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TOTAL SYNTHESIS OF ANTHRASTEROIDS—II[1]

PREPARATION OF SOME ANTHRAESTRONE AND ANTHRAEQUILENINE DERIVATIVES

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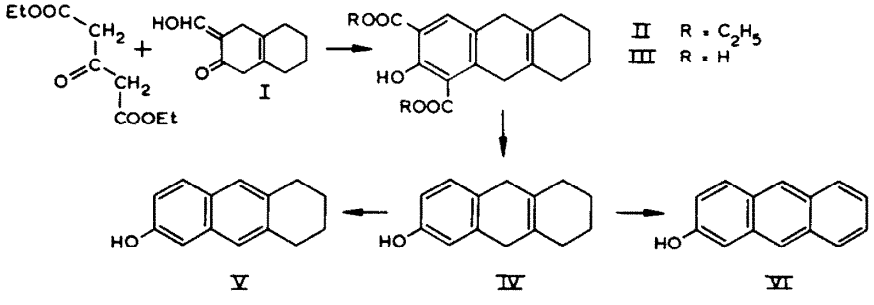
Abstract—Utilizing the method studied in the conversion of the model compound 3-hydroxymethylene-$\Delta^{9(10)}$-octalone-2 (I) into 2-hydroxyanthracene, the synthesis of the C-17 alcohols of 8-dehydroanthraestrone and anthraequilenine from the tricyclic system *trans*-1β-hydroxy-8β-methyl-4,5-(3'-hydroxymethylene-4'-oxo-2',3',4',5'-tetrahydrobenzo)-hydrindane (VII) has been achieved. Additional evidence for the structures of the prepared anthrasteroids has been obtained by mass spectrometry.

IN the preceding paper,[1] the synthesis and structure proof of *trans*-1β-hydroxy-8β-methyl-4,5-(3'-hydroxymethylene-4'-oxo-2',3',4',5'-tetrahydrobenzo)hydrindane (VII) was described. The object of the present investigations was the conversion of this intermediate into anthraestrone and anthraequilenine derivatives possessing a *trans* ring C/D configuration.

Although α-hydroxymethylene ketones have been used frequently as starting materials in cyclization reactions leading to polycyclic cyclohexenone derivatives (e.g. by treatment with alkylvinylketones[4]), relatively few examples are known of their conversion into phenols by condensation with esters of β-ketoglutaric acid.[5] As will be shown below, initial studies with the model compound 3-hydroxymethylene-$\Delta^{9(10)}$-octalone-2 (I)[1] established that this cyclization reaction could be applied successfully in the synthesis of more extended systems. Thus, the base catalyzed condensation of I with diethyl β-ketoglutarate afforded the phenol II in 65% yield.

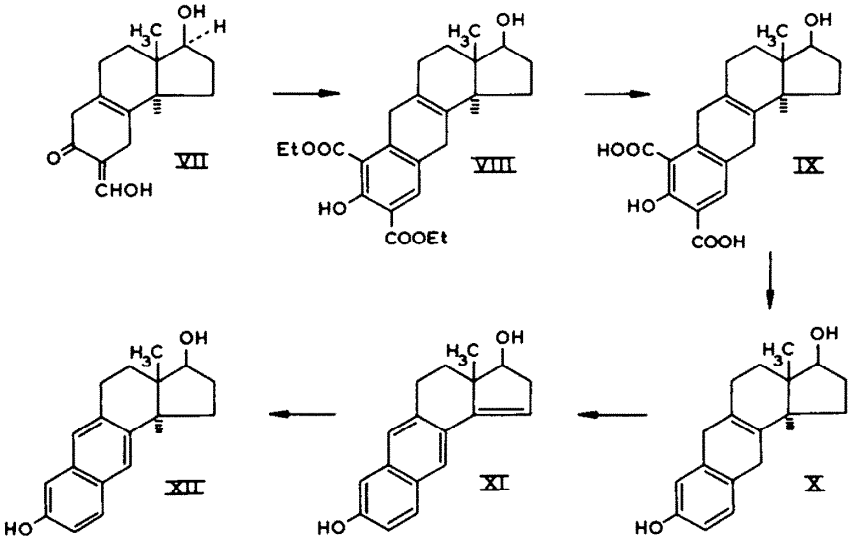


Its structure was suggested from its absorption characteristics in the IR, NMR and UV[5c] and was confirmed by the transformation reactions described in the sequel.

