SYNTHETIC INVESTIGATION ON TESTOSTERONE AND ITS ANALOGUES—II[1]

Syntheses[2] of 8-Iso-19-Noranthratestosterone[3] and 8-Iso-10-Iso-19-Nortestosterone

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ABSTRACT

The total synthesis of the anthracene analogue of 8-iso-19-nortestosterone has been described. *dl*-Dihydroequilenin and the ethylene ketal of *d*-equilenin have been converted to *dl*- and *d*-8-iso-17β-hydroxy-19-norandrost-5 (10)-en-3-one respectively, which were isomerized to *dl*- and *d*-8-iso-10-iso-19-nortestosterone, the ORD data of the latter confirming the configuration.

FOLLOWING the reported synthesis[1b] of 8-isotestosterone (VIII, *b*) and its anthracene analogue (VI, *b*), investigation on the synthesis of the corresponding 19-nor analogues was undertaken in view of the interesting physiological properties[4, 5] of 8-isotestosterone and 19-nortestosterone.

In the preparation of *trans*-1 β-hydroxy-8-methyl-4, 5-(4′–methoxybenzo)-hydrindane (I, *a*), the starting material, from 6-methoxytetralone by the previously described method,[6] improvements could be effected at two stages, *viz.*, Stobbe condensation of 2-methyl-2-cyano-6-methoxytetralone with dimethyl succinate and the decarboxylation of 1β-hydroxy-8-methyl-4, 5-(4′-methoxybenzo)-$\Delta^{3(9)}$-hydrindene-3-carboxylic acid.

Demethylation of (I, *a*) with pyridinium chloride afforded the hydroxy phenol (I, *b*) in 80% yield, methyl magnesium iodide giving only 65%. In contrast to our previous observation[1b] with the higher homologue (I, *c*), the acetoxy phenol (I, *d*) was obtained in an overall yield of 86% from (I, *b*) by selective saponification of the diacetate (I, *e*), whereas preferential acetylation gave 56%. This is obviously due to the absence of the methyl group *ortho* to the phenol, which sterically hindered acetylation and deacetylation of the aromatic hydroxy and the acetoxy groups in (I, *f*) and (I, *g*) respectively.

Catalytic hydrogenation of the acetoxy phenol (I, *d*) with either Raney nickel (W 2)[7] or ruthenium on carbon (5%)[8] catalyst gave a gum which on chromatography over neutral alumina[9] furnished four fractions which were eluted in the following order: (A) crystalline solid, m.p. 96–97° and 108–111° (polymorphs); (B) crystalline solid, m.p. 92–93°; (C) gum; (D) crystalline solid, m.p. 152–153°. The major product, fraction (A), has been assigned the structure and configuration (II, *a*) on the basis of infrared (nujol) bands at 3660 cm.$^{-1}$ (free O—H), 3413–3333 cm.$^{-1}$ (bonded O—H), 1742 cm.$^{-1}$ (acetate C=O), 1244 cm.$^{-1}$ (acetate C – O), 1048 and 1028 cm.$^{-1}$ (acetoxy C—O and hydroxy C—O), chromatographic behaviour, and hydrogenation, according to Linstead's concept[10], leading to the attack of hydrogen from the less hindered α-side. The elemental analysis, chromatographic behaviour, and infrared (nujol) absorptions at 3413 cm.$^{-1}$, 1730 cm.$^{-1}$, 1244 cm.$^{-1}$, 1058 cm.$^{-1}$ and 1036 cm.$^{-1}$ of the fraction (B), formed in very small quantity, indicated it to be an isomer of (II, *a*). Oxidation of fractions (A and B) with Jones' reagent[11] to give the identical keto acetate (IV, *a*), m.p. 136°, in good and moderate yields respectively proved that the latter was the epimer (III, *a*) at C-6. The mode of hydrogenation and the presence of non-bonded O—H and comparatively lower C—O stretching frequencies in the infrared spectrum (II, *a*) showed axial conformation of its 6-hydroxyl; presumably epimerization to the equatorial hydroxyl to form (III, *a*) occurred during hydrogenation or chromatography. Oxidation of the gummy fraction (C) yielded a small quantity of the keto acetate (IV, *a*). Attempts to crystallize the residual noncrystalline material, showing characteristic acetate and saturated ketone carbonyl infrared absorptions, were not successful. Analytical and spectral data led to assignment of the structure (II, *b* or III, *b*) to the crystalline fraction (D), obviously formed by hydrogenolysis of the acetate group. Hydrolysis of the hydroxy acetate (II, *a*), however, furnished a diol different from the first one. But, oxidation of the two diols gave the identical diketone (V, *a*) proving the diols to be epimers at C-6. The possibility of epimerization of the C-6 axial hydroxyl of (II, *a*) during saponification to give (III, *b*), coupled with the fact that this diol moved more slowly in the thin layer chromatography, permitted tentative assignment of configurations at C-6 (II, *b*) and (III, *b*) to the first and second diols respectively. Conversion of the diol (II, *b*) to the hydroxy ketone (IV, *b*), which could be utilized in our synthesis, was also investigated because of considerable accumulation of the former from several hydrogenation experiments. Selective oxidation and ketalization of the diol (II, *b*) and the diketone (V, *a*) respectively, following Ringold's exchange ketalization procedure[13] in the latter case, were not successful.

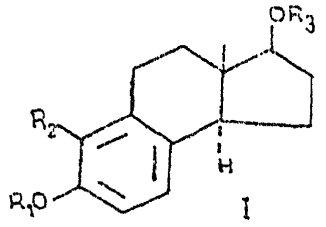
Subsequently, the monoketal (V, *b*) was prepared using one molar equivalent of ethylene glycol and *p*-toluenesulphonic acid catalyst. Treatment of (V, *b*) with sodium borohydride followed by cleavage of the ketal furnished the hydroxy ketone (IV, *b*) identical with the authentic sample prepared from the keto acetate (IV, *a*).

Treatment of (IV, *a*) with ethyl formate and potassium methoxide yielded a hydroxymethylene derivative. To determine the position of the hydroxymethylene group, 5 or 7, the crude product was methylated according to the method of Tsuda and Nozoe[13] followed by treatment with alcoholic hydrochloric acid to give a gummy product which on treatment with acetic anhydride furnished a crystalline keto acetate, m.p. 117–117·5°, in which the methyl group should be equatorial because of the equilibrating condition of the cleavage of the formyl group. This compound was found to be different from the previously described[1b] *dl*-1 β, 2 α-(3′ β-acetoxycyclopentano)-2, 5-dimethyl-6-keto-1 α, 2, 3, 4, 4 *a* α, 5 α, 6, 7, 8,-8 *a* α-decahydronaphthalene (IV, *c*), m.p. 159–160°, in which the methyl group was proved to be equatorial by the equilibration experiment. Therefore, the methylated keto acetate should be represented by (IV, *d*) and the hydroxymethylene group attached to the 7-position. The crude hydroxymethylene derivative was next condensed with methyl vinyl ketone in presence of potassium *t*-butoxide to afford the crystalline 8-iso-19-noranthratestosterone (VI, *a*), m.p. 151–153°, besides a minute quantity of another crystalline product, m.p. 148-149·5°, whose infrared spectrum showed the presence of saturated ketone (1718 cm.$^{-1}$) and alcohol (3610 cm.$^{-1}$) groups. We presumed it to be the β, γ-isomer (VII).

At this stage, Velluz *et al.* in a short communication[14] disclosed the total synthesis of *d*-8-iso-19-nortestosterone[15] (VIII, *a*) and its ethylenic isomer (IX) by direct condensation of methyl vinyl ketone with the *d*-keto acetate (IV, *a*). This was followed by a more detailed account[16] in which they claimed the preparation of (VIII, *a*), 8-iso-10-iso-19-nortestosterone (X), and the β, γ-isomer (IX), all in two antipodal forms. For the preparation of *d*- and *l*-keto acetates (IV *a*) from the corresponding antipodes of (I, *a*) they followed identical steps described by us[1b] for the preparation of *dl*-8-isotestosterone (VIII, *b*).

