406. *Steroids Containing an Aromatic Ring* A. *Part IV.* The Dienol–Benzene Rearrangement in the* C_{21}*-Series.*

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Reduction of the ketal derivatives (Ib and c) of prednisolone with metal hydrides and subsequent aromatisation with aqueous acid yields the 4-methyl-19-nor-9α-pregna-1,3,5(10)-triene derivatives (IIa and c, respectively). In the 11-oxo-series epimerisation at C-9 has been observed and has been shown to be mainly base-catalysed. The infrared spectra of several steroids with an oxygen-free aromatic ring A and a 1- or 4-methyl group are discussed.

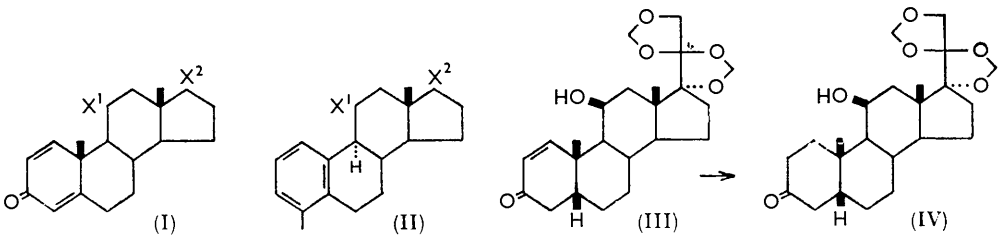
In previous publications the synthesis of steroids in which ring A is aromatic by dienol–benzene rearrangement [1] or by hydrogenolysis of compounds with a phenolic ring A [2] was described. In this paper the dienol–benzene rearrangement in the C_{21} series is reported.

Initially, attempts were made to carry out the rearrangement in the protected prednisone 17,20:20,21-bismethylenedioxy-derivative (Ia). However, when this was reduced with lithium aluminium hydride in tetrahydrofuran and then treated as previously described,[1] only 17,20:20,21-bismethylenedioxypregn-4-ene-3β,11β-diol (V) was obtained. Compound (V) was dehydrated by brief treatment with acid to 17,20:20,21-bismethylenedioxypregna-3,5-dien-11β-ol (VI). The 3β-hydroxy-configuration was assigned in analogy with previous observations.[1] Consequently, the protected prednisolone ketal derivative (Ib) was reduced with lithium aluminium hydride in tetrahydrofuran at −70° and the reduced steroids were then treated briefly with warm aqueous hydrochloric acid; chromatography of the

* Part III, *Chem. and Ind.*, 1962, 1716.

[1] Caspi, Grover, Grover, Lynde, and Nussbaumer, *J.*, 1962, 1710.
[2] Caspi, Cullen, and Grover, *J.*, 1963, 212.

recovered steroids on alumina gave two products, namely, 4-methyl-17,20:20,21-bismethylenedioxy-19-nor-9α-pregna-1,3,5(10)-trien-11β-ol (IIa) and 11β-hydroxy-17,20:20,21-bismethylenedioxy-5β-pregn-1-en-3-one (III). The product (IIa) was assigned the



(I) a, X^1 = :O; b, X^1 = H, OH; X^2 = O, O, O, O
c, X^1 = H, OH, X^2 = $CH_2 \cdot OAc$, O, O, OH

(II) a, X^1 = H, OH; b, X^1 = :O; X^2 = O, O, O, O
c, X^1 = H, OH, X^2 = $CH_2 \cdot OH$, CO, OH