Saponification of II with aqueous sodium hydroxide yielded the corresponding diacid, III, which could also be obtained directly from I in 70% yield. The phenolic

diacid III was decarboxylated in refluxing quinoline in excellent yield and the resulting phenol, IV, was converted into 6-hydroxy-1,2,3,4-tetrahydroanthracene (V) in 93% yield by dehydrogenation with one equivalent of dichlorodicyanobenzoquinone (DDQ). The presence of a 2-naphthol moiety in this system was confirmed by its UV characteristics[6] and the NMR absorption evidenced the existence of four high field methylene, four benzylic and five aromatic protons. Although complete aromatization of IV with an excess of DDQ proved unsuccessful, 2-hydroxyanthracene (VI)[7] was obtained in 65% yield when IV was treated with Pd–C in boiling quinoline.

As was suggested from these model experiments, condensation of the tricyclic hydroxymethylene ketone VII with diethyl β-ketoglutarate afforded 2,4-diethoxycarbonyl-8-dehydroanthraestradiol (VIII) in a yield of 68%. Its UV absorption was similar to that of II. The non-conjugated position of the double bond in VIII was confirmed by the NMR spectrum (Fig. 1) which gave no signal in the vinylic proton region and showed a singlet at δ 3·22 integrating for the four benzylic protons at C_7



and C_{10}. Whereas the triplet absorptions of both the ester methyl groups are centered at δ 1·38, with $J_{CH_3-CH_2}$ 7·0 c/s, the methylene groups of these ester functions appear as two distinguishable pairs of quartets, centered at δ 4·40 and δ 4·44 (coupling constant in both cases 7·0 c/s). Serially diluted IR data showed the existence of intramolecular hydrogen bonding between the phenolic proton and ester carbonyl function which may account for the observed difference in chemical shifts of the ester methylene groups.

Treatment of the diester VIII with a solution of sodium hydroxide in aqueous ethanol afforded the corresponding diacid IX in 80% yield. Under appropriate conditions this system could also be obtained directly from VII in a yield of 80%.

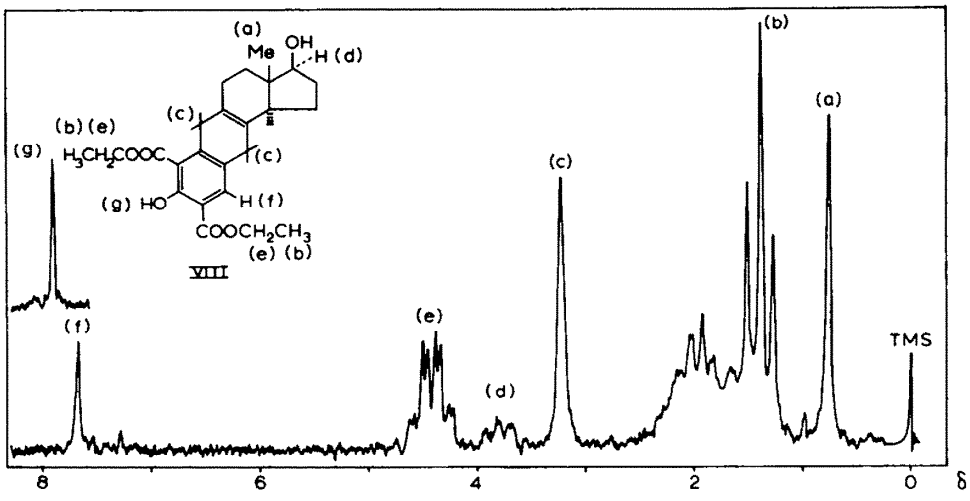


FIG. 1

Conversion of this diacid into the desired 8-dehydroanthraestradiol (X) was achieved by decarboxylation in refluxing quinoline in 93% yield.

It is interesting to note that the benzylic protons in the compounds II, IV, VIII and X always appear as a singlet peak in the NMR spectrum.* The absence of any geminal coupling can be explained by assuming a non-rigid ring system for these substances. Dreiding models strongly suggest a boat conformation for the benzocyclohexene ring, a situation comparable to that reported for 9,10-dihydroanthracene.[9] The appearance of a single peak resonance in the spectra of the compounds under consideration probably indicates a rapid interconversion of one boat form into another, thus averaging out the differences in deshielding influence of the neighbouring aromatic ring current on the pseudo axial and pseudo equatorial methylene protons.