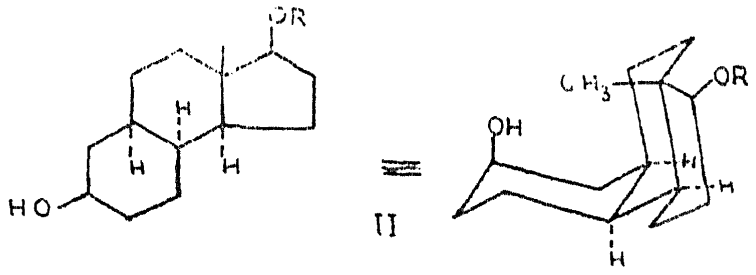
These results necessitated an unambiguous synthesis of (IX) and (X), for which the authentic 8-isooestradiol (XI, *a*) appeared to be an ideal starting material. Dauben and co-workers[17] hydrogenated *d*-equilenin (XII, *a*) in presence of Raney nickel (W_5)[18] in an alkaline medium to obtain, besides the neutral B-ring aromatic compounds[19], *d*-8-isooestradiol (XI, *a*) in 14%

yield. Later, Johnson,[20] following the same conditions, obtained *dl*-(XI, *a*) in 16% yield from racemic equilenin. Similar hydrogenation of *dl*-dihydroequilenin (XII, *b*) furnished, along with neutral products, a pure phenolic material in 21% yield which was shown to be *dl*-(XI, *a*) by comparing it and its monobenzoate with authentic samples[21]. Formation of *dl*-8-



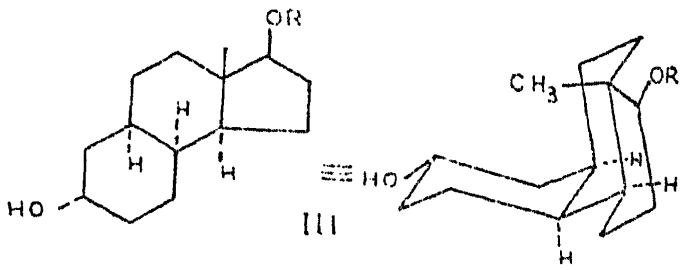
I

a, R_1=CH_3; R_2=R_3=H : d, R_1=R_2=H; R_3=CH_3CO
b, R_1=R_2=R_3=H : e, R_1=R_3=CH_3CO; R_2=H
c, R_1=R_2=CH_3; R_3=H : f, R_1=R_3=H; R_2=CH_3
g, R_1=R_3=CH_3CO; R_2=CH_3



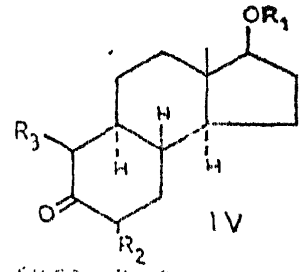
II

a, R=CH_3CO : b, R=H



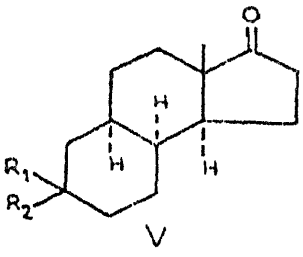
III

a, R=CH_3CO : b, R=H



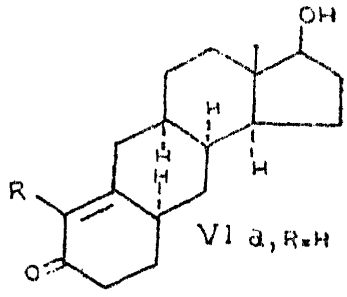
IV

a, R_1=CH_3CO; R_2=R_3=H
b, R_1=R_2=R_3=H
c, R_1=CH_3CO; R_2=H; R_3=CH_3(e)
d, R_1=CH_3CO; R_2=CH_3(e); R_3=H

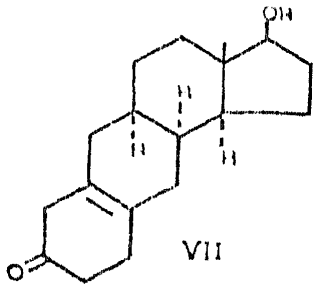


V

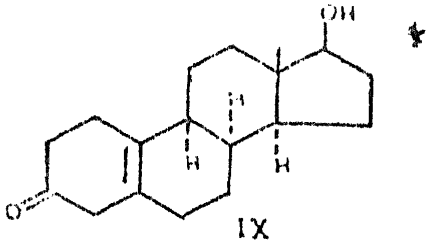
a, R_1, R_2 = O
b, R_1, R_2 = O.CH_2.CH_2.O



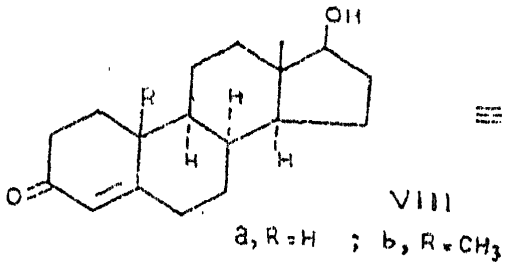
VI a, R=H ; b, R=CH_3



VII

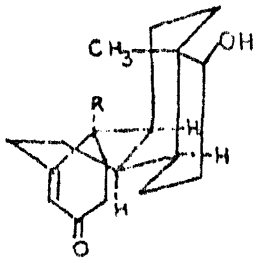


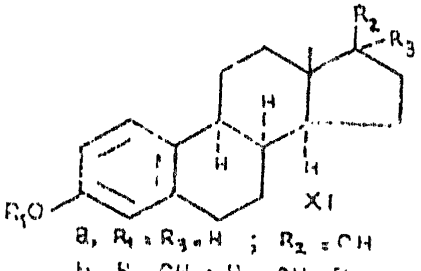
IX



VIII

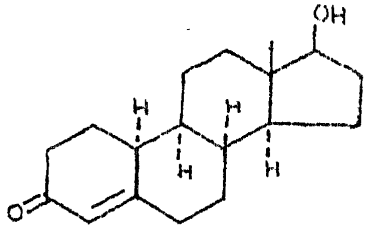
a, R=H ; b, R=CH_3

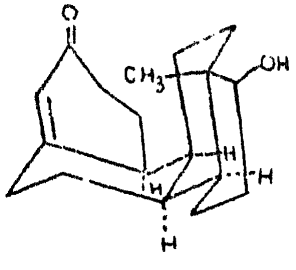


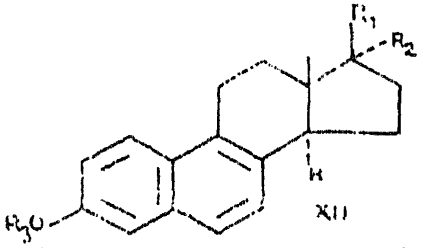


XI

a, R_1=R_3=H ; R_2=OH
b, R_1=CH_3; R_2=OH; R_3=H







XII

a, R_1, R_2 = O ; R_3 = H : c, R_1=OH; R_2=H; R_3=CH_3
b, R_1=OH; R_2=R_3=H : d, R_1, R_2=O.CH_2.CH_2.O; R_3=H

isooestrone methyl ether by treatment of the phenolic product with dimethyl sulphate and potassium carbonate followed by oxidation with chromium trioxide-pyridine completely characterised it. For a large-scale preparation of *dl*-dihydroequilenin 3-methyl ether (XII, *c*), from which the pure (XII, *b*) was prepared by demethylation with pyridinium chloride in 89% yield, the method of Johnson[22]-Banerjee[6] was modified by preparing *dl*-3-methoxy-17-ketooestra-1, 3, 5 (10), 6, 8, 14-hexaene by Johnson's method followed by sodium borohydride reduction and catalytic hydrogenation, as decarboxylation of comparatively large quantities of *dl*-3-methoxy-15-carboxy-17β-hydroxyoestra-1, 3, 5 (10), 6, 8, 14-hexaene by Banerjee's[6] method was found unsuitable.

