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SYNTHESES OF DERIVATIVES OF OESTRANE AND 19-NORSTEROIDS FROM 6-METHOXY-TETRALONE AND 6-HYDROXYTETRALONE

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Abstract—The corresponding derivatives of $\Delta^{1,3,5(10),9,(11)}$-8,14-seco-D-homo-oestratetraen-3-ol-14,17a-dione(VII, VIII, IX) have been obtained by the condensation of 3-methoxy-, 3-hydroxy-, and 3-tetrahydropyranyloxy-1-vinyltetralols (IV, V, VI) with methyldihydroresorcinol. The diketones VIII and IX cyclize to form $\Delta^{1,3,5(10),8,14}$-D-homo-oestrapentaen-3-ol-17a-one (XIII), and the diketone (VII) may be converted, according to conditions, into 3-methoxy-$\Delta^{1,3,5(10),8,14}$-D-homo-oestrapentaen-17a-one (X), 3-methoxy-$\Delta^{1,3,5(10),9(11)}$-D-homo-oestratetraen-14-ol-17a-one (XIV), and D-homoequilenin (XI). Hydrogenation of the ketones X and XIII leads to the dihydroketones XV and XVI with a *trans* junction of the *C* and *D* rings. Reduction or hydrogenation of XV gives the methyl ethers of D-homo-oestrone and 8-iso-D-homo-oestrone XIX and XVII which have been converted into the methyl ethers of (±)-oestrone and 8-iso-oestrone (XX and XXI). 19-Nor-D-homotestosterone (XXV) and its methyl and ethyl analogues, which possess anabolic activity, have been obtained by a series of reactions from the ketones X and XV.

IT IS well known that 19-norsteroids obtained from oestrone have acquired great importance, since some of them have a greater physiological activity than natural hormones with a 19-CH_3 group. Thus, 19-norprogesterone is 4–5 times more active than progesterone,[1] 19-nordeoxycorticosterone is 2–4 time more active than deoxycorticosterone,[2] and 19-nortestosterone and its derivatives have found employment in medicine as anabolic agents.[3] In addition, there are indications that D-homosteroids also possess hormone activity.[4] These facts induced us to undertake an investigation of the complete synthesis of derivatives of oestrane and D-homo-oestrane.

The starting materials were 6-methoxytetralone (I) and 6-hydroxytetralone (II), which are readily obtained from nerolin and β-naphthol, respectively. The reaction of the two ketones (I and II), and the pyranyl derivative of 6-hydroxytetralone (III), with vinylmagnesium bromide yielded the corresponding vinyl carbinols (IV, V, and VI). In the presence of alkaline agents, all these carbinols react with methyldihydroresorcinol, giving the tricyclic diketones (VII, VIII and IX). This interesting reaction was studied in detail for vinyl carbinol (IV). It was found that the use of caustic

[1] J. S. Mills, H. J. Ringold and C. Djerassi, *J. Amer. Chem. Soc.* **80**, 6118 (1958); C. Djerassi, L. Miramontes, G. Rosenkranz, *J. Amer. Chem. Soc.* **75**, 4440 (1953).

