alkaline and the product was extracted with ether. This extract was washed, dried, and evaporated to give a gum (19 g) consisting of a mixture of amines **13a** and **14a** in the ratio 4:1 (TLC). The mixture was treated with dry HCl as described above and the product was crystallised from methanol–ether to give the 11-*anti*-amine **13a** as the hydrochloride salt (12.6 g), identical with that prepared by the previously described method.

Reaction of 2-*Chloro*-5,6,9,10-*tetrahydro*-5,9-*methanobenzo*-[8]*annulen*-11-*one* **10b** *with Methylamine and Sodium Boranuide*.—Methylamine (1.4 dm^3) was added to a solution of the ketone **10b** (2.1 kg) in ethanol (3 dm^3) and the solution kept at room temperature for 48 h before being cooled. Sodium boranuide (420 g) was added in portions, and the reaction mixture was stirred for 4 h, poured into water and acidified with dil. hydrochloric acid. The mixture was extracted with ether, and the extract was discarded. The aqueous solution was made alkaline with aq. sodium hydroxide and the product was extracted with ether. The extract was washed, dried and evaporated to give a gum (1.84 kg) as a mixture (4:1) of amine isomers **13b** and **14b** (GLC). The product was converted into the hydrochloride salt, as described above, and the product was crystallised from methanol–ether to give the 11-*anti*-methylamine hydrochloride **13b** (1.17 kg), in two crops, identical (IR) with that prepared above. Fractional recrystallisation of the mother liquors gave the 11-*syn*-methylamine hydrochloride **14b** (198 g), identical (IR) with that prepared above.

(5α,9α)-N,N-*Dimethyl*-5,6,9,10-*tetrahydro*-5,9-*methanobenzo*[8]*annulen*-11-*amines* **17** *and* **18**.—The ketone **10a** (5.3 kg) was converted into a mixture of (5α,9α)-*N*-methyl-5,6,9,10-

tetrahydro-5,9-methanobenzo[8]annulen-11-amine **1b** in a manner similar to that described above for the ketone **10b**, and this mixture (3.65 kg) was crystallised as the hydrochloride salt to give the 11-*anti*-methylamine, which on methylation with formalin and formic acid, followed by conversion into the hydrochloride salt as described above, gave (5α,9α,11S*)-N,N-*dimethyl*-5,6,9,10-*tetrahydro*-5,9-*methanobenzo*[8]*annulen*-11-*amine hydrochloride* **17**, m.p. 251–253 °C (sublimes); δ(100 MHz) 2.19 (1 H, d, 6-H), 2.95 (6 H, s, NMe_2), 2.6–3.6 (5 H, m), 5.78 (2 H, CH=CH), 7.2 (4 H, m, ArH) and 11.4 (1 H, s, HCl) (Found: C, 72.3; H, 8.2; N, 5.6; Cl, 14.4. $C_{15}H_{20}ClN$ requires C, 72.1; H, 8.1; N, 5.6; Cl, 14.2%).

The mother liquors from the crystallisation of the crude *N*-methylamine were converted into the free base and this was methylated with formic acid and formalin as described above. The crude dimethylamine was crystallised as the fumarate salt to give the pure 11-*syn*-dimethylamine **18**, which was re-converted into the free base and treated with dry HCl–ether to give (5α,9α,11R*)-N,N-*dimethyl*-5,6,9,10-*tetrahydro*-5,9-*methanobenzo*[8]*annulen*-11-*amine* **18** as the *hydrochloride salt*, m.p. > 230 °C (sublimes); δ(100 MHz) 2.31 (1 H, d, 6-H), 2.72 (6 H, s, NMe_2), 2.8–3.7 (5 H, m), 5.4–5.9 (2 H, m, CH=CH), 7.0–7.3 (4 H, m, ArH) and 11.95 (1 H, s, HCl) (Found: C, 70.9; H, 8.1; N, 5.5; Cl, 14.0. $C_{15}H_{20}ClN{\cdot}\frac{1}{2}H_2O$ requires C, 70.85; H, 8.0; N, 5.5; Cl, 13.9%.