Birch reduction[23] of (XI, *b*) using a large excess of lithium and subsequent hydrolysis of the crude enol ether with oxalic acid in methano afforded the pure *dl*-8-iso-17β-hydroxy-19-norandrost-5 (10)-en-3-one (IX), m.p. 158–160°, in 74% yield. The compound (IX) on treatment with methanolic hydrochloric acid under nitrogen gave a mixture of β, γ- and α, β-unsaturated keto alcohols, with the former predominating as evident from the infrared spectrum, which were separated by "Inverted Dry Column Chromatography (IDCC[24]. The infrared spectrum of the α, β-unsaturated keto alcohol was different from that of (VI, *a*), described earlier, and their mixture melting point was also depressed. Djerassi[25] suggested a boat conformation (VIII) for the ring B in 8-isotestosterone on the basis of ORD data. But, the C-10 hydrogen of the 19-nor compound, being enolizable, may be expected to assume the α-configuration with the preferred all-chair arrangement (X) under equilibrating conditions employed for isomerization of the β, γ-isomer (IX). Considering that ORD data of the optically active 19-nor compound might prove the configuration, we catalylically, hydrogenated *d*-17, 17-ethylenedioxyoestra-1, 3, 5 (10), 6, 8-pentaen-3-ol (XII, *d*), prepared by heating *d*-equilenin[27] with ethylene glycol and ethyl orthoformate in presence of *p*-toluenesulphonic acid,[26] as it was also a part of our programme[19] to prepare B-ring aromatic compounds with the 17-keto group intact. The resulting phenolic fraction consisted of two compounds which could be separated by TLC, IDCC, or fractional crystallization. The major and the minor components were found to be *d*-8-isooestrone and *d*--9-isooestrone repectively by comparison[21] of their infrared spectra (CH_2Cl_2) with those of authentic racemic samples[28]. The more hindered β-approach of hydrogen to form *d*-9-isooestrone to a small extent has obviously been facilitated by the α-linkage of the ethylenedioxy group; a similar observation in the hydrogenation of the 9 (11)-ethylenic

linkage of 3-methoxy-17, 17-ethylenedioxyoestra-1, 3, 5 (10), 9 (11)-tetraene was recorded.[29] *d*-8-Isooestrone was methylated and converted to the β, γ- and α, β-unsaturated keto alcohols following the previously described procedure. The considerable difference between the positive ORD curve[43] (Fig. 1) of the latter compound, m.p. 167–170° (C, 0·68 mg./ml.; dioxane; $[\alpha]_{589}$ +796°; peaks at 370, 354, 338 and 325 mμ, troughs at 360, 345 and 330 mμ, and shoulder at 316–310 mμ) and that of 8-isotestosterone (peaks at 372 and 355 mμ, inflections at 340–345 mμ, 327·5–330 mμ, and troughs at 362·5 and 317·5 mμ) along with the previously discussed energy considerations led us to assign α-configuration to the C-10 hydrogen (X). The ORD curve of the sample of *d*-8-iso-10-iso-19-nortestosterone, m.p. 170–172° (176°)[30]; (C, 0·80 mg./2 ml.; dioxane; $[\alpha]_D$ +268), furnished by Dr. Nomine and Dr. Bucourt, was identical with that of our authentic compound (X); the mixture m.p. was not depressed. Later, we could obtain a sample of 8 α, 10 α-testosterone,[31, 45] whose ORD curve exhibited positive Cotton effect and the fine structure (C, 1·00 mg./2 ml.; dioxane $[\alpha]_D$-80°; peaks at 370, 355, 337·5 and 325 mμ, troughs at 383, 363, 345 and 329 mμ and shoulder at 315–300 mμ) was very similar to that of our compound (X) except that it had a negative background. The ORD curve of the sample of 8-iso-19-nortestosterone furnished by Dr. Nomine and Dr. Bucourt also exhibited a positive ORD curve[32] (C, 0·78 mg./2 ml.; dioxane $[\phi]_D$-137°; peak at 360 mμ and trough at 400-390 mμ) but was considerably different from that of 8-isotestosterone and, therefore, is not likely to have the structure assigned to it[42]. Torgov *et al.* claimed the preparation of *dl*-8-iso-19-nortestosterone (VIII, *a*), *i.e.*, the C-10 hydrogen with β-configuration, by the Birch reduction of *dl*-8-isooestradiol 3-methyl ether and subsequent hydrolysis. Later, Smith[34] and co-workers carried out the same experiment and suggested the possibility of the presence of 10 α compound in the mixture, they obtained. On the basis of the present work, Torgov's compound should have α-hydrogen at C-10.

EXPERIMENTAL[35]

Methyl 1-keto-8-methyl-4, 5-(4′-methoxybenzo)-$\triangle^{3(9)}$-hydrindene - 3-carboxylate.—The yield in the Stobbe condensation was considerably increased by the following modification of the earlier preparation.

To a flame-dried flask containing big lumps of dry 2-methyl-2-cyano-6-methoxytetralone (18 g.) under N_2 was added with stirring a mixture of dimethyl succinate (28 ml.) and potassium *t*-butoxide, prepared from potassium (7·2 g.) and *t*-butanol (180 ml.; finally dried by refluxing over

aluminium *t*-butoxide), in two lots at an interval of 1 hr. The stirring was continued until the solid completely dissolved (*ca.* 8 hr.). After standing overnight, the cooled reaction mixture was acidified with 1 : 1 HCl. Most of the *t*-butanol was removed under suction at room temperature, and the residue was diluted with water and thoroughly extracted with ether.

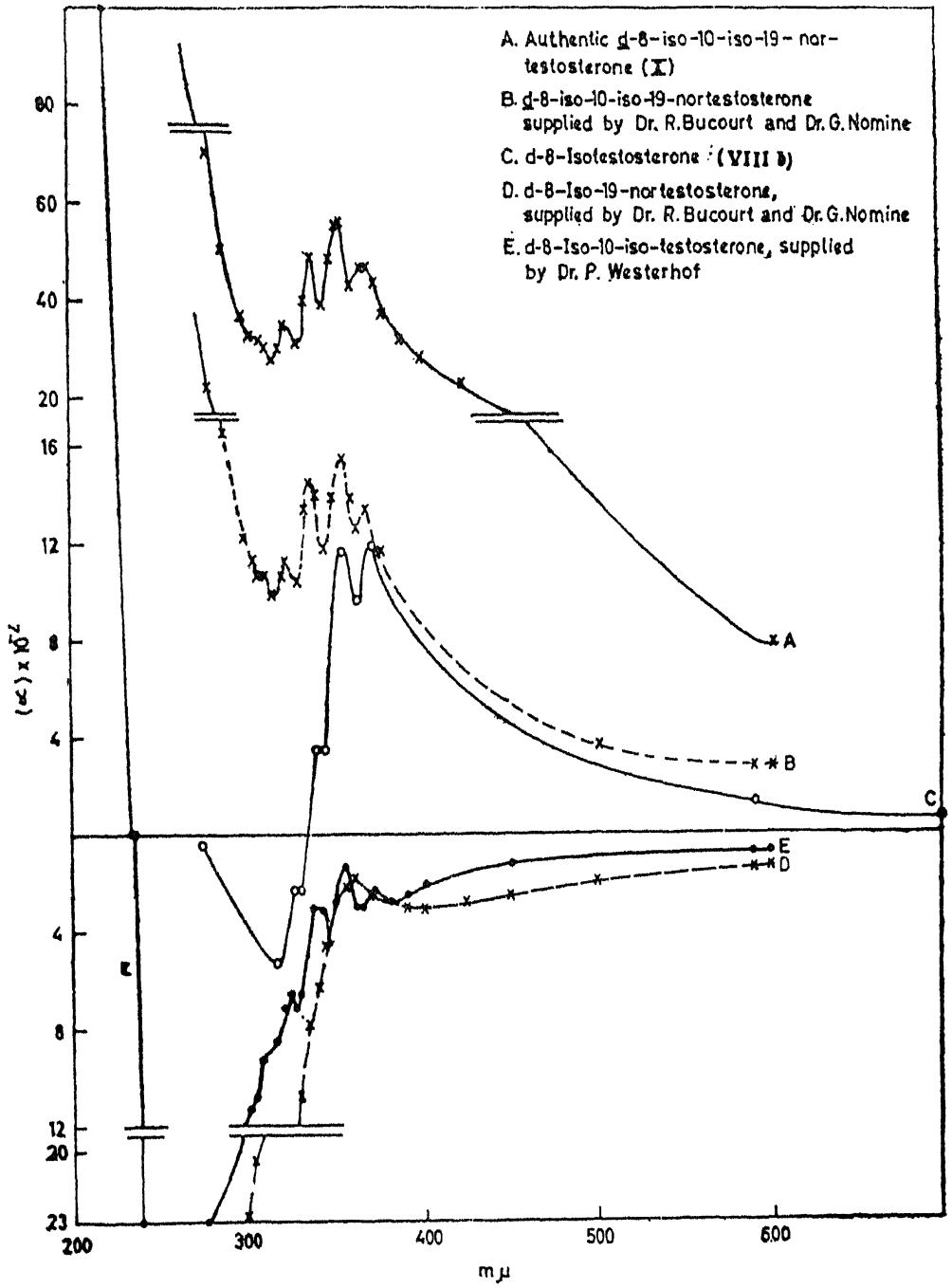


FIG. 1

The extract was washed successively with water, 2% NaOH aq. and water. Removal of the solvent afforded the Stobbe product (16·5 g.; 70%, reported 47–49%); after one crystallization from ether—pet. ether, m.p. 112–114°.