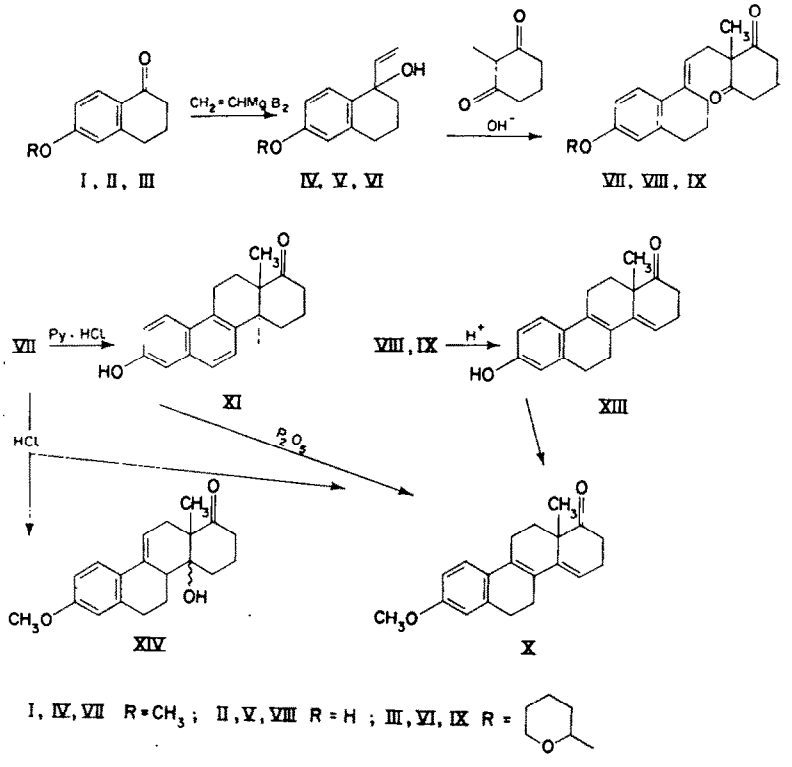
[2] A. Sandoval, L. Miramontes, G. Rosenkranz, C. Djerassi, F. Sondheimer, *J. Amer. Chem. Soc.* **75**, 4117 (1953).

[3] T. Bersin, *Biochemie der Hormone*, 182 (1959); F. B. Colton, L. N. Nysted, B. Riegel, A. L. Raymond, *J. Amer. Chem. Soc.* **79**, 1123 (1957).

[4] A. J. Birch, H. Smith, *J. Chem. Soc.*, 4090 (1956); L. Ruzicka, N. Wahba, P. T. Herzig, H. Heusser, *Chem. Ber.*, **85**, 491 (1952).

potash or potassium t-butoxide gives 18–19 per cent of the diketone (VII), while the use of benzyltrimethylammonium hydroxide (Triton B) enabled the yield to be raised to 50 per cent. With the vinyl carbinol (VI) the best yield was 42 per cent, and with the carbinol (V) only 21 per cent.

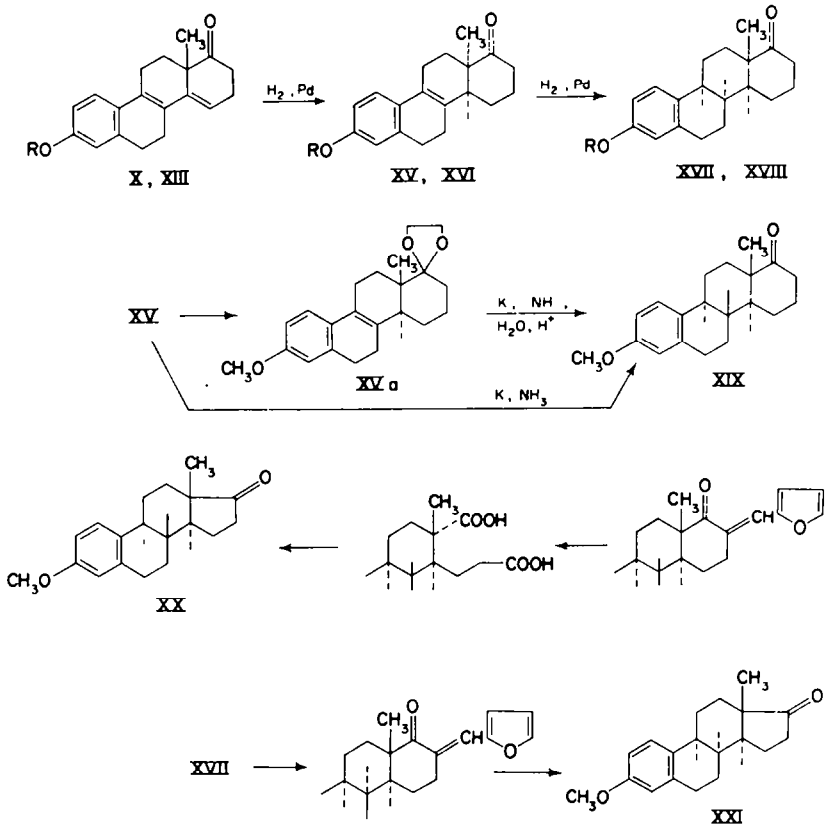
The diketones (VII, VIII and IX) readily undergo cyclization under the influence of various acidic agents. Thus, the diketone (VII), on heating with a small amount of phosphoric anhydride, cyclizes with a yield of 90 per cent to form the tetracyclic steroid ketone (X), which subsequently became the main intermediate in the synthesis of the derivatives of D-homo-oestrane and oestrane. On heating the diketone (VII) with pyridine hydrochloride, three reactions take place successively: cyclization, demethylation, and isomerization, leading to a 55 per cent yield of (±)-D-homo-equilenin (XI), which is readily converted[5] into (±)-equilenin (XII).