(II) d, X^1 = H, OH, X^2 = :O
e, X^1 = :O, X^2 = :O
f, X^1 = H_2, X^2 = H, OH

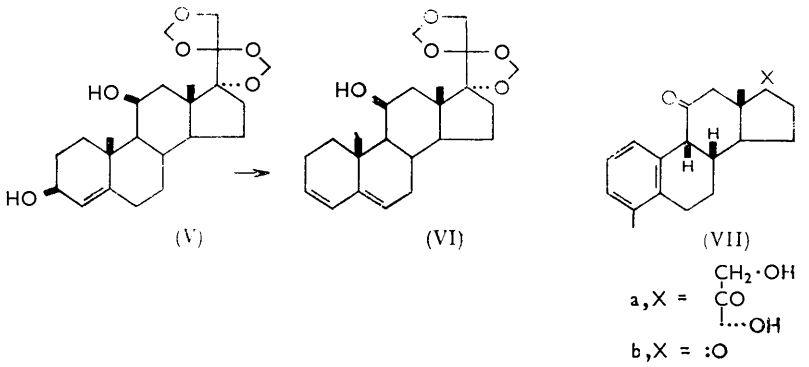
structure on account of its analysis, an infrared band at 1575 cm.$^{-1}$ for the aromatic unsaturation, and a band at τ 7·76 in the nuclear magnetic resonance spectrum for a methyl group on an aromatic ring. Evidence for the position of the methyl group was provided by the presence of infrared bands at 760, 745, and 725 cm.$^{-1}$. Compound (III) absorbed ultraviolet light (227 mμ) and on hydrogenation over palladium–charcoal gave 11β-hydroxy-17,20:20,21-bismethylenedioxy-5β-pregnan-3-one (IV), identical with a sample prepared from 11β,17α,21-trihydroxy-5β-pregnane-3,20-dione.

Removal of the protective group [3] in the product (IIa) proceeded in poor yield. When the compound was heated with 60% aqueous formic acid and the recovered steroids were saponified with potassium hydrogen carbonate, 11β,17α,21-trihydroxy-4-methyl-19-nor-9α-pregna-1,3,5(10)-trien-20-one (IIc) was obtained. This compound gave the correct analysis, a positive test with blue tetrazolium,[4] and on treatment with sodium bismuthate [5] the known 11β-hydroxy-4-methyl-9α-œstra-1,3,5(10)-trien-17-one (IId),[1] the formation of which proved the location of the methyl group at position 4 and confirmed the structures.

As removal of the protective group in the product (IIa) proceeded in poor yield, this compound (IIa) was oxidised to the corresponding 11-ketone (IIb). Cleavage of the methylenedioxy-groups then proceeded in satisfactory yield, but epimerisation took place. When the protected ketone (IIb) was treated with 60% aqueous formic acid, and the partially esterified steroids were saponified with aqueous-methanolic potassium hydrogen carbonate, 17α,21-dihydroxy-4-methyl-19-nor-9β-pregna-1,3,5(10)-triene-11,20-dione (VIIa) was obtained, that gave the expected analyses and a blue tetrazolium reaction and was cleaved with sodium bismuthate or lead tetra-acetate to 4-methyl-9β-œstra-1,3,5(10)-triene-11,17-dione (VIIb) (cf. Fig. a). The product (VIIb) (m. p. 178—180°) was different from the known 9α-isomer [1] (m. p. 203—205°) (Fig. b), indicating that epimerisation took place, probably at the doubly activated position 9. In the 9β(H) conformation ring C would assume a pseudo-chair form. The 8- and 9-hydrogen atoms could not be assigned unequivocal conformations in the conventional sense of axial and equatorial orientation. The 9-hydrogen would be rather equatorial in respect to ring C and pseudo-axial to ring B. On the other hand, the 8β-hydrogen would be rather axial towards ring C and pseudo-equatorial to ring B. The estimated dihedral angle of the hydrogen atoms is about 45°,

[3] Beak, Jackson, and Pike, *J. Org. Chem.*, 1962, **27**, 1752.
[4] Caspi, *J. Org. Chem.*, 1956, **21**, 729.
[5] Caspi, *J. Org. Chem.*, 1959, **24**, 669; Rigby, *J.*, 1950, 1907; Appleby, Gibson, Norymberski, and Stubbes, *Biochem. J.*, 1955, **60**, 453.