Dehydrogenation of the anthraestradiol X with *one* equivalent of DDQ resulted in a *mixture* of anthrasteroids from which on treatment with acetone a crystalline compound (m.p. 228°) was isolated in 40% yield. Careful chromatography of the remaining fraction over florisil afforded a second product that melted at 188–191°. The latter compound, obtained in a yield of 20%, proved to be the desired anthraequilenine alcohol XII. The structural assignment of XII was made on the basis of its UV absorption, identical to that of V and its NMR spectrum which indicated the presence of a 2-naphthol moiety. The observed upfield position of the angular Me group (δ 0·54) in the NMR spectrum of XII is in accordance with the anticipated 14α or C/D *trans* fusion of the system. As indicated by inspection of Dreiding models, the protons of the C_{18} Me group are lying over the aromatic ring B and consequently considerably shielded by the field associated with the ring current. The resulting diamagnetic shift for this group is in agreement with similar observations in comparable anthrasteroid systems.[10]

The compound melting at 228° was identified as anthraestra-1,3,5,7,9,14-hexaene-3,17β-diol (XI). The UV spectrum suggested a conjugated position for the additional

* In contrast, a multiplet absorption at δ 3·22 is observed for the corresponding protons in the analogous phenyl substituted quinazoline system XIII.

double bond in this system and the NMR spectrum displayed an absorption at δ 6·06, integrating for one proton. This vinyl resonance strongly supported the 14(15) position for the double bond and excluded the alternative conjugated 11(12) position. The C_{18} methyl absorption was found at δ 0·93, in good agreement with the value measured in the NMR spectrum of the related anthracholesta-5,7,9,14-tetraene (δ 0·87[11]).

When the anthraestradiol X was dehydrogenated with *two* equivalents of DDQ, the hexaene XI was obtained in a yield of 70%. Comparable to the observation with the analogous steroidal system,[12] catalytic reduction of XI proceeded in a stereoselective manner to give the 14α isomer of the C-17 alcohol of anthraequilenine (XII) as the only reaction product in a yield of 70%.

Mass spectra

Corroboratory evidence for the assigned structure of the prepared anthrasteroidal systems was obtained from the mass spectra. Comparison of the mass spectrum of the anthraequilenine diol XII (Fig. 3) with that of the 17β-alcohol of equilenine (XIV)[13] (Fig. 2) revealed a striking correspondence and indicated a closely related