The diketones (VIII and IX) cyclize with exceptional facility even under the influence of dilute mineral acids in the cold, giving in both cases, with almost quantitative yields, $\Delta^{1,3,5(10),8,14}$-D-homo-oestrapentaen-3-ol-17-one (XIII), which on methylation is converted into the ketone (X). Cyclization of the diketone (VII) under these conditions leads to two products—the ketone (X) and the tetracyclic ketol (XIV). The presence of the $\Delta^{9(11)}$ double bond in the diketones (VII–IX) and the ketone (XIV) in confirmed by the value of λ_{max} (265–267 mμ, in alcohol), which is characteristic for a tri-substituted double bond conjugated with a benzene ring. A $\Delta^{8(9)}$ position of the double

[5] Chang Chin, *Acta chim. sinica* (2), **21**, 190 (1955).

bond is excluded, since in this case λ_{max} will fall within range 275–277 mμ, as has been shown on the basis of numerous examples by Robins and Walker[6] and has been confirmed by us.[7] The heteroannular position of the double bonds in the ketones (X and XIII) is shown by hydrogenation, leading (see below) to $\Delta^{8(9)}$ compounds with λ_{max} 275–277 mμ, and also by further conversions.



X, XV, XVII R = CH_3 ; XIII, XVI, XVIII R = H

On selective hydrogenation of the ketone (X) in the presence of palladium on calcium carbonate, the addition of a molcule of hydrogen takes place from the less hindered side, and the ketone (XV, λ_{max} 276 mμ) with a *trans* junction of the *C* and *D* rings is formed with a yield of 75 per cent. Analogous hydrogenation of the ketone (XIII) leads to the *trans* ketone (XVI, λ_{max}277 mμ). Exhaustive hydrogenation of the ketone (X) gives the methyl ether of 8-iso-D-homo-oestrone (XVII). Hydrogenation of the ketone (XIII) under the same conditions leads to 8-iso-D-homo-oestrane (XVIII), which is converted by methylation into the ketone (XVIII).

Two routes are extremely convenient for passing from the ketone (XV) to the methyl ether of D-homo-oestrane (XIX). By the first route, the ethylene ketal of the ketone XV (XVa) is reduced by potassium in liquid ammonia to the ethylene ketal of XIX (XIXa), which gives the ketone (XIX) on hydrolysis, the overall yield (calculated

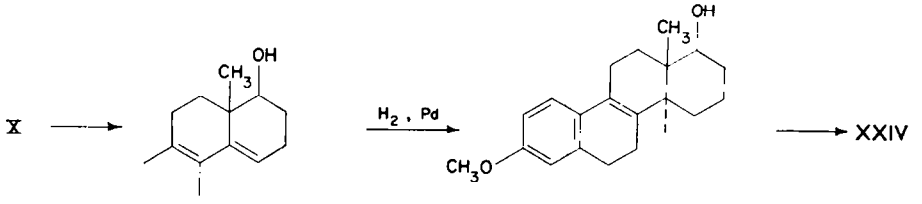
[6] P. A. Robins, J. Walker, *J. Chem. Soc.*, 3249, 3260 (1956).