1β-*Hydroxy*-8-*methyl*-4, 5-(4′-*methoxybenzo*)-$\triangle^{3(9)}$-*hydrindene*.—A vigorously stirred suspension of 1β-hydroxy-8-methyl-4, 5-(4′-methoxybenzo)-$\triangle^{3(9)}$-hydrindene-3-carboxylic acid (6·5 g.) in 1 : 1 HCl (600 ml.) was heated at 80° for 40 min. The solid was filtered, washed with water, 5% $NaHCO_3$ aq., and water again and dried. After trituration with pet. ether, the product (4·6 g.; 86%, reported 90%) melted at 145–147°.

dl-trans-1 β-*Hydroxy*-8-*methyl*-4, 5-(4′-*hydroxybenzo*)-*hydrindane* (*I*, b).—(*a*) A solution of (I, *a*) (0·5 g.) in dry ether (10 ml.) was added dropwise under N_2 to the Grignard reagent, prepared from Mg (0·2 g.), methyl iodide (2 ml.), and dry ether (15 ml.). The ether was removed under suction and the residue was heated at 100–120° at 30 mm. for 1 hr. The whole system was then flushed with N_2 and the heating continued at 175° for 3/4 hr. when there was brisk evolution of gas. The swollen fibrous content was treated with pet. ether and ethyl acetate, followed by the addition of cold dilute sulphuric acid. The mixture was thoroughly extracted with ether and the ether layer was washed with water, and repeatedly extracted with cold 5% NaOH aq. The alkaline solution was acidified and the separated solid filtered, washed with water, and dried, m.p. 143–148°. On crystallization from dil. alcohol, the pure hydroxy phenol (I, *b*) (0·3 g.; 65%), m.p. 152–153°, was obtained (Found: C, 77·05; H, 8·20. $C_{14}H_{18}O_2$ requires: C, 77·03; H, 8·31%); UV $\lambda_{max.}$ 282 mμ (ε 1950); IR (KBr) $\nu_{max.}$ 3413–3344 (O—H), 1600 and 1572 (aromatic C=C), 1190 (phenol C—O), 1063 (alcohol C—O) $cm.^{-1}$.

(*b*) A mixture of (I, *a*) (4·5 g.) and dry pyridine hydrochloride (100 g.) was heated at 175–180° for 40 min. under N_2. Dil. HCl (200 ml.) was added to the cooled reaction mixture and then thoroughly extracted with ether. The extract was worked up as before to give the hydroxy phenol (I, *b*) (3·3 g.; 80%), m. p. 152–153°.

dl-trans-1 β-*Acetoxy*-8-*methyl*-4, 5-(4′-*hydroxybenzo*)-*hydrindane* (*I*, d).—(*a*) A mixture of the hydroxy phenol (I, *b*) (3 g.), acetic anhydride (4·5 ml.), and acetic acid (12 ml.) was heated for 4½ hr. on a steam-bath. It was then diluted with water and extracted with ether. The ether layer was washed successively with water, $NaHCO_3$ aq. and water and dried (Na_2SO_4). The residue, obtained after removal of the solvent, solidified in contact with pet. ether. Crystallization from pet. ether furnished the pure *dl-trans*-1 β-*acetoxy*-8-*methyl*-4, 5-(4′-*acetoxybenzo*)-*hydrindane* (I, *e*) (3·85-g.; 92%), m.p. 82–83° (Found: C, 71·36; H, 7·29. $C_{18}H_{22}O_4$ requires: C 71·50; H, 7·33%). UV $\lambda_{max.}$ 275 mμ (ε 770). IR (nujol) $\nu_{max.}$ 1754

(phenol acetate C=O), 1724 (alcohol acetate C=O), 1613 and 1587 (aromatic C=C), 1250 cm.$^{-1}$ (C—O).

A mixture of the diacetate (3·85 g.), ethanol (20 ml.), water (16·8 ml.), and K_2CO_3 (1·2 g.) was heated for ½ hr. on a steam-bath. The cooled reaction mixture was diluted with water and neutralized with dil. HCl. The precipitated solid was filtered, washed with water, and dried. On crystallization from dil. alcohol the acetoxyphenol (I, *d*) (3·1 g.; 93·6%), m. p. 130–132°, was obtained (Found : C, 73·45 ; H, 7·71. $C_{16}H_{20}O_3$ requires: C, 73·82; H, 7·74%). UV $\lambda_{max.}$ 282 mμ (ϵ 6200). IR (nujol) $\nu_{max.}$ 3636 (O—H), 1721 (acetate C=O), 1613 and 1581, 1258, 1193 (phenol C—O) cm.$^{-1}$.

(*b*) A mixture of the hydroxy phenol (I, *b*) (0·106 g.), acetic acid (1 ml.), and *p*-toluenesulphonic acid (0·01 g.) was heated for 1 hr. at 120°, cooled, diluted with water, and extracted with ether. The extract was washed with water, $NaHCO_3$ aq. and water and dried ($NaSO_4$). The residue, obtained after removal of the solvent, on crystallization from ethyl acetate-hexane, afforded the acetoxy phenol (I, *d*) (0·06 g.; 54%), m.p. 133–134°.

Catalytic hydrogenation of dl-trans-1*β-acetoxy*-8-*methyl*-4, 5- (4′-*methoxybenzo*)-*hydrindane* (*I*, d).—A solution of (I, *d*) (1 g.) either in cyclohexane (50 ml.) using Raney nickel (W 2)[7] catalyst (1 g.) or in alcohol using ruthenium on carbon (5%)[8] catalyst was hydrogenated at 175 atm. and 125°; the absorption of hydrogen ceased after *ca.* 6 hr. After removal of the catalyst and the solvent, the residual gum, which did not show any absorption maximum in 220–300 mμ region, was chromatographed over neutral alumina (30 g.) to furnish four fractions eluted in the following order: (A) a gum (0·46 g., 1 : 1 pet. ether-benzene, benzene, and 2 : 1 benzene-ether) which solidified in contact with pet. ether, m.p. 78–82°, and on crystallization from pet. ether furnished pure *dl*-1 *β*, 2 *α*-(3′, *β-acetoxy-cyclopentano*)-2-*methyl*-6 *β-hydroxy*-1 *α*, 2, 3, 4, 4 *a α*, 5, 6, 7, 8, 8 *a*-*α*-*deca-hydronaphthalene* (II, *a*), m.p. 96–97° and 108–111° (polymorphs) (Found: C, 71·73; H, 9·81. $C_{16}H_{26}O_3$ requires: C, 72·14; H, 9·84%); (B) a solid (0·12 g.), m.p. 85–90°, obtained only once from the same solvent mixture when the compound (I, *d*) (3·5 g.) was hydrogenated using ruthemium on carbon catalyst, which on crystallization from pet. ether afforded *dl*-1 *β*, 2 *α*-(3′ *β-acetoxycyclopentano*)-2-*methyl*-6 *α-hydroxy*-1 *α*, 2, 3, 4, 4 *a α*, 5, 6, 7, 8, 8 *a α-decahydronaphthalene* (III, *a*), m. p. 92–93° (Found: C, 72·28; H, 9·72. $C_{15}H_{26}O_3$ requires: C, 72·14 ; H, 9·84%) ; mixture m.p. of A and B was depressed ; (C), a gum (0·41 g., ether); (D) (9 : 1 ether-ethanol), obtained in small quantities, crystallized from acetone to furnish

dl-1 β, 2 α-(3′β-*hydroxycyclopentano*)-2-*methyl*-6 β-*hydroxy*-1 α, 2, 3, 4, 4 *a* α, 5, 6, 7, 8, 8 *a* α,-*decahydronaphthalene* (II, *b*), m. p. 152–153° (Found: C, 74·80; H, 10·42. $C_{14}H_{24}O_2$ requires: C, 74·95; H, 10·78%). IR (nujol) $\nu_{max.}$ 3436 cm.$^{-1}$, 1053 cm.$^{-1}$.

dl-1 β-2 α-(3′ β-*Acetoxycyclopentano*)-2-*methyl*-6-*keto*-1 α, 2, 3, 4, 4 *a* α, 5,-6, 7, 8, 8 *a* α-*decahydronaphthalene* (IV, a).—(*a*) To a solution of the fraction A (II, *a*) (0·45 g.) in acetone (60 ml.; purified by distillation over $KMnO_4$) was added carefully Jones' reagent below 30° with constant swirling until a pale orange colour persisted. After 2–3 min. water was added, and the crystalline precipitate was filtered, washed with water, and dried. Crystallization from acetone afforded the pure keto acetate (IV, *a*) (0·31 g., 70%), m. p. 136° (Found: C, 72·59; H, 9·04. $C_{16}H_{24}O_3$ requires: C, 72·69; H, 9·15). UV $\lambda_{max.}$ 277 mμ (ε 30). IR ($CHCl_3$) $\nu_{max.}$ 1718 (acetate C = O), 1701 (ketone C = O), 1250 cm.$^{-1}$ (C—O).