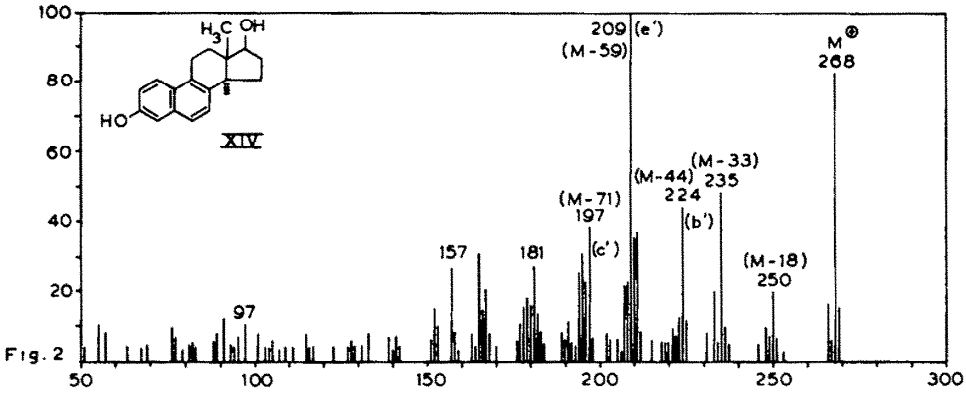


Fig. 2

FIG. 2

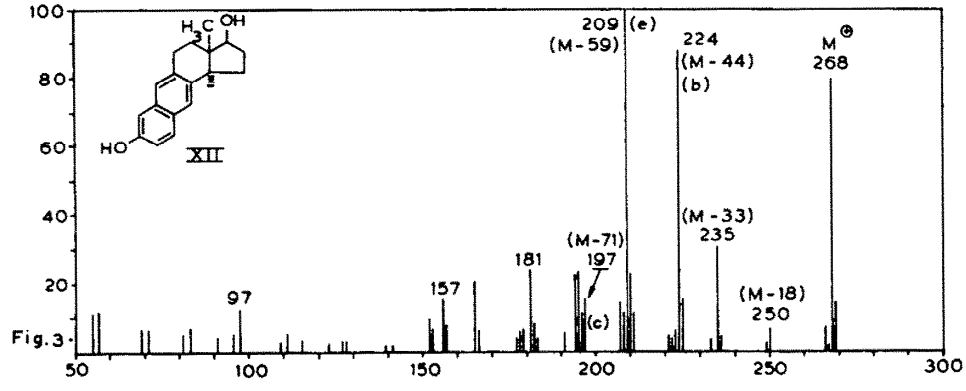


Fig. 3

FIG. 3

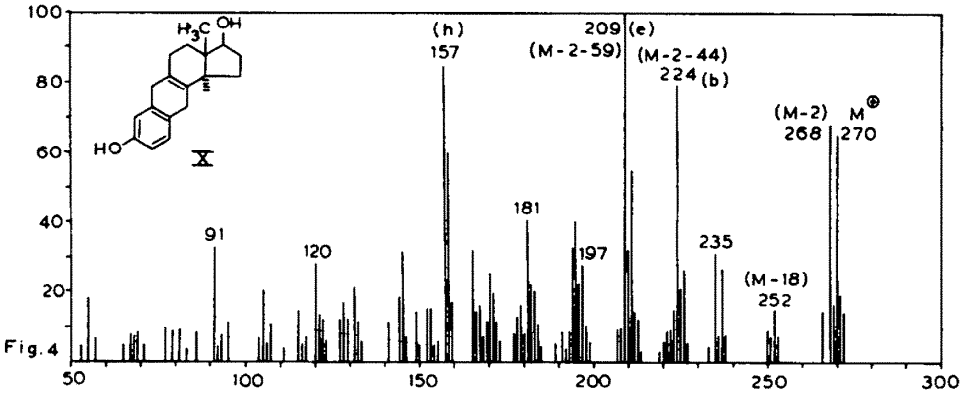
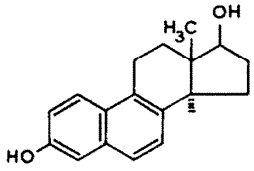
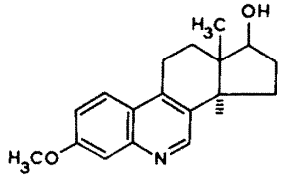


FIG. 4

fragmentation pattern for these structural isomers. The absence of mass spectral data for the equilenine alcohol XIV prompted us to examine the probable origin of some characteristic peaks in these spectra.