(5α,8α,9α,11R*)-2,3-*Dichloro*-11-*dimethylamino*-5,6,7,8,9,10-*hexahydro*-5,9-*methanobenzo*[8]*annulen*-8-*ol Hydrochloride* **20**.—Benzoyl chloride (650 cm^3) was added dropwise to a stirred solution of (5α,8ξ,9α)-2,3-dichloro-8-hydroxy-5,6,7,8,9,10-hexahydro-5,9-methanobenzo[8]annulen-11-one **3c** and **4c** (692 g), prepared from the enamine **2c**[2] as described above, in pyridine (2 dm^3) at 10 °C. The temperature was maintained between 5 and 15 °C during the addition and the mixture was then stirred at room temperature for 5 h and poured onto ice–water (6 dm^3). The mixture was stored overnight, the water was decanted, and the gummy solid was stirred with dichloromethane. The insoluble product was filtered off and dried to give (5α,8α,9α)-8-benzoyloxy-2,3-dichloro-5,6,7,8,9,10-hexahydro-5,9-methanobenzo[8]annulen-11-one **19** (414 g) in two crops.

A solution of this benzoate in DMF (400 cm^3), formic acid and hydrated $MgCl_2$ (60 g) was distilled until the reaction temperature was > 150 °C and then the mixture was boiled under reflux overnight. A further amount of distillate was removed from the mixture to maintain the reaction temperature > 150 °C and the reaction was allowed to continue at reflux for a further 24 h. The reaction mixture was then cooled, diluted with water (5 dm^3), extracted with ether, and the extract was discarded. The aqueous solution was basified with aq. sodium hydroxide and the product was extracted with dichloromethane. The extract was washed, dried and evaporated to give a gum (320 g), which was dissolved in methanol (1 dm^3) containing aq. potassium hydroxide (200 cm^3; 10 mol dm^{-3}) and the solution was boiled under reflux for 1 h, cooled, diluted with water (3 dm^3) and allowed to crystallise. The crystals were filtered off, washed with water and dissolved in dichloromethane. The solution was dried, and evaporated to dryness, and the product was crystallised from aq. methanol to give the pure 8-*hydroxy*-11-anti-*dimethylamine* **20** (218 g), which was treated with dry HCl–ether to give the *hydrochloride salt*, m.p. > 230 °C (decomp.); δ[100 MHz; $(CD_3)_2SO$] 1.3 and 2.2 (3 H and 1 H, both m, CH_2CH_2), 2.96 (9 H, m, NMe_2, 9-H and 10-H_2), 3.37, 3.61 and 3.88 (each 1 H, br s, 5-, 11- and 8-H), 6.1 and 8.6 (each 1 H, br peaks which disappear on deuteriation, OH and HCl) and 7.47 (2 H, each s, 1- and 4-H) (Found: C, 53.4; H, 6,05; N, 4.2; Cl, 31.3. $C_{15}H_{20}Cl_3NO$ requires C, 53.5; H, 6.0; N, 4.2; Cl, 31.6%).

2′-*Chlorospiro*{1,3-*dioxolane*-2,11′-(5′,6′,7′,8′,9′,10′-*hexahydro*-5′,9′-*methanobenzo*[8]*annulen*)}-8′-*one* **21**.—Ethylene glycol (290 cm^3) and toluene-*p*-sulfonic acid (11 g) were added to a solution of the ketol mixture **3b** and **4b** (580 g) in toluene (2.3 dm^3) and the mixture was boiled under reflux, using a Dean–Stark water separator, for 24 h. The solution was cooled, washed with water, and evaporated to give a gum (700 g), which was dissolved in acetone (18 dm^3). Jones' reagent (840 cm^3) was added over a period of 15 min, while the temperature was allowed to rise to 32 °C, and the mixture was stirred for a further 1 h and then poured into water. The precipitate was collected, and dissolved in dichloromethane. The solution was washed, evaporated to low volume, diluted with methanol, and allowed to crystallise to give the crude product **21** (650 g) in two crops. Recrystallisation from dichloromethane–ether gave the pure *keto ketal* **21**, m.p. 173–175 °C; ν_{max}(KCl)/cm^{-1} 1715 (C=O); δ(60 MHz) 2.78 (1 H, dd, *J* 17.5 and 6.7, 10′β-H) and 3.98 (4 H, narrow m, OCH_2CH_2O) (Found: C, 64.8; H, 5.4; Cl, 13.0. $C_{15}H_{15}ClO_3$ requires C, 64.6; H, 5.4; Cl, 12.7%).