and the coupling constant estimated from Karplus's [6] curve about 4 c./sec. This is in contrast to the diaxial orientation in regard to both rings B and C of the 9α,8β-hydrogen atoms in the diketone (IIe), in which the dihedral angle is about 180° and the estimated coupling constant is 9·5 c./sec. The nuclear magnetic resonance spectrum of 4-methyl-9β-œstra-1,3,5(10)-triene-11,17-dione (VIIb) gave a fairly narrow band centred at about τ 6·2



for the 9β-hydrogen. In contrast, its 9α-isomer (IIe) showed a broad unresolved band centred at τ 6·38 consistent with an axial proton (9α) coupled to another axial proton (8β). The shapes of the bands of the 9-proton and the upfield shift of this band in the 9α-isomer (IIe) are consistent with the assigned structures.

It was then of interest to find out whether the epimerisation was acid- or base-catalysed. When 4-methyl-8β,9α-œstra-1,3,5(10)-triene-11,17-dione (IIe) was agitated with aqueous-methanolic potassium hydrogen carbonate, complete epimerisation to the 8β,9β-isomer (VIIb) took place. With 60% aqueous formic acid a mixture of products was obtained, from which the 8β,9β-isomer (VIIb) was isolated. In the absence of a ketone group at position 11, epimerisation did not take place, as shown by recovery of unchanged 4-methyl-8β,9α-œstra-1,3,5(10)-triene-17β-ol (II*f*) after treatment with acid or base. Thus it could be concluded that the epimerisation is mainly base-catalysed and an 11-keto-group seems to be requisite. On one occasion, after several recrystallisations of 4-methyl-9β-œstra-1,3,5(10)-triene-11,17-dione (VIIb), a third isomer was obtained, which had a different infrared spectrum (Fig. c), though it showed the same melting point as (VIIb). Unfortunately lack of material precluded its identification.

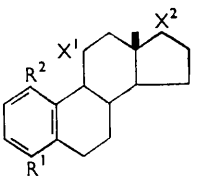
In view of the difficulties encountered in the removal of the protective groups in 11β-hydroxy-4-methyl-17,20:20,21-bismethylenedioxy-19-nor-9α-pregna-1,3,5(10)-trien-11β-ol (IIa), it was hoped that the synthesis could be carried out more successfully starting from the 20-ethylenedioxy-21-acetate (Ic). This prednisolone derivative (Ic) was prepared from the analogous cortisol derivative by dehydrogenation with 2,3-dichloro-5,6-dicyano-benzoquinone.[2,7] When the compound (Ic) was reduced with lithium hydrido-t-butoxy-aluminate [8] in anhydrous t-butyl alcohol or lithium aluminium hydride in tetrahydrofuran, and the reduced product was briefly treated with acid, 11β,17α,21-trihydroxy-4-methyl-19-nor-9α-pregna-1,3,5(10)-triene-20-one (IIc) was obtained upon chromatography.

We previously demonstrated [1] that in the presence of a 17β-hydroxy-, 17β-hydroxy-17α-methyl-, or 17-oxo-group, or a dihydroxyacetone residue at position 17, and irrespective of the presence or absence of an oxygen function at position 11, the dienol–benzene rearrangement yielded the 4-methyl compound. This generalisation can now be extended to the side chains present in compounds (Ib and c).

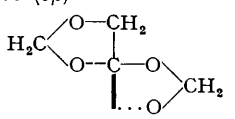
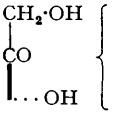
[6] Karplus, *J. Chem. Phys.*, 1959, **30**, 11.
[7] Burn, Kirk, and Petrow, *Proc. Chem. Soc.*, 1960, 14.
[8] Brown and McFarlin, *J. Amer. Chem. Soc.*, 1956, **72**, 252; Wheeler and Mateos, *Canad. J. Chem.*, 1958, **36**, 1431.