(*b*) The fraction B (III, *a*) (0·11 g.) on oxidation under similar conditions furnished the identical keto acetate (IV, *a*) (0·06 g., 55%).

(*c*) The gummy fraction C (1·5 g.) in acetone (200 ml.) was treated with Jones' reagent as before. Part of the solvent was removed under diminished pressure and the residual solution diluted with water. The separated oil was extracted with ether and the ether layer washed with water and dried (Na_2SO_4). The gum (1·1 g.), obtained after removal of the solvent, was dissolved in pet. ether and cooled to furnish the keto acetate (IV, *a*) (0·1 g.), m.p. 134–136°. The residue from the mother liquor, on chromatography over neutral alumina, gave a little more (0·015 g.) of the keto acetate. The remaining portion, which resisted all attempts to crystallize, showed IR peaks at 1718 and 1700 cm.$^{-1}$.

dl-1 β, 2 α-(3′β-*Hydroxycyclopentano*)-2-*methyl*-6α-*hydroxy*-1 α, 2, 3, 4, 4 *a* α, 5, 6, 7, 8, 8 *a* α-*decahydronaphthalene* (*III*, b).—A mixture of the hydroxy acetate (II, *a*) (0·075 g.) in ethanol (2 ml.) and NaOH (0·06 g.) in water (1 ml.) was left for 3 hr. at room temperature. Dilution with water gave silky needles of the diol (III, *b*) (0·055 g., 77%), m.p. 152–156°. Crystallization from acetone furnished the pure diol, m.p. 161–162° (Found: C, 74·65; H, 10·56. $C_{14}H_{24}O_2$ requires: C, 74·47; H, 10·78%). IR (nujol) $\nu_{max.}$ 3448, and 1053 cm.$^{-1}$. Its mixed m.p. with the diol (II, *b*) was depressed. In TLC on silica gel using benzene-ethyl acetate (1 : 1), the Rf values of diols, (II, *b*) and (III, *b*), were 0·43 and 0·33 respectively.

dl-1 β, 2 α-(3′-*ketocyclopentano*)-2-*methyl*-6-*keto*-1 α, 2, 3, 4, 4, aα, 5, 6, 7, 8,-8 *a* α-*decahydronaphthalene* (*V*, a).—(*a*) (i) Oxidation of the diol (II, *b*)

(0·1 g.) in acetone (10 ml.) with Jones' reagent as before gave the diketone (V, *a*) (0·06 g., 49%), m.p. 116–118° (Found: C, 76·56; H, 9·50; $C_{14}H_{20}O_2$ requires: C, 76·32; H, 9·15%). IR (nujol) $\nu_{max.}$ 1739 (cyclopentanone C=O), 1724 (cyclohexanone C=O) cm.$^{-1}$.

(ii) A mixture of a solution of the diol (II, *b*) (0·38 g.) in acetone (40 ml.), methenol (10 ml.), and water (10 ml.) and N-bromosuccinimide (2·76 g.) was kept for 5 hr. in the dark at 5–10° and then poured into 5% sodium sulphite solution (100 ml.) and left overnight. The solution was saturated with ammonium chloride and extracted with ether. The extract was washed with water, dried, and the solvent removed. The residual pale yellow solid was purified by short-path distillation, 120° (bath temp.) λ 7·7 × 10^{-2} mm. followed by crystallization from ether-hexane to give the diketone (V, *a*) (0·26 g., 56%).

(*b*) Oxidation of the diol (III, *b*) (0·04 g.) in acetone (2 ml.) with Jones' reagent afforded the diketone (V, *a*) (0·0281 g., 57%), m.p. 116–118°.

Attempted selective oxidation of the diol (*II*, b).—To a solution of the diol (II, *b*) (0·224 g.) in acetone (20 ml.) was added dropwise at 25° chromic acid solution (2·9 ml. of 0·688 N). The product on working up showed IR peaks at 1739 and 1724 cm.$^{-1}$, indicative of the presence of both five- and six-membered ring ketones.

Attempted selective ketalization of the diketone (*V*, a).—A mixture of the diketone (V, *a*) (0·15 g.), 2-methyl-2-ethyl-1, 3-dioxalane (2·5 ml.), and *p*-toluenesulphonic acid (5 mg.) was slowly distilled till 1·25 ml. of the distillate was collected (*ca.* 3 hr.). The solution was diluted with benzene, washed with 5% $NaHCO_3$ aq. and water and the solvent removed. the residue was crystallized from methanol containing a trace of pyridine to afford *dl*-1 β, 2 α-(3′, 3′-*ethylenedioxycyclopentano*)-2-*methyl*-6, 6-*ethylenedioxy*-1 α, 2, 3, 4, 4*a* α, 5, 6, 7, 8, 8 *a* α-*decahydronaphthalene* (V, *c*) (0·2 g, 90%), m.p. 95–96° (Found: C, 69·78; H, 8·87; $C_{18}H_{28}O_4$ requires: C, 70·10; H, 9·15%). IR spectrum was free from carbonyl absorption.

dl-1 β, 2 α-(3′-*Ketocyclopentano*)-2-*methyl*-6, 6-*ethylenedioxy*-1 α, 2, 3, 4, 4 a α, 5,6,7,8, 8 a α-*decahydronaphthalene* (*V*, b).—From a mixture of the diketone (V, *a*) (0·15 g.), ethylene glycol (0·05 g.), benzene (100 ml.), and *p*-toluenesulphonic acid (0·01 g.) benzene (50 ml.) was slowly removed by distillation (*ca.* 5 hr.). The benzene solution was washed with 5% $NaHCO_3$ aq. and water and the solvent removed. The residue (0·145 g.) was chromatographed over Brockmann alumina (4 g., activated at 150°/

30 mm. for 6 hr.), and the following fractions were collected: (A) (65 mg., pet. ether) and (B) (10 mg., 4 : 1 pet. ether and benzene), which showed the absence of six-membered ketone IR absorption, were crystallized from pet. ether to give the monoketal (V, *b*), m.p. 70–72° (Found: C, 73·28; H, 9·37. $C_{16}H_{24}O_3$ requires: C, 72·69; H, 9·15%); IR (nujol) $\nu_{max.}$ 1733 (cyclopentanone C=O), 1176, 1156, 1133, 1111 cm.$^{-1}$; (C) a gum (40 mg., pet. ether-benzene 1 : 1) (D), (20 mg., benzene) which was found to be the diketone (V, *a*).