[7] I. N. Nazarov, I. V. Torgov, and G. N. Verkholetova, *Dokl. Akad. Nauk SSSR* **112**, 1067 (1957).

on XV) amounting to 35 per cent. By the second route, the ketone (XV) is reduced directly with potassium in liquid ammonia; the overall yield on XV reaches 32 per cent.

By Johnson's method,[8] the ketone (XIX) yielded[9] the methyl ether of (±)-oestrane (XX) with an overall yield of 50 per cent. In a similar manner, and with almost the same yield, the ketone (XVII) yielded[10] the methyl ether of 8-iso-oestrane (XXI).

The synthesis of 19-norsteroids was also carried out from the readily available tetracyclic ketones (X and XV). Reduction of the ketone (X) gives an 88 per cent yield of the carbinol (XXII), which is converted by selective hydrogenation into the dihydro carbinol (XXIII). Reduction of the latter with potassium, lithium, and alcohol in liquid ammonia yields the carbinol (XXIV), hydrolysis of which in the presence of



XXII XXIII

mineral acid gives 19-nor-D-homotestosterone (XXV). Hydrolysis of the carbinol (XXIV) with oxalic acid leads to the isomeric ketone (XXVa), in which the double bond is not conjugated with the keto group. Condensation of the ketone (XV) with methylmagnesium iodide gives a mixture of the carbinol (XXVI) and its epimer (XXVIa). Reduction of the carbinol (XXVI) under the conditions of the reduction of the carbinol (XXIII), with subsequent hydrolysis, gives 17a-methyl-19-nor-D-homotestosterone (XXVII).

Ethinylation of the ketone (XV) yields the ethinyl carbinol (XXVIII), and hydrogenation of the latter gives the 17a-ethyl carbinol (XXIX). The latter is also formed by the Grignard reaction from the ketone (XV), together with the 17a-epimer (XXIXa). Reduction of the carbinol (XXIX) by Birch's method (with subsequent hydrolysis) gives 17a-ethyl-19-nor-D-homotestosterone (XXX). The β-configuration of the OH group in the carbinol (XXII) is assumed on the basis of analogies in the D-homosteroid series.[11] The same configuration of the OH group is also assumed for the carbinol (XXVII), since it possesses high physiological activity, which is characteristic for 17-substituted testosterones and D-homotestosterones. The 17-isotestosterones and 17a-iso-D-homotestosterones are physiologically inactive.[11,12]

Physiological tests have shown that 19-nor-D-homotestosterone (XXV) and its β-phenylpropionate (XXVb) and the carbinols (XXIV) and XXVII possess considerable anabolic activity, that of the compounds XXIV and XXV being higher than for testosterone propionate. The highest values of the index (ratio of the anabolic and androgenic activities) were shown by the conpounds XXVb and XXVII (11–15 and 6–7 respectively).