The exclusive formation of the alcohol (V) by reduction of Ia with lithium aluminium hydride merits comment. In the cases thus far investigated,[1] some saturation of the 1,2-double bond was observed. A model of the bismethylenedioxy-derivative (Ia) revealed a close proximity of the 1-hydrogen atom and the 11-ketone group, making interaction between the two (*e.g.*, hydrogen bonding) a distinct possibility. Should this be the case, it would greatly facilitate the observed 1,4-addition of the reducing species.

A summary of certain infrared bands of the steroids containing an oxygen-free aromatic ring A synthesized in our laboratory is compiled in the annexed Table. The 1-methyl



Characteristic bands in the infrared spectra, in the 800—700 cm.$^{-1}$ region, of 4-methyl and 1-methyl steroids containing oxygen-free aromatic ring A (in KBr).

R^1	R^2	X^1	X^2			
Me	H	H_2	H_2	775s	735s	
Me	H	H_2	H, β-OH	780s	738s	
Me	H	H_2	:O	780s	738s	719m
Me	H	H, β-OH	H, β-OH	763s	750s	713w
Me	H	H, β-OH	:O	783m	746s	707m
Me	H	:O	:O (9α)	790s	755s	730m
Me	H	:O	:O (9β)	760w	742s	713w
Me	H	H, β-OH		760s	745s	725w
Me	H	:O		780m	745s	720w
Me	H	H, β-OH	 9α	760w	750s	
Me	H	:O	9β	782s	742s	713w
H	Me	H_2	:O	770s	746m	
H	Me	:O	:O (9-)	785s	743w	704m

compounds gave a series of three bands in the regions 785—770, 750—740, and ~700 cm.$^{-1}$. Of the three, the most pronounced was that at the highest frequency. The band at 750—740 cm.$^{-1}$ was much less intense. The third band (~700 cm.$^{-1}$) was weak but discernible and never appeared at a frequency higher than 707 cm.$^{-1}$. For 4-methyl compounds two almost equally strong bands were observed, in the 780—760 and the 755—735 cm.$^{-1}$ region; however, the band at the lower frequency was the more intense, in contrast to the 1-methyl series. In all cases when an 11-oxygen function was present a band at 730—707 cm.$^{-1}$ appeared. Our results are an extension of previous observations on infrared spectra of aromatic steroids.[9]

Experimental

Infrared spectra were taken for potassium bromide in paper blotters. Ultraviolet spectra were taken for methanol solutions on a Cary spectrophotometer, model 11MS. M. p.s were determined on a hot stage and are corrected. Nuclear magnetic resonance spectra were determined for deuterated chloroform solutions as previously described.[1] Neutral alumina, of activity 1, supplied by Woelm-Eschwege was used for chromatography. Thin-layer chromatography was carried out on silica gel purchased from Brinkmann Instruments Inc., Great Neck L.I., New York.

4-*Methyl*-17,20:20,21-*bismethylenedioxy*-19-*nor*-9α-*pregna*-1,3,5(10)-*trien*-11β-*ol* (IIa).—To a stirred solution of the 17,20:20,21-bismethylenedioxy-prednisolone derivative (Ib) (9·0 g.) in anhydrous tetrahydrofuran (1 l.) at −70°, lithium aluminium hydride (11·0 g.) was added, and

[9] Dannenberg and Neuman, *Annalen*, 1961, **646**, 148.