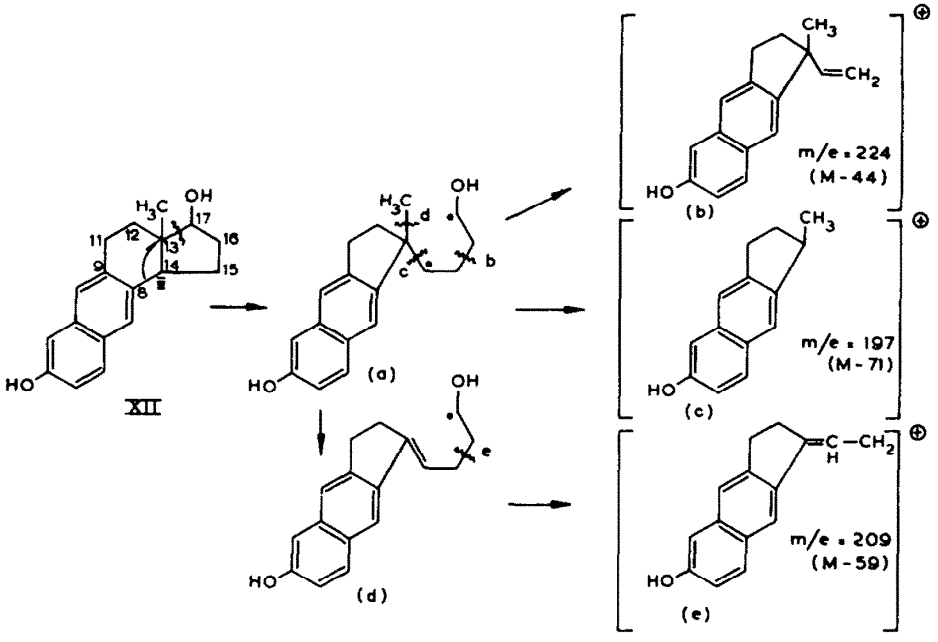
XIV



XV

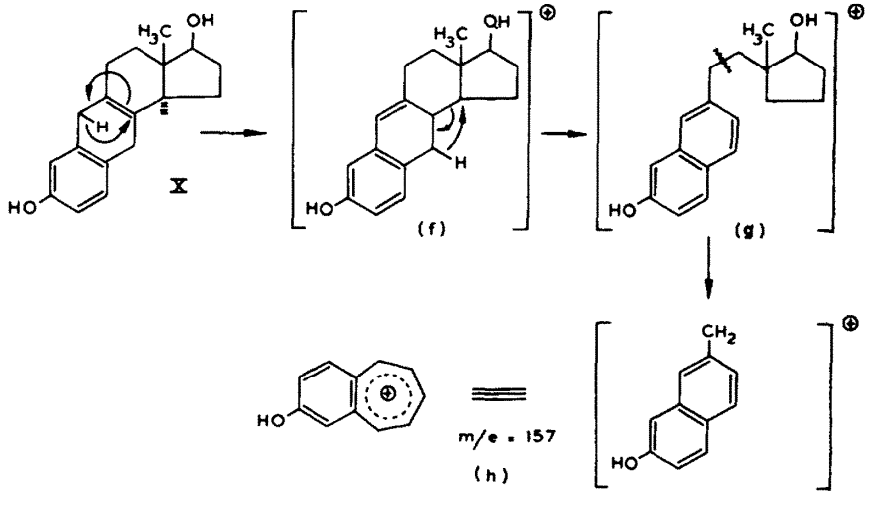
Of significance was the observation of a metastable ion peak at m/e 187·5 in the spectrum of XII, indicating a process $268^{\oplus} \rightarrow 224^{\oplus} + 44$ (calc.: 187·3). A possible pathway for this fragmentation is described in scheme A. Rearrangement of XII by a synchronous process of ring D fission at C_{13}–C_{17} and bond formation at C_8–C_{13} may result in the formation of species (a), which can subsequently serve as the precursor for ion (b). Ample evidence for this ring C contraction mechanism induced by electron impact processes has been provided in the case of the closely related methyl ether of 6-azaequileninediol (XV).[14] Similar to the described fragmentation of this heterocyclic analog, formation of the ions *m/e* 209 (M-59) and *m/e* 197 (M-71) can be explained in terms of a breakdown of ion (a) to yield the fragments (e) and (c) respectively.

In the mass spectrum of 8-dehydroanthraestradiol (X) (Fig. 4) the intensity of the molecular ion peak at m/e 270 is surpassed by that of the fragment *m/e* 268 (M-2). It is likely that a thermal or an electron induced aromatization occurred to yield XII, which is not surprising in view of the observed chemical behaviour of X. The presence and intensity of the peaks at *m/e* 224, 209 and 197 also found in the mass spectrum of XII supports this assumption. A significant difference in the spectrum of X compared with that of XII is the display of the characteristic peak at *m/e* 157, representing



Scheme A

a fragment $C_{11}H_9O$ (Calc.: 157·0653;[15] Found: 157·0658), corresponding to the energetically favoured hydroxybenzotropilium ion (h). Formation of this fragment has been observed in related steroid systems (e.g. 6-dehydroestrone[16] and 7-dehydroestrone[16]) for which the same ionic structure (h) was proposed. A plausible although hypothetical mechanism for the generation of this species (h) is proposed in scheme B. The process is initiated by the migration of the double bond in ring B to the conjugated 9(10) position (f), followed by migration of the C_7 hydrogen and



Scheme B

cleavage of the allylically activated 8(14) bond (g). Further fission of the benzylic 11(12) bond may then yield the substituted tropilium ion (h).

In preliminary biological experiments 8-dehydroanthraestradiol (X) showed a strong uterotropic activity (no antiuterotropic effect) in the Rubin test in mice (effect measured against that of estradiol monobenzoate). The corresponding diacid IX was found to be ineffective in the Rubin test, and showed no androgenic activity in rats (against the effect of testosterone). The tricylic hydroxymethylene ketone VII displayed a weak uterotropic and a weak androgenic activity.

EXPERIMENTAL

M.ps are uncorrected. UV, IR and NMR measurements were conducted as described in part I.[1] NMR spectra were taken with $CDCl_3$ as a solvent, unless otherwise stated. Mass spectral measurements were carried out on a A.E.I. Spectrometer Type MS 2-H. Spectra of the compounds X and XII were in addition taken on a A.E.I. double-focusing Mass Spectrometer Type MS 9. The ionization potential employed was 70 eV.