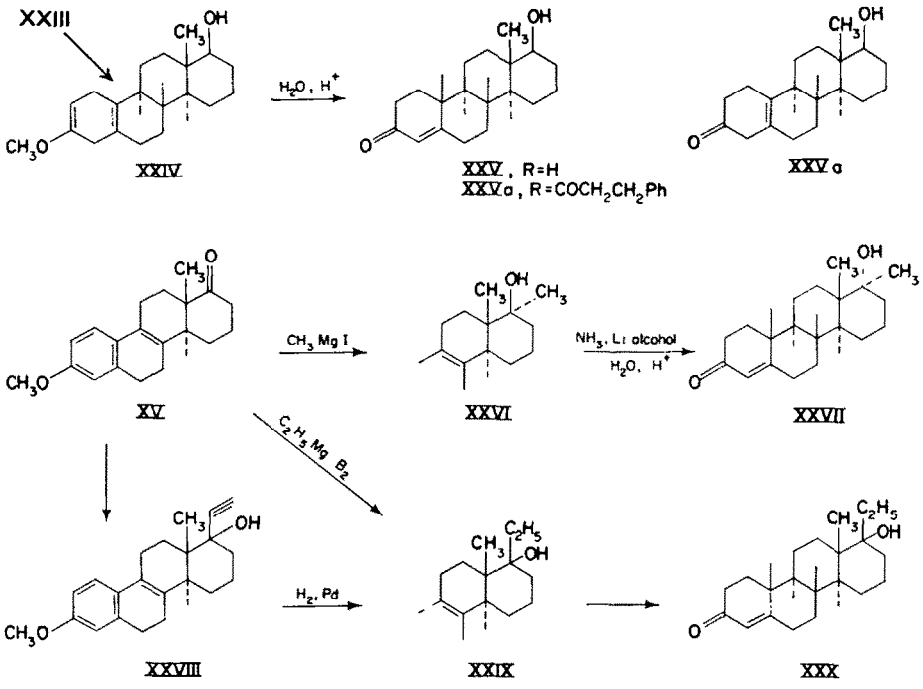
[8] W. S. Johnson, D. K. Banerjee. *J. Amer. Chem. Soc.* **74**, 2832 (1952).

[9] S. N. Ananchenko, V. N. Leonov, A. V. Plaronova, and I. V. Torgov, *Dokl. Akad. Nauk SSSR* **135**, 73 (1960).

[10] V. N. Leonov, S. N. Ananchenko, and I. V. Torgov, *Dokl. Akad. Nauk SSSR* **138**, 384 (1961).

[11] R. O. Clinton, H. C. Neumann, A. J. Manson, S. C. Laskovski, R. G. Christiansen, *J. Amer. Soc.* **79**, 6475 (1957); **80**, 3395 (1958).

[12] C. H. Robinson, O. Gnoj, E. P. Oliveto, *J. Org. Chem.* **25**, 2247 (1961).



EXPERIMENTAL

All substances were dried in a vacuum of 0·5 — 1 mm over phosphoric anhydride at 80° before analysis.

For identification, testing the homogeneity of the materials and following the course of the reactions, non-bound thin-layer chromatography[13] was employed, using alumina of II–III activity (according to Brockman) with a layer thickness of 1 mm; the spots were developed by UV light or iodine vapour. The IR spectra were taken on an IKS-14 double-beam spectrophotometer, and the UV spectra on a SF-4 spectrophotometer.

The 6-methoxytetralone (I) was obtained by the oxidation of 6-methoxytetralin with chromic acid in acetone;[14] yield 61%, m.p. 78° (from methanol). The 6-hydroxytetralin was obtained by the hydrogenation of β-naphthol with Raney nickel by Stork's method[15] with a yield of 75–80%. m.p. 62° (from pet ether); acetate of 6-hydroxytetralin (obtained in almost quantitative yield by boiling the 6-hydroxytetralin with a 4-fold amount of acetic anhydride in the presence of pyridine): b.p. 158° at 14 mm; n_D^{20} 1·5310.

Preparation of 6-acetoxytetralone and 6-hydroxytetralone (II)

A solution of 200 g chromic anhydride in 40 ml water and 600 ml acetic acid was added to a solution of 200 g 6-acetoxytetralin in 800 ml glacial acetic acid and 150 ml acetic anhydride at 10–15° during 3·5 hr. The mixture was stirred for 1 hr at 15° and 4 hr at 20° and left overnight.

On the next day, it was stirred for 3 hr at 50°, the greater part of the acetic acid was removed *in vacuo* on the water bath, and the residue was mixed with 500 ml water and extracted with ether. The extract was neutralized with sodium carbonate solution and washed with water, and then distilled yielding 79 g of a first fraction consisting mainly of the initial acetoxytetralin and 89 g (41·5% of theory) of 6-acetoxytetralone, b.p. 152–154° at 1 mm, which crystallized on standing. After recrystallization from pet. ether, 86 g ketone m.p. 62·5° was obtained. (Found: C, 70·56; H, 5·92. Calc. for $C_{12}H_{12}O_3$: C, 70·57; H, 5·92%).