the mixture was kept at −70° for 18 hr. The reaction was terminated by adding acetone and water, and the precipitate filtered through Celite. The filtrate was concentrated to a small bulk to which 2N-hydrochloric acid (5 ml.) was added. The solution was set aside at room temperature for 1 hr., then diluted with water and extracted several times with ethyl acetate. The combined extracts were washed with aqueous sodium hydrogen carbonate and with water, dried (Na_2SO_4), and evaporated. The oil obtained was dissolved in benzene and chromatographed on neutral alumina (activity 1). Elution with benzene gave a colourless oily *product* (IIa) which crystallised from methylene chloride and methanol as needles, m. p. 164—166°, $[\alpha]_D^{27}$ +207° (in $CHCl_3$), $\lambda_{max.}$ (in MeOH), 265 mμ (ε 270); $\nu_{max.}$ (in KBr) 3550, 3450, 1580, 1100, 1085, 762, 750 cm.$^{-1}$, τ 2·93, 4·93, 5·99, 7·77, 8·88 (Found: C, 71·3; H, 7·8. $C_{23}H_{30}O_5$ requires C, 71·5; H, 7·8%).

Further elution of the column with benzene containing 0·5% of ethyl acetate yielded 17,20:20,21-*bismethylenedioxy*-5β-*pregn*-1-*en*-17β-*ol* (III) which crystallised from methylene chloride–methanol as prisms, m. p. 257—258°, $[\alpha]_D^{27}$ +44° (in $CHCl_3$), $\lambda_{max.}$ (in MeOH) 227 mμ (ε 10,000), $\nu_{max.}$ (in KBr) 3480, 1678, 1610, 1093 cm.$^{-1}$ (Found: C, 68·0; H, 7·7. $C_{23}H_{32}O_6$ requires C, 68·3; H, 8·0%).

11β-*Hydroxy*-17,20:20,21-*bismethylenedioxy*-5β-*pregnan*-3-*one* (IV).—(i) A solution of 17,20:20,21-bismethylenedioxy-5β-pregn-1-en-11β-ol (III) (72 mg.) in ethyl acetate (200 ml.) and methanol (30 ml.) was agitated with 10% palladium–charcoal in hydrogen. The steroids were recovered with methylene chloride and ether (1 : 3). The colourless dihydro-derivative crystallised from methanol as leaves, m. p. 202—204°, $\nu_{max.}$ (in KBr) 3450, 1700, 1085 cm.$^{-1}$.

(ii) To a solution of dihydro-5β-cortisol (30 mg.) in chloroform (4 ml.) were added concentrated hydrochloric acid (0·3 ml.) and 37% aqueous formaldehyde (0·4 ml.), and the mixture was agitated for 2 hr., diluted with ether, washed with aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and evaporated to a residue. The oil obtained was chromatographed on a thin layer of silica gel with chloroform containing 5% of ethyl acetate as the developing solvent. The colourless oil crystallised from ethanol as leaves, m. p. and mixed m.p. with the sample obtained as above 202—204°. The infrared spectra were identical.

17,20:20,21-*Bismethylenedioxypregn*-4-*ene*-3β,11β-*diol* (V).—To a solution of compound (Ia) (200 mg.) in anhydrous tetrahydrofuran (20 ml.) at 0°, a cooled suspension of lithium aluminium hydride (400 mg.) in anhydrous tetrahydrofuran (10 ml.) was added, and the mixture was kept at 0° for 3 hr. Reaction was ended by addition of water, and the steroids were recovered with ethyl acetate and chromatographed on neutral alumina. Elution with benzene containing 1% of ethyl acetate gave a colourless oil which crystallised from methanol as needles, m. p. 176—178°, $\nu_{max.}$ (in KBr) 3400, 1650, 1100, 1080 cm.$^{-1}$.

17,20:20,21-*Bismethylenedioxypregna*-3,5-*dien*-11β-*ol* (VI).—To the diol (V) (10 mg.) in acetone (2 ml.), 2N-hydrochloric acid (0·5 ml.) was added, and the solution warmed on a water-bath for 5 min. The separated solid was filtered off and recrystallised from methanol, yielding needles of the *pregnadienol*, m. p. 188—190°, $\lambda_{max.}$ (in MeOH) 227 (ε 14,900), 237 (ε 16,750), and 242 mμ (ε 11,470), $\nu_{max.}$ (in KBr) 3650, 1600, 1100, 1080 cm.$^{-1}$ (Found C, 71·1; H, 8·3. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%).