5,7-Diethoxycarbonyl-6-hydroxy-1,2,3,4,9,10-hexahydroanthracene (II)

To a soln of 0·37 g (0·016 at) Na in 40 ml dry EtOH was added 2·00 g (0·011 mole) of I[1] and 3·50 g (0·017 mole) freshly destilled diethyl β-ketoglutarate. The resulting mixture was refluxed under N_2 for 3 hr. After evaporating the solvent, the residue was stirred with a mixture of ether and dil. HCl aq in order to liberate II from the corresponding sodium phenolate. The ethereal soln was washed with water, sat. NaCl aq, and dried ($MgSO_4$). Evaporation of the solvent yielded 2·5 g (65%) of II, m.p. after recrystallization from EtOH–water 125–126°. (Found: C, 69·82; H, 7·05; O, 23·39; $C_{20}H_{24}O_5$ requires: C, 69·75; H, 7·02; O, 23·23%); UV (EtOH): 247 (ε = 10,000) and 318 (ε = 4600) nm; IR (KBr): 3200, 1720, 1680, 1620, 1590, 1225, 1195, 1030 and 795 cm^{-1}. The NMR spectrum displayed absorptions at δ 1·40 (t 6p, ester Me), δ 3·19 (s 4p, 9-H_2 and 10-H_2), δ 4·39 (q 2p, ester CH_2), δ 4·44 (q 2p, ester CH_2) and δ 7·62 (s 1p, PhH).

6-Hydroxy-1,2,3,4,9,10-hexahydroanthracene-5,7-dicarboxylic acid (III)

a. *From 3-hydroxymethylene-$\Delta^{9(10)}$-octalone-2* (I). To a soln of 0·34 g (0·015 mole) Na in 60 ml dry EtOH was added 2·50 g (0·014 mole) of I[1] and 3·00 g (0·015 mole) freshly destilled diethyl β-ketoglutarate. After refluxing this mixture under N_2 for 30 hr, a soln of 3·5 g NaOH in 12 ml water was added, after which refluxing was continued for an additional 5 hr. Evaporating the solvent and adding 3% NaOH aq to the residue yielded a brown soln that was washed with ether and cooled to 0°. The soln was acidified with dil. HCl aq (pH 6) and the resulting ppt was collected, dried and recrystallized from MeOH–water to yield 2·8 g (70%) of III, m.p. > 250°. UV (EtOH): 219 (ε = 24,000), 238 (ε = 10,000) and 357 (ε = 4100) nm; IR (KBr): 3400–2500, 1690, 1615, 1590, 1280, and 1230 cm^{-1}.

b. *From the diester* II. Refluxing of a soln of 1·65 g II and 1·12 g KOH in a mixture of 40 ml EtOH and 10 ml water for 6 hr afforded after following the working-up procedure described immediately above, 1·10 g (80%) of III.

6-Hydroxy-1,2,3,4,9,10-hexahydroanthracene (IV)

A soln of 2·06 g of III in 10 ml quinoline was refluxed for 2 hr. To the cooled soln ether was added and the resulting mixture was washed with dil HCl aq, water, sat NaCl aq and dried ($MgSO_4$). Evaporating the solvent afforded 1·25 g (87%) of IV, m.p. after repeated sublimation (180°, 20 mm) 117–120°. (Found: C, 83·96; H, 7·99; O, 8·03; $C_{14}H_{16}O$ requires: C, 83·96; H, 8·05; O, 7·99%); UV(EtOH): 220–230 (ε = 10,000), 271 (sh.), 281 (ε = 2700), 288 (sh), and 336 (ε = 350) nm; IR(KBr): 3330, 1610, 1590, 1510, 1465, 1235, 870 and 800 cm^{-1}. In the NMR spectrum the following absorptions were observed: δ 1·69 (4p, 2-H_2 and 3-H_2), δ 1·92 (4p, 1-H_2 and 4-H_2) and δ 3·10 (s 4p, 9-H_2 and 10-H_2).