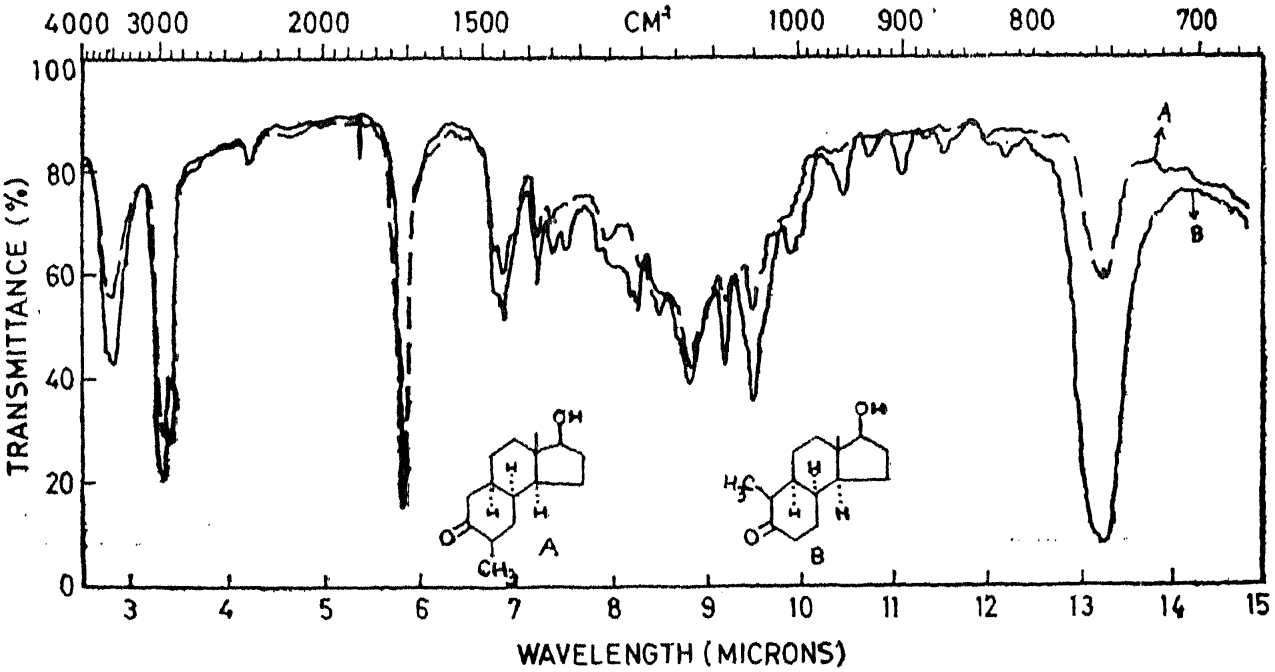
dl-1 *β*, 2 *α* - (3′ *β* -*Hydroxycyclopentano*)-2-*methyl*-6-*keto* - 1 *α*, 2, 3, 4, 4 a *α*,-5, 6, 7, 8 a *α*-*decahydronaphthalene* (*IV*, b).– To a solution of the monoketal (V, *b*) (50 mg.) in methanol (3 ml.) was added $NaBH_4$ (25 mg.) and the mixture allowed to stand overnight. Part of the methanol was removed under reduced pressure and the residue diluted with water and extracted with ether. The ether layer was washed with water and dried (Na_2SO_4) and the solvent removed. The residue was heated under reflux for 14 hr. with acetone (5 ml.) and *p*-toluenesulphonic acid (20 mg.). The mixture was diluted with water and extracted with ether. The extract was washed with 5% $NaHCO_3$ aq. and water and dried (Na_2SO_4). The residue, obtained after removal of the solvent, was chromatographed over neutral alumina (3 g., activated at 160–170°/30 mm. for 4 hr.). The solid (40 mg.), obtained on elution with pet. ether-benzene (1 : 1) and benzene was crystallized from pet. ether-ether to give the hydroxy ketone (IV, *b*), m.p. 113–114° (Found: C, 75·6; H, 9·88. $C_{14}H_{22}O_2$ requires: C, 75·61; H, 9·98%). IR (nujol) $\nu_{max.}$ 3448 and 1709 cm.$^{-1}$. This product was identified with the hydroxy ketone obtained by saponification of the keto acetate (IV, *a*) through mixture m.p. determination and comparison of the IR spectra.

dl-1 *β*, 2 *α*-(3′ *β*-*Acetoxycyclopentano*)-2, 7 - *dimethyl*-6-*keto*-1 *α*, 2, 3, 4,-4 a *α*, 5, 6, 7, 8, 8 a *α*-*decahydronaphthalene* (*IV*, d).– To a stirred suspension of dry potassium methoxide, prepared from K (20 mg.) in methanol (1 ml.) followed by removal of the excess methanol, in benzene (10 ml.) was added under N_2 at 0° a solution of the keto acetate (IV, *a*) (0·13 g.) in benzene (2 ml.). After 15 min. ethyl formate (50 mg.) in benzene (2 ml.) was added and the stirring continued for 2 hr. and then allowed to stand overnight. The mixture was treated with iced water, the aqueous layer separated and the benzene layer repeatedly extracted with 2% KOH aq. The combined aqueous solution was extracted once with ether and then acidified with cold dil. HCl followed by extraction with ether. The ether extract was washed with cold water, dried, and the solvent removed to

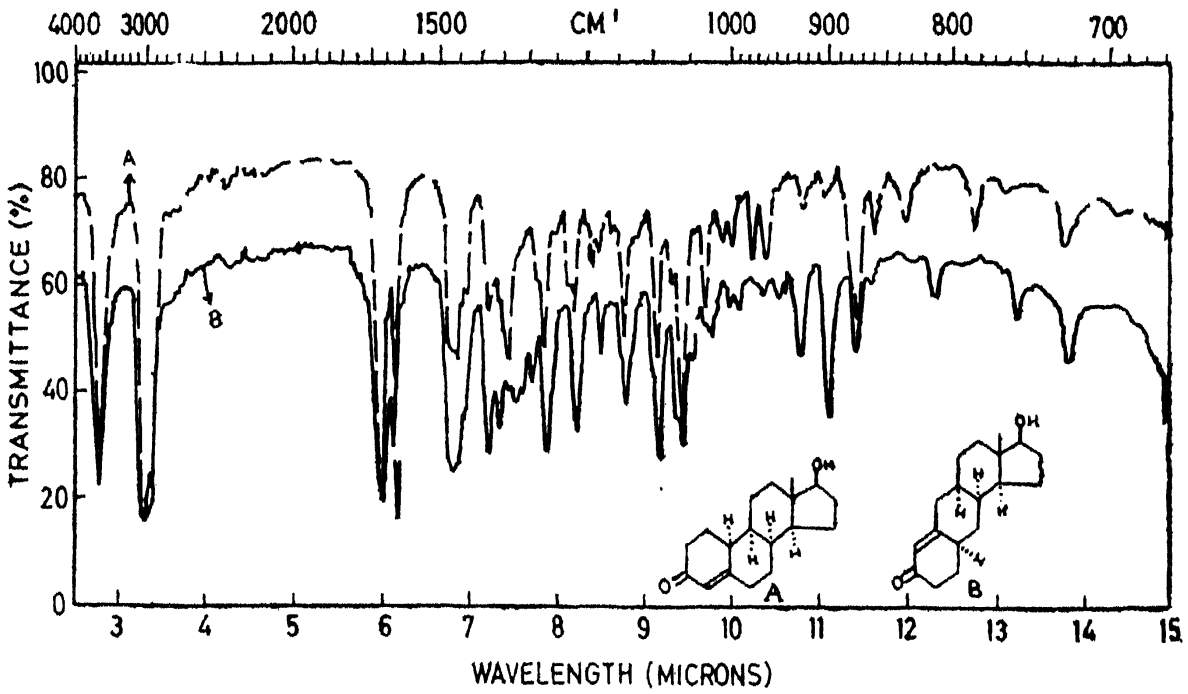
give a gum (0·1 g.) which showed positive $FeCl_3$ test, UV $\lambda_{max.}$ 288 mμ (ϵ 4200).

A mixture of the aforementioned crude hydroxymethylene derivative (0·1 g.) dry acetone (4 ml.), dry K_2CO_3 (0·12 g.), and methyl idodide (1 ml.) was refluxed for 24 hr., cooled, poured into ice-cold 2% NaOH aq., and extracted with ether. The ether layer was washed with water and dried (Na_2SO_4). The residue, obtained after removal of the solvent under reduced pressure, was refluxed with 10% ethanolic HCl (2 ml.) for 2 hr. The cooled solution was diluted with water and extracted with ether. The gum obtained after working up in the usual way was purified by short-path distillation, 150–155° (bath temp.) $12·3 \times 10^{-2}$ mm. to furnish *dl*-1 β, 2 α-(3′ β-*hydroxycyclopentano*)-2, 7-*dimethyl*-6-*keto*-1 α, 2, 3, 4, 4 a α, 5, 6, 7, 8, 8 a α-*decahydronaphthalene* (80 mg.) as a colourless viscous product (Found: C, 76·42; H, 10·28. $C_{15}H_{24}O_2$ requires: C, 76·22; H, 10·24%). IR (film) $\nu_{max.}$ 3571, 1724 cm.$^{-1}$

A mixture of the above product (75 mg.), acetic anhydride (0·25 ml.), and acetic acid (1·5 ml.) was heated for 4 hr. on a steam-bath, cooled, poured into ice-cold water, and extracted with ether. The extract was washed successively with water, $NaHCO_3$ aq. and water. The residue, obtained after removal of the solvent, solidified, m.p. 96–108°, and was purified by passing through a column of neutral alumina to afford the methylated keto acetate (IV, *d*) (60 mg.) which on crystallization from hexane melted at 117–117·5° (Found: C, 72·88; H, 8·85. $C_{17}H_{26}O_3$ requires: C, 73·35; H, 9·41%). IR (Fig. 2).