11β,17α,21-*Trihydroxy*-4-*methyl*-19-*nor*-9α-*pregna*-1,3,5(10)-*trien*-20-*one* (IIc).—Nitrogen was bubbled through 60% formic acid (36 ml.), heated on a steam-bath for 5 min., then the bismethylenedioxy-derivative (IIa) (100 mg.) was added and heating continued for 20 min. The mixture was cooled and poured over an excess of aqueous sodium hydrogen carbonate. The steroids were recovered with methylene chloride and ether (1 : 3). The extracts were washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. The oil obtained was dissolved in methanol (40 ml.), and a solution of potassium hydrogen carbonate (200 mg.) in water (20 ml.) was added (both the methanol and the water solution were previously flushed with nitrogen). The solution was left at room temperature for 48 hr. Acetic acid (2 ml.) was then added, and the methanol was removed under reduced pressure. The solution was diluted with water and the steroids were recovered with methylene chloride and ether (1 : 3). The residual oil crystallised from ethyl acetate as colourless needles, m. p. 191—193°.

(ii) To a saturated solution of lithium aluminium hydride in anhydrous tetrahydrofuran–ether (1 : 1) (50 ml.) at 0° was added dropwise a solution of the 20-ethylenedioxy-21-acetate (Ic) (225 mg.) in tetrahydrofuran (10 ml.). The mixture was allowed to come to room temperature and was stored at room temperature for 4 hr. The excess of lithium aluminium hydride was decomposed with acetone and water, then the steroids were recovered as previously described,

and were dissolved in acetone (10 ml.). 2N-Hydrochloric acid (1 ml.) was added and the solution was warmed on the water-bath for 5 min. Water was added and the steroids were recovered with ethyl acetate. The oil obtained crystallised from ethyl acetate as needles, m. p. 191—193°.

(iii) To a solution of the ethylenedioxy-21-acetate (Ic) (100 mg.) in anhydrous t-butyl alcohol (25 ml.), lithium hydrido-t-butoxyaluminate (250 mg.) was added, and the solution was heated under reflux for 2·5 hr. Water was added, t-butyl alcohol was removed under reduced pressure, and the solution was extracted with ethyl acetate. The extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residual oil (93 mg.) was dissolved in acetone (5 ml.), 2N-hydrochloric acid (0·5 ml.) was added, and the solution warmed on the water-bath for 10 min. Acetone was removed under reduced pressure and the solution extracted with ethyl acetate. The extract was washed with water, dried (Na_2SO_4), and concentrated. The resulting syrup was chromatographed in benzene on silica gel. Eluates of chloroform containing 2—5% of ethyl acetate gave a colourless oil which crystallised from ethyl acetate and hexane as needles, m. p. 191—193°. The *products* (IIc) from the three experiments gave identical infrared spectra and the mixed m. p.s were undepressed. Data are $[\alpha]_D^{27}$ +112° (in $CHCl_3$), $\lambda_{max.}$ (in MeOH) 265 mμ (ε 540), $\nu_{max.}$ (in KBr) 3450, 1700, 1575, 750 cm.$^{-1}$, τ 2·87, 7·78, 9·06 (Found: C, 73·1; H, 8·2. $C_{21}H_{28}O_4$ requires C, 73·2; H, 8·2%).

11β-*Hydroxy*-4-*methyl*-9α-*œstra*-1,3,5(10)-*trien*-17-*one* (IId).—(i) To a solution of the trihydroxy-ketone (IIc) (10 mg.) in acetic acid (3 ml.) and water (3 ml.), sodium bismuthate (100 mg.) was added and the mixture was agitated for 16 hr. The excess of sodium bismuthate was reduced with 40% aqueous sodium hydrogen sulphite, and hydrochloric acid was added to dissolve the salts. The solution was extracted with ethyl acetate and the extract washed with 2N-sodium hydroxide and water, dried (Na_2SO_4), and evaporated under reduced pressure. The oil obtained crystallised from methylene chloride as colourless prisms, m. p. 244—246°, with a change of structure at 224—226°.