6-Hydroxy-1,2,3,4-tetrahydroanthracene (V)

To a soln of 0·40 g (0·002 mole) of IV in 10 ml dry benzene, was added 0·45 g (0·002 mole) DDQ dissolved in 10 ml anhyd benzene. The resulting mixture was refluxed for 1·5 hr, cooled and filtered to remove the formed quinol. The filtrate was diluted with ether, washed with water and dried ($MgSO_4$). Evaporation of

the solvent yielded 0·37 g (93%) of V, m.p. after repeated sublimation (140°, 15 mm) 162·5–163·5°. (Found: C, 84·42; H, 6·98; O, 8·60; $C_{14}H_{14}O$ requires: C, 84·81; H, 7·12; O, 8·07%); UV(EtOH): 230 (ε = 70,000), 268 (ε = 5500), 282 (ε = 5500), 293 (ε = 4900), 325 (ε = 2500) and 338 (ε = 2700); IR(KBr): 3350, 1630, 1605, 1575, 1510, 1225, 1185, 870 and 810 cm^{-1}. In the NMR spectrum absorptions were observed at δ 1·82 (4p, 2-H_2 and 3-H_2), δ 2·90 (4p, 1-H_2 and 4-H_2) and δ 7·0–7·7 (5p, ArH).

2-Hydroxyanthracene (VI)

A mixture of 0·15 g V, 0·22 g Pd–C (10%) and 5 ml quinoline was refluxed for 5 hr. After cooling and removing the Pd–C, ether was added and the resulting soln was washed with dil HCl aq, water and dried. Evaporation of the solvent gave 0·10 g (68%) of VI, purified by sublimation (150°, 20 mm) m.p. 188–195° (dec). UV(EtOH): 238 (ε = 55,000), 248 (ε = 80,000), 256 (ε = 107,000), 316 (ε = 2000), 332 (ε = 4150), 349 (ε = 4500), 377 (ε = 4300) and 395 (ε = 3900).[7] IR(KBr): 3500, 1630, 1610, 1580, 1160, 955, 885 and 740 cm^{-1}.

(±)-*2,4-Diethoxycarbonyl-8-dehydroanthraestradiol* (VIII)

Sodium (0·030 g; 0·013 at) was dissolved in 6 ml dry EtOH and to the resulting soln was added 0·230 g (0·001 mole) of VII,[1] followed by a soln of 0·350 g (0·0017 mole) diethyl β-ketoglutarate in 4 ml anhyd EtOH. After following the procedure described for the preparation of II 0·260 g (68%) of VIII was obtained, m.p. 165–168°, after recrystallization from EtOH 175–177°. (Found: C, 69·34– H, 7·33; O, 23·35; $C_{24}H_{30}O_6$ requires: C, 69·54; H, 7·30; O, 23·16%); UV(EtOH): 214 (ε = 24,000), 244 (ε = 9600, sh) and 319 (ε = 4700) nm; IR(KBr): 3560, 3150, 1700, 1670, 1620, 1590, 1470, 1270, 1225, 1195, 1010 and 795 cm^{-1}. NMR signals were displayed at δ 0·74 (s 3p, 18-Me), δ 1·38 (t 6p, ester Me), δ 3·22 (s 4p, 7-H_2 and 10-H_2), δ 4·40 (q 2p, ester CH_2), δ 4·44 (q, 4p, ester CH_2), δ 7·68 (s 1p, PhH) and δ 10·88 (s 1p, phenolic H).

(±)-*8-Dehydroanthraestradiol-2,4-dicarboxylic acid* (IX)

a. *From the tricyclic hydroxymethylene ketone* VII. A soln of 0·100 g (0·004 at) Na, 0·900 g (0·0036 mole) VII[1] and 1·00 g (0·005 mole) diethyl β-ketoglutamate in 15 ml EtOH was refluxed under N_2 for 40 hr as was described for the preparation of III (under a). After addition of a soln of 0·85 g NaOH in 12 ml water, the reaction mixture was refluxed for an additional 4 hr and then worked up according to the procedure described for III. Isolated was 1·06 g (80%) of the diacid IX. Recrystallization from MeOH–water gave the pure compound, m.p. >250°. (Found: C, 66·50; H, 6·25; O, 26·56; $C_{20}H_{22}O_6$ requires: C, 67·02; H, 6·19; O, 26·79%); UV(EtOH); 216 (ε = 26,000), 237 (ε = 12,500, sh), 329 (ε = 3800) and 357 (ε = 4400) nm; IR(KBr): 3500, 3400–2400, 1695, 1610, 1590, 1435, 1280, 1230, 1050 and 800 cm^{-1}. The NMR spectrum (of a soln in $(CD_3)_2SO$) showed the C_{18}-Me at δ 0·68 (s 3p) and the methylene protons of C_7 and C_{10} at δ 3·20 (s 4p).

b. *From the diester* VIII. Treatment of 0·160 g of VIII with 0·080 g NaOH in a mixture of 5 ml EtOH and 1·5 ml water according to the procedure described for III (under b) yielded 0·115 g (83%) of the diacid IX.