dl-1 β, 2 α- (3′ β-*Hydroxycyclopentano*)-2-*methyl*-7-*keto*-1 α, 2, 3, 4, 4 *a* α, 5, 7, 8, 9, 9 a α, 10, 10 a α-*dodecahydroanthracene* (*VI*, a).—To a cooled, stirred mixture of the crude hydroxymethylene derivative (1·2 g.), potassium *t*-butoxide, prepared from K (50 mg.) and *t*-butanol (3 ml.), and *t*-butanol (10 ml.) was added freshly distilled methyl vinyl ketone (0·5 g.) under N_2. The stirring was continued for 3 hr. and then left overnight. The reaction mixture was poured into ice-cold 2% NaOH aq. (150 ml.) and extracted with ether. The extract was washed with water, the solvent removed under diminished pressure, and the residue stirred with a solution of KOH (4 g.) in methanol (40 ml.) and water (4 ml.) for 2 hr. under N_2 at room temperature. The mixture was poured into brine (300 ml.) and extracted with ether. The gummy residue (0·8 g.), obtained after working up in the usual manner, was chromatographed over neutral alumina (80 g., activated at 150°/30 mm. for 3 hr.) to obtain mainly two fractions: A (25 mg., benzene-ether 7 : 3) was rechromatographed over neutral alumina (2·5 g.) and crystallized from acetone-hexane to furnish a small quantity of the β, γ-unsaturated ketone (IX), m.p. 148–149·5° (Found: C, 77·84; H, 9·36. $C_{18}H_{26}O_2$ requires: C, 78·77; H, 9·55%) (Fig. 2). B (0·11 g., benzene-ether 3 : 2), which solidified in contact with pet. ether, was rechromatographed over neutral alumina (10 g.) and crystallized from acetone-hexane to give the α, β-unsaturated ketone (VI, *a*) (50 mg.), m.p. 151–153° (Found: C, 79·11; H, 9·85. $C_{18}H_{26}O_2$ requires: C, 78·77; H, 9·55%) UV $\lambda_{max.}$ 240 mμ (14,000). IR (Fig. 3).



dl-3-*Methoxyoestra*-1, 3, 5 (10), 6, 8, 14-*hexaen*-17 *β-ol*,—*dl*-3-Methoxy-oestra-1, 3, 5 (10), 6, 8, 14-hexaen-17-one was prepared by the method of Johnson[22] from 1-keto-7-methoxy-1, 2, 3, 4 tetrahydrophenanthrene, the latter being prepared from *β*-naphthol methyl ether by the method of Stork[37, 38].

A suspension of dl-3-methoxy-oestra-1, 3, 5 (10), 6, 8, 14-hexaen-17-one (800 mg.) in methanol (100 ml.) was treated with sodium borohydride (500 mg.) and left overnight. The mixture was acidified with acetic acid and the solvent removed under suction. Following the addition of water, the residue was filtered, washed and dried. The crude product (800 mg.) melted at 176–178·5°; one crystallization from methanol gave the pure material (700 mg.; 87%), m.p. 180·5-181·5° (reported 187–190°). IR (nujol) $\nu_{max.}$ 3497, 1621, 1597, 1248, 855, 864, 820, 800 cm.$^{-1}$.

dl-*Dihydroequilenin* (*XII*, b).—A mixture of *dl*-dihydroequilenin methyl ether (XII, *c*) (2·0 g.) and pyridinium chloride (55 g.) was heated at 185°[44] for 1 hr. under N_2. The mixture was cooled, warmed with dil. HCl, filtered and washed with water. The residue was crystallized from ethyl acetate-hexane to afford the pure *dl*-dihydroequilenin (XII, *b*) (1·7 g., 89%), m.p. 225 and 245° (polymorph). (Found: C, 80·34; H, 7·42. $C_{18}H_{20}O_2$ requires C, 80·56; H, 7·51%). IR (nujol) $\nu_{max.}$ 3650, 3257, 1626, 1603, 1460, 1170, 810, 793 cm.$^{-1}$.

Hydrogenation of dl-*dihydroequilenin* (*XII*, b).—A suspension of *dl*-dihydroequilenin (2·5 g.) in 2·5% KOH aq. (400 ml.) and Raney nickel (W_5) (10 ml.) was stirred in an atmosphere of H_2 at 85–90° and an initial pressure of 200 atm. until absorption of H_2 ceased (4 hr.). After cooling, 2% KOH aq. and benzene were added, and the mixture was warmed with stirring and then filtered. The precipitate, obtained after acidification of the alkali layer, was filtered, washed with water, and dried to give *dl*-8-isooestradiol (XI, *a*) (550 mg.; 21%), m.p. 185–186° [reported m.p. 184–188° and 208·5–210° (sweat at 170°)]; this showed a single spot in TLC (20% ethyl acetate in chloroform), the mixed m.p. with the authentic sample was not depressed (Found: C, 79·56; H, 8·91. $C_{18}H_{24}O_2$ requires: C, 79·37; H, 8·88%). UV $\lambda_{max.}$ 280·5 mμ (ϵ 1908); IR (nujol) $\nu_{max.}$ 3700–3100 (broad), 1610, 1585, 1499, 1450, 818 cm.$^{-1}$. *dl*-8-Isooestradiol monobenzoate was prepared and crystallized from ethyl acetate, m.p. 189–191° (reported 179–185°); IR (KBr) identical with that of the authentic sample.

dl-8-*Isooestradiol* 3-*methyl ether* (*XI*, b).—A mixture of the diol (XI, *a*) (400 mg.) in acetone (50 ml., distilled over $KMnO_4$), dimethyl sulphate

(0·225 ml.), and anhydrous K_2CO_3 (1·5 g.) was refluxed for 28 hr. The solvent was removed under reduced pressure, water added, and the mixture extracted with ether. The ether layer was washed with 2% KOH aq. and water, and the solvent was removed. The residue was crystallized from methanol to give the pure methyl ether (XI, *b*) (328 mg.; 78%), m.p. 99-100°. Recrystallization afforded the analytical sample, m.p. 101·5–102° (Found: C, 79·25; H, 9·26. $C_{19}H_{26}O_2$ requires: C, 79·68; H, 9·15%), UV $\lambda_{max.}$ 278 mμ (ϵ 2040). IR $\nu_{max.}$ (CCl_4) 3831, 3546, 1613, 1495, 1037, 840 cm.$^{-1}$

dl-8-*Isooestrone methyl ether*.—A solution of (XI, *b*) (36·5 mg.) in dry pyridine (2 ml.) was added to a mixture of chromic anhydride (700 mg.) in dry pyridine (7 ml.) and kept at room temperature overnight. The reaction mixture was poured into water and extracted with ether-benzene. The organic layer was washed with $NaHCO_3$ aq. and water. Removal of the solvent followed by chromatography of the residue over neutral alumina (4 g.) yielded the pure keto ether (16·4 mg.; 45%), m.p. 152–153° (reported m.p. 152–154°[20]); mixture m.p. with the authentic sample was not depressed.

dl-17 *β-Hydroxy-8-iso-19-norandrost-5* (10) *-en-3-one* (*IX*). — Anhydrous liquid ammonia (40 ml.) was distilled into a 3-necked flask fitted with a liquid oxygen condenser and stirrer. The methyl ether (XI, *b*) (180 mg.) in a mixture of dry tetrahydrofuran (16 ml.) and dry *t*-butanol (16 ml.) was added, followed by a portionwise addition of lithium (450 mg.) during 10 min. with vigorous stirring. After 2 hr., dry methanol (10 ml.) was carefully added followed by saturated brine solution (40 ml.). The ether extract of the reaction mixture was washed with water, the solvent removed, and the residue dried to give the enol ether (180 mg.), a methanolic solution (100 ml.) of which was treated with oxalic acid (230 mg. in 2 ml. of water) and kept at room temperature for 40 min. The mixture was diluted with water and extracted with ether. The ether solution was washed with saturated $NaHCO_3$ aq. and water, the solvent removed, and the residue dried to give the crude *dl*-(IX) (175 mg.), m.p. 153–155°. On crystallization from ether afforded the pure product (125 mg., 74%), m.p. 158–160°; the analytical sample m.p. 160–161° (reported 166–168°[33]; 170–172°[34]) (Found: C, 79·04; H, 9·48. $C_{18}H_{26}O_2$ requires: C, 78·79; H, 9·55%). IR ($CHCl_3$), $\nu_{max.}$ 3590, 1710 cm.$^{-1}$.