(5′α,7′α,9′α)-7′-*Bromo*-2′-*chlorospiro*{1,3-*dioxolane*-2,11′-(5′,6′,7′,8′,9′,10′-*hexahydro*-5′,9′-*methanobenzo*[8]*annulen*)}-8′-*one*.—A solution of bromine (133 cm^3; 1.05 mol dm^{-3}) in dichloromethane (280 cm^3) was added, over a period of 45 s, to a well stirred solution of the keto ketal **21** (682 g) in dichloromethane (8.5 dm^3) at 4 °C, and the mixture was stirred at 4 °C for 40 min. Aq. sodium hydrogen sulfite was added, part of the dichloromethane layer was distilled off, and the remainder was diluted with methanol, and allowed to crystallise to give 7α-*bromo*-2′-*chlorospiro*{1,3-*dioxolane*-2-11′-(5′,6′,7′,8′,-9′,10′-*hexahydro*-5′,9′-*methanobenzo*[8]*annulen*)}-8′-*one* (758 g) in two crops. An analytical sample had m.p. 161–163 °C; ν_{max}(KCl)/cm^{-1} 1732 (C=O); δ(100 MHz) 4.25 (1 H, dd, *J* 7.5 and 12.5, CHBr) (Found: C, 50.1; H, 4.1; Hal., 30.1. $C_{15}H_{14}BrClO_3$ requires C, 50.4; H, 3.9; Hal., 32.3%).

2′-*Chlorospiro*{1,3-*dioxolane*-2,11′-(5′,8′,9′,10′-*tetrahydro*-5′,9′-*methanobenzo*[8]*annulen*)}-8′-*one* **22**.—DMA (5.5 dm^3) was heated to just below boiling point, Li_2CO_3 (700 g), LiBr (196 g), and the foregoing bromo ketal (660 g) were added, and the mixture was boiled under reflux for 1 h. DMA (3.5 dm^3) was distilled off under reduced pressure, the mixture was cooled and filtered, and the residue was washed with hot ethanol (1.5 dm^3). The washings were partly evaporated and the remainder was added to the initial filtrate, which was poured into water. The product was collected, dissolved in dichloromethane (5.5 dm^3), and the solution was dried, partly evaporated, and the residue was diluted with ethanol (4.2 dm^3) and treated with charcoal (96 g). The solution was finally reduced in volume and allowed to crystallise to give the product **22** (433 g). Recrystallisation from dichloromethane–methanol gave the pure αβ-*unsaturated ketone* **22**, m.p. 191–197 °C; ν_{max}(KCl)/cm^{-1} 1680 (C=O); λ_{max}(EtOH)/nm 217 (ε 16 700); δ(100 MHz) 2.91 (1 H, d, *J* 18.4, 10′-H), 2.98 (1 H, br d, *J* 8.0, 9′-H), 3.44 (1 H, dd, *J* 18.4 and 8.0, 10′-H), 4.06 (4 H, s, OCH_2CH_2O), 6.01 (1 H, d, *J* 9.9, 7′-H) and 7.10 (1 H, dd, *J* 9.9 and 3, 6′-H) (Found: C, 65.0; H, 4.8; Cl, 12.6. $C_{15}H_{13}ClO_3$ requires C, 65.1; H, 4.7; Cl, 12.8%).

2′-*Chloro*-6′,7′-*epoxyspiro*{1,3-*dioxolane*-2,11′-(5′,6′,7′,8′,9′,10′-*hexahydro*-5′,9′-*methanobenzo*[8]*annulen*)}-8′-*one*.—Aq. sodium hydroxide (330 cm^3; 4 mol dm^{-3}) and aq. hydrogen peroxide (426 cm^3; 30%) were added simultaneously during 5 min to a stirred suspension of the αβ-unsaturated ketone **22** (463 g) in ethanol (6.5 dm^3) at 0–10 °C and the mixture was stirred at this temperature for 15 min and then was allowed to attain room temperature during the next 30 min. Dichloromethane (3.7 dm^3) was added to dissolve the suspended solid and the