(±)-*8-Dehydroanthraestradiol* (X)

The acid IX (0·46 g) was refluxed in 5 ml quinoline for 2·5 hr. After cooling the mixture was poured in 5% HCl aq at 0°. The collected crystalline ppt was washed with water and dried to yield 0·32 g (92%) of X, m.p. after recrystallization from MeOH–water 198·5–200°. (Found: C, 79·94; H, 8·21; O, 11·93; $C_{18}H_{22}O_2$ requires: C, 79·96; H, 8·20; O, 11·84%); UV(EtOH): 220–232 (ε = 12,500), 271 (sh), 281 (ε = 2500), 288 (sh), 324 and 336 (ε = 250) nm; IR(KBr): 3460, 3230, 1609, 1505, 1455, 1225, 1045 and 810 cm^{-1}. NMR signals were displayed at δ 0·74 (s, 3p, 18-Me), δ 3·09 (s 4p, 7-H_2 (and 10-H_2) and δ 3·70 (t 1p, 17-H).

(±)-*Anthraestra-1,3,5,7,9,14-hexaene-3,17β-diol* (XI)

To a soln of 0·500 g (0·002 mole) of X in 50 ml anhyd benzene was added 0·900 g (0·004 mole) DDQ dissolved in 40 ml dry benzene. After stirring at 60° for 30 min, the mixture was cooled to room temp and the ppt was filtered off. Evaporation of the solvent afforded a yellowish crystalline residue that was recrystallized from acetone to yield 0·35 g (70%) of the hexaene XI, m.p. after further recrystallization from EtOH 228°. (Found: C, 81·15; H, 6·92; O, 11·95; $C_{18}H_{18}O_2$ requires: C, 81·17; H, 6·81; O, 12·02%); UV(EtOH): 243 (sh), 249 (ε = 34,000), 261 (ε = 30,200), 270 (ε = 30,700), 306 (ε = 8500), 318, 341 and 358 (ε = 3300) nm; IR(KBr): 3590, 3250, 1640, 1610, 1575, 1500, 1300, 1200 and 1070 cm^{-1}. NMR signals were measured at δ 0·93 (s 3p, 18-Me) and δ 6·06 (1p, 15-H) (soln in $(CD_3)_2SO$).

(±)-*Anthraestra*-1,3,5,7,9-*pentaene*-3,17β-*diol* (XII)

A mixture of 0·070 g of XI and 0·10 g Pd–C (10%) in 60 ml EtOH was shaken with H_2 at room temp and atm press until saturation. The catalyst was filtered off and the filtrate evaporated. Recrystallization of the residue from EtOH–water yielded 0·050 g (70%) of XII, m.p. after further recrystallization 190–192°. (Found: C, 80·40; H, 7·57; O, 11·86; $C_{18}H_{20}O_2$ requires: C, 80·56; H, 7·51; O, 11·93%); UV(EtOH): 234 (ε = 79,000), 261, 270 (ε = 3800). 292, 324 and 337 (ε = 1950) nm; IR(KBr): 3400, 1640, 1610, 1575, 1510, 1190, 1060, 870 and 805 cm^{-1}. The NMR spectrum (CD_3OD) showed absorptions at δ 0·54 (s 3p, 18-Me) and δ 3·80 (t 1p, 17-H).

Treatment of 8-*dehydroanthraestradiol* (X) *with* one *equivalent of DDQ*

To a soln of 1·470 g (0·0055 mole) X in 150 ml anhyd benzene was added 1·260 g (0·0055 mole) DDQ in 70 ml dry benzene. The resulting mixture was stirred at 60° for 30 min, cooled, filtered and evaporated to yield 1·45 g of yellowish crystalline material. Treatment with warm acetone afforded 0·56 g (40%) of a crystalline product, m.p. 228°, identical in IR, UV and NMR with XI, described earlier.

The remaining fraction of the reaction product was chromatographed over florisil. Elution with a mixture of cyclohexane and acetone (10:1) gave 0·30 g (20%) of a crystalline product, m.p. 185–190°, after recrystallization from EtOH–water 188–191°. The compound showed IR, UV and NMR absorptions, identical with those for XII, described earlier.

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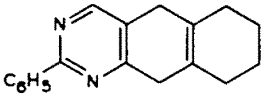

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