(ii) To a solution of the trihydroxy-ketone (IIc) (10 mg.) in chloroform (3 ml.), lead tetra-acetate (60 mg.) was added and the solution kept in the dark for 16 hr. Ethylene glycol (0·2 ml.) was added and after 1 hr. the solution was diluted with ether and washed with aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and evaporated under reduced pressure. The oil obtained crystallised from methylene chloride as colourless prisms, m. p. 244—246, with a change of structure at 224—226°. The mixed m. p. with an authentic sample was undepressed and the infrared spectra were identical.

4-*Methyl*-17,20:20,21-*bismethylenedioxy*-19-*nor*-9α-*pregna*-1,3,5(10)-*trien*-11-*one* (IIb).—Compound (IIa) (50 mg.) in pyridine (2 ml.) was added to a suspension of chromic acid (60 mg.) in pyridine (1 ml.). The mixture was left at room temperature for 3 hr. Ethyl acetate was added and the solution filtered through Celite, washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried (Na_2SO_4), and evaporated. The solid *ketone* (IIb) obtained recrystallised from methylene chloride–hexane, yielding the ketone as colourless needles, m. p. 188—192°, $[\alpha]_D^{27}$ +117° (in $CHCl_3$), $\lambda_{max.}$ (in MeOH) 267 mμ (ε 400), $\nu_{max.}$ (in KBr), 3010, 1700, 1575, 1100, 1085, 780, 745, 730 cm.$^{-1}$, τ 2·88, 4·76, 4·96, 6·00, 6·03, 7·77, 9·09 (Found: C, 71·8; H, 7·3. $C_{23}H_{28}O_5$ requires C, 71·7; H, 7·4%).

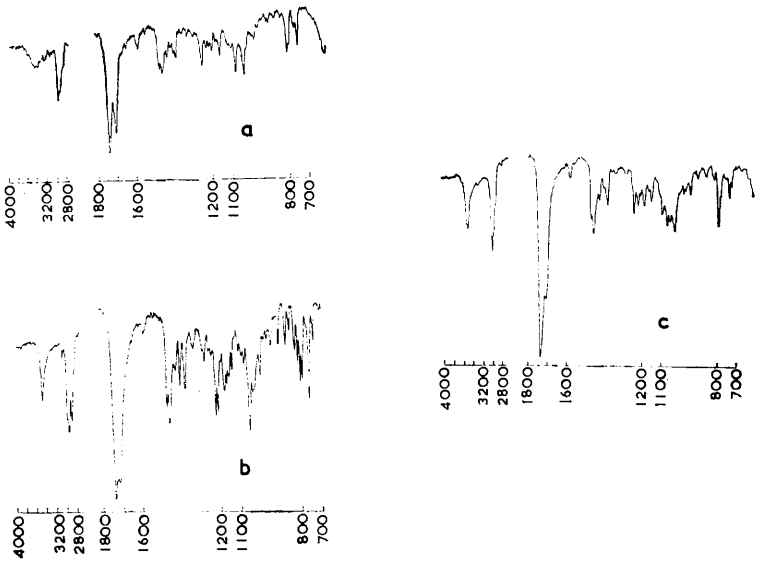
17α,21-*Dihydroxy*-4-*methyl*-19-*nor*-9β-*pregna*-1,3,5(10)-*triene*-11,20-*dione* (VIIa).—4-Methyl-17,20:20,21-bismethylenedioxy-19-nor-9α-pregna-1,3,5(10)-trien-11-one (IIb) (270 mg.) was treated with formic acid as previously described. The solution was cooled and poured on an excess of aqueous sodium hydrogen carbonate. The steroids were recovered as previously described. The oil obtained was dissolved in methanol (100 ml.) and to it was added potassium hydrogen carbonate (550 mg.) in water (55 ml.) (methanol and aqueous solutions had been flushed with nitrogen). The solution was kept at room temperature for 48 hr. Acetic acid (5 ml.) was added and the steroids were recovered as previously described. The oily *diketone* (VIIa) obtained crystallised from ethyl acetate as colourless prisms, m. p. 168—171°, $[\alpha]_D^{27}$ +237° (in $CHCl_3$), $\lambda_{max.}$ (in MeOH), 267 mμ (ε 310), $\nu_{max.}$ (in KBr) 3500, 3010, 1710, 1690, 1575, 780, 740, 716 cm.$^{-1}$, τ 2·92, 3·00, 3·13, 3·21, 5·57, 5·73, 6·32, 7·76, 9·28 (Found: C, 73·9; H, 7·5. $C_{21}H_{26}O_4$ requires C, 73·7; H, 7·7%).