Isomerization of dl-*β*, *γ-unsaturated keto alcohol* (*IX*) *to* dl-8-*iso*-10-*iso*-19-*nortestosterone* (*X*).—A mixture of *dl*-(IX) (110 mg.) in methanol (20 ml.) and 5% HCl aq. (4 ml.) was refluxed for 20 min. under oxygen-free

$_2$, cooled, diluted with water, and extracted with ether. The ether extract as washed with saturated $NaHCO_3$ aq. and water and evaporated to give gum (110 mg.) which slowly solidified. IR showed more intense peak : 1712 cm.$^{-1}$ than at 1653 cm.$^{-1}$. IDCC of the material using a column ·7 cm. diameter, 22 cm. length) of silica gel and developed by 20% ethyl cetate in chloroform gave five fractions: (A) a gum (6·1 mg.); (B) a gum 6 mg.) which solidified in contact with hexane; crystallization from ether ave pure *dl*-8-iso-10-iso-19-nortestosterone (X) (10 mg.; 9%), m.p. 148·5–52° (Found: C, 79·16; H, 9·55. $C_{18}H_{26}O_2$ requires: C, 78·79; H, ·55%); UV $\lambda_{max.}$ 244 mμ (ϵ 16, 318); mixed m.p. with *dl*-(VI, *a*) was depressed and IR spectra (Fig. 3) of the two were different; (C), a gum (3·7 mg.) hose IR spectrum showed it to be a mixture of *dl*-α, β- and β, γ-unsaturated keto alcohols, (X) and (IX); (D) and (E) a crystalline solid (54 mg., 0%), which was pure *dl*-β, γ-unsaturated keto alcohols (IX).

d-*Equilenin ketal.*—A mixture of *d*-equilenin (1 g.), ethylene glycol, 2·5 ml.), ethyl orthoformate (3·5 ml.), and *p*-toluenesulphonic acid ·085 mg.) was refluxed for 1 hr., poured into saturated $NaHCO_3$ aq. he precipitated solid was filtered, washed with water, dried and crystalzed from benzene-hexane to give light yellow needles (1·024 g., 80%), m.p. 75–176·5° (Found: C, 77·56; H, 7·33. $C_{20}H_{22}O_3$ requires: C, 77·39; I, 7·14%); IR (nujol) $\nu_{max.}$ 3436, 1623, 1600, 1570, 1477, 1176, 1161, 042, 820, 799 cm.$^{-1}$.

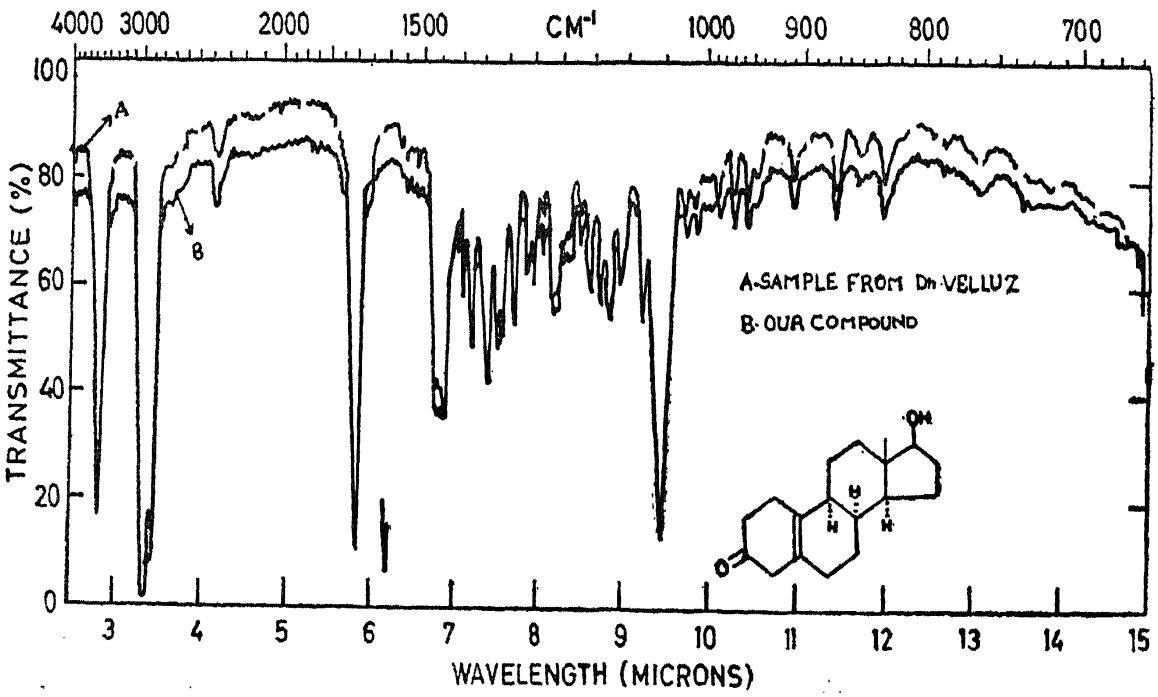
Hydrogenation of d-*equilenin ketal.*—*d*-Equilenin ketal (1 g.) was hydroenated, as described earlier, in 2·5% KOH aq. (135 ml.) using Raney ickel (W_5) at 100–120° and an initial pressure of 200 atm. The mixture as warmed with 2% KOH aq. and benzene and filtered. The filtrate was xtracted with benzene, and the aqueous layer acidified to give very little henolic material. The combined benzene extract was washed with water nd evaporated. The residue was dissolved in ether and extracted with Claisen alkali[39]. The alkaline extract was washed twice with ether and cidified with cold dil. HCl, warmed on a water-bath and then cooled. The precipitate was filtered, washed, and dried to give the phenolic material 291 mg., 31%), m.p. 190–199°. Crystallization from benzene gave *d*-8-sooestrone (180 mg.), m.p. 245–246°. Analytical sample, m.p. 247–248°, (reported 247–248°[40]) (Found: C, 80·15; H, 8·38. $C_{18}H_{22}O_2$ requires: C, 79·96; H, 8·20%). IR (CH_2Cl_2) was identical with that of the authentic sample. IDCC (10% ethyl acetate in chloroform) of the gum 49 mg.), obtained from the mother liquor, on a column (1·5 cm. diameter, 22 cm. length) of silica gel furnished three fractions: (A) gum (3 mg.); (B)

solid, which crystallized from benzene to give pure *d*-9-isooestrone (8 mg.), m.p. 200–200·5° (reported 200°[41]). (Found: C, 79·64; H, 8·60. $C_{18}H_{22}O_2$ requires: C, 79·96; H, 8·20%); IR (CH_2Cl_2) was identical with that of the authentic *dl*-9-isooestrone; (C) solid, which on crystallization from benzene gave pure *d*-8-isooestrone (7 mg.), m.p. 245–246°. Separation of the above isomers of oestrone by crystallization was less efficient.

d-8-*Isooestrone methyl ether.*—*d*-8-Isooestrone (250 mg.) was methylated using dimethyl sulphate (0·15 ml.) and anhydrous K_2CO_3 (1·5 g.) in acetone (50 ml.) as before. Crystallization from methanol afforded pure *d*-8-isooestrone methyl ether (205 mg., 78%), m.p. 81–82°. (Found: C, 79·48; H, 8·40. $C_{19}H_{24}O_2$ requires: C, 80·24; H, 8·51%). IR ($CHCl_3$) was identical with that of the *dl*-authentic sample.

d-17β—*Hydroxy*-8-*iso*-19-*norandrost*-5 (10)-*en*-3-*one* (*IX*).-*d*-8-Isooestrone methyl ether (200 mg.) in dry tetrahydrofuran (20 ml.) and *t*-butanol (20 ml.) was treated with lithium in liquid ammonia (40 ml.) and the crude dihydroenol ether was hydrolyzed with oxalic acid (260 mg.) in methanol (100 ml.) as described earlier for *dl*-(XI, *l*). The crude product on IDCC over a column of silica gel gave pure *d*-17 β-hydroxy-8-iso-19-norandrost-5 (10)-en-3-one (IX), (70 mg., 37%), m.p. 187–190°; mixture m.p. with the sample supplied by Dr. Velluz was not depressed. IR (nujol) Fig. 4 was identical with that of the latter.

Isomerization of d-β, γ-*unsaturated keto alcohol* (*IX*) to d-8-*iso*-10-*iso*-19-*nortestosterone* (*X*).—Isomerization of *d*-(IX) (25 mg.) was carried out



as described earlier for *dl*-(IX), and the IDCC of the product over a column of silica gel furnished four fractions: (A) a gum (1 mg.); (B) and (C), a solid which on two crystallizations from ether-hexane afforded the pure *d*-(X) (2 mg., 8%), m.p. 167–170°, UV $\lambda_{max.}$ 242·5 mμ; mixture m.p. with the sample obtained from Dr. Bucourt and Dr. Nomine was not depressed; mass spectrum: M^+ ion at m/e 274. (D) a crystalline solid (12 mg.) which was found to be pure *d*-β, γ-unsaturated keto alcohol (IX).

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