solution was stirred for 2 h and poured into water. The organic layer was evaporated and the residue was crystallised from ether to give the *epoxide* (467 g). A sample was recrystallised from CH_2Cl_2–methanol to give the pure product, m.p. 161–163 °C; ν_{max}(KCl)/cm^{-1} 1715 (C=O); δ(100 MHz) 2.84 (1 H, d, *J* 7.5, 9′-H), 2.90 (1 H, d, *J* 18, 10′-H), 3.15 (1 H, m, 5′-H), 3.45 (1 H, dd, *J* 18 and 7.5, 10′-H), 3.55 (2 H, m, 6′-and 7′-H), 4.0 (4 H, m, OCH_2CH_2O) and 7.17 (3 H, m, ArH) (Found: C, 61.3; H, 4.5; Cl, 12.0. $C_{15}H_{14}ClO_4$ requires C, 61.5; H, 4.5; Cl, 12.1%).

(5′α,6′α,9′α)-2′-*Chlorospiro*{1,3-*dioxolane*-2,11′-(5′,6′,7′,8′,9′,10′-*hexahydro*-5′,9′-*methanobenzo*[8]*annulen*)}-6′-*ol* **23**.—The preceding epoxy ketone (50 g) was dissolved in a mixture of methanol (225 cm^3) and dichloromethane (325 cm^3). The solution was cooled to 0 °C and glacial acetic acid (4.3 cm^3) was added, followed by hydrazine hydrate (32.5 cm^3) over a period of 10 min, while the temperature of the solution was kept between 0 and 10 °C. The solution was stirred at 0 °C for 15 min and at room temperature for 2.5 h. Water was added and the organic layer was evaporated to give an orange solid, which was dissolved in ethanol. The solution was treated with charcoal, filtered, and allowed to crystallise to give the product (31.7 g) in two crops. Recrystallisation from dichloromethane–methanol gave the pure *alcohol* **23**, m.p. 149–152 °C; δ(100 MHz) 4.03 (4 H, m, OCH_2CH_2O), 3.52 (1 H, d, OH), 4.06 (1 H, m, CHOH) and 5.57 (2 H, m, CH=CH) (Found: C, 64.5; H, 5.5; Cl, 13.0. $C_{15}H_{15}ClO_3$ requires C, 64.6; H, 5.4; Cl, 12.7%).

Hydrolysis of the Hydroxy Ketal **23**.—A solution of the hydroxy ketal **23** (1.5 g) in acetic acid (10 cm^3)–sulfuric acid (10 cm^3; 2.5 mol dm^{-3}) was boiled under reflux for 1 h. The solution was poured into water and the product was extracted with ether. The extract was washed, dried, and evaporated to give a gum (1.3 g) which consisted of a mixture of the ketols **7** and **8**. [GLC, $SiMe_3$ derivative, t_R 1.25 (31%) and 1.29 (48%)]. Chromatography by HPLC with toluene–ethyl acetate (2:1) as the mobile phase gave, after crystallisation from ether, (5α,6β,9α)-2-*chloro*-6-*hydroxy*-5,6,7,8,9,10-*hexahydro*-5,9-*methanobenzo*[8]*annulen*-11-*one* **8** (150 mg), m.p. 135–139 °C; ν_{max}(KCl)/cm^{-1} 3320 (OH) and 1720 (C=O); δ(200 MHz) 2.75 (1 H, narrow m, 9-H), 3.10 (1 H, d, *J* 19, 10β-H), 3.46 (1 H, q, *J* 19 and 7.5, 10α-H), 3.65 (1 H, d, *J* 4, 5-H) and 4.05 (1 H, ddd, *J* 11.6, 4 and 4, axial 6-H). (Irradiation at δ 3.65 caused the signal at δ 4.05 to collapse to dd, *J* 11.5 and 4) (Found: C, 65.8; H, 5.7; Cl, 15.4. $C_{13}H_{13}ClO_2$ requires C, 66.0; H, 5.5; Cl, 15.0%).

Other fractions from the column were mixtures of the two ketols **7** and **8** which could not be further separated.

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