4-*Methyl*-9β-*œstra*-1,3,5(10)-*triene*-11,17-*dione* (VIIb).—(i) To the 17α,21-dihydroxy-11,20-diketone (VIIa) (20 mg.), dissolved in acetic acid (5 ml.) and water (5 ml.), sodium bismuthate (200 mg.) was added and the mixture was agitated for 16 hr., then worked up as previously described. The colourless oil obtained crystallised from ethyl acetate as needles, m. p. 178—180°.

(ii) To the same diketone (VIIa) (10 mg.) in chloroform (3 ml.), lead tetra-acetate (60 mg.) was added and the solution stored in the dark for 16 hr. Ethylene glycol (0·5 ml.) was added and the mixture worked up as previously described. The colourless syrup obtained crystallised from ethyl acetate as needles, m. p. 178—180°.

(iii) 4-Methyl-9α-œstra-1,3,5(10)-triene-11,17-dione (IIe) (25 mg.) was dissolved in methanol (20 ml.) and to it was added potassium hydrogen carbonate (50 mg.) in water (5 ml.) (methanol and aqueous solutions had been flushed with nitrogen). The solution was kept at room temperature for 24 hr. The steroids were recovered as previously described. The colourless syrup crystallised from ethyl acetate as needles, m. p. 178—180°.

(iv) 4-Methyl-9α-œstra-1,3,5(10)-triene-11,17-dione (40 mg.) was treated with 60% formic acid (20 ml.) in the manner previously described. The oil obtained was chromatographed on a



Infrared spectra of (a) 4-methyl-9β- and (b) 4-methyl-9α-œstra-1,3,5(10)-triene-11,17-dione and (c) the unidentified product (see text).

thin layer of silica gel with chloroform as the developing solvent. The syrup obtained crystallised from ethyl acetate as colourless needles, m. p. 178—180° alone or mixed with samples obtained as above. This *diketone* (VIIb) had $[\alpha]_D^{27}$ +329° (in $CHCl_3$), $\lambda_{max.}$ (in MeOH) 267 mμ (ε 470), $\nu_{max.}$ (in KBr) 3010, 1720, 1700, 1580, 760, 742 cm.$^{-1}$, τ 2·91, 2·98, 3·13, 6·17, 6·27, 7·68, 7·75, 8·39, 9·05 (Found: C, 80·7; H, 7·8. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·8%). On multiple crystallisation on one occasion another product was obtained, having m. p. 178—180° and giving the infrared spectrum shown in Fig. c.

Treatment of 4-*Methyl*-9α-*œstra*-1,3,5(10)-*trien*-17β-*ol* (IIf) *with* (*a*) *Formic Acid and* (*b*) *Potassium Hydrogen Carbonate*.—This 9α-compound (20 mg.) was treated (*a*) with 60% formic acid (7 ml.) or (*b*) with potassium hydrogen carbonate as previously described. The steroids were recovered with ethyl acetate and from methanol gave colourless needles, m. p. 113—115° alone or mixed with the starting material, and having the same infrared spectrum.

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