[13] E. A. Mistryukov, *Coll. Czech. Chem. Comm.* **26**, 2071 (1961).

[14] S. N. Ananchenko, A. V. Platonova, V. N. Leonov, and I. V. Torgov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* 1074 (1961).

[15] G. Stork, *J. Amer. Chem. Soc.* **69**, 577 (1947).

In other experiments, a polymorphic modification of 6-acetoxytetralone, m.p. 42° (from pet ether) was obtained. Both modifications on chromatography on plates, gives spots with the same R_f; on saponification they form the same 6-hydroxytetralone.

On oxidizing the first fraction in a manner similar to that described above, 6-acetoxytetralone was obtained (yield, 35%), the total yield of the ketone being 54%. It must be noted that the oxidation of 6-acetoxytetralin with chromic acid in acetone (under similar conditions to the oxidation of 6-methoxytetralin) does not take place at all and the initial acetate is recovered unchanged.

Preparation of 6-*hydroxytetralone* (II).

A solution of 10 g acetoxytetralone and 15 g potassium hydroxide in 250 ml methanol was boiled for 30 min and poured into 5 times the volume of water. The solution was acidified to pH 1 and extracted with ether. The extract was washed with a solution of sodium bicarbonate and with water, and dried with sodium sulphate, yielding after removing the solvent, 8 g (100% of theory) crystals m.p. 120–121°. Recrystallization from water with the addition of sodium hydrosulphite gave a product m.p. 121–121·5°. UV spectrum: $\lambda_{max}^{EtOH} m\mu$ 225, 278 (log ϵ 4·11, 3·98). (Found: C, 74·07; H, 6·22. Calc. for $C_{10}H_{10}O_2$: C, 74·05; H, 6·21%).

In other experiments, a polymorphic modification, m.p. 153° was obtained. On chromatography on plates the two forms give spots with the same R_f; on methylation they form thesame 6-methoxytetralone m.p. 80°.

Preparation of 6-*tetrahydropyranyloxytetralone* (III)

Acetyl chloride (19 ml) and then 121 g 6-hydroxytetralone were added to a mixture of 1 l. benzene, 16 ml absolute methanol, and 25 ml absolute pyridine; a solution of 310 g dihydropyran in 1 l. benzene was run in, and the mixture allowed to stand for 1 week. Benzene (1 l.) was added to the reaction mixture and it was neutralized by shaking with conc sodium carbonate solution and then with water. After evaporation *in vacuo*, the crystalline residue (183 g) was recrystallized from methanol to yield 179 g ketone (III) as pinkish crystals m.p. 84–86°. UV spectrum: $\lambda_{max}^{EtOH} m\mu$ 221, 273 (log ϵ 4·13. 4·21). (Found: C, 73·48; H, 7·31. Calc. for $C_{15}H_{18}O_3$: C, 73·14; H, 7·37%).

Preparation of the vinyl carbinols (IV, V and VI)

1-Vinyl-6-methoxytetralol (IV) was obtained from 6-methoxytetralone (I) and vinylmagnesium bromide in tetrahydrofuran.[7] The carbinol (IV), a viscous liquid with n_D^{20} 1·5620, was found to be sufficiently pure for the following reaction. 1-Vinyltetralin-1,6-diol (V) was similarly obtained from 6-hydroxytetralone (II) and vinylmagnesium bromide in the form of a crystalline mass; on recrystallization it suffered partial change, and the product was therefore only washed with ether cooled to −30°, yield about 70%. The product formed a white crystalline powder decomposing at about 140° (turns brown) and m.p. 210–215°. IR spectrum: ν_{max}^{nujol} cm^{-1} 1602, 1607 (C=C), 3245 (phenol), 3448 (OH). UV spectrum: λ_{max}^{EtOH} 219, 276 (log ϵ 3·94, 3·22). (Found: C, 75·65; H, 7·50. Calc. for $C_{12}H_{14}O_2$: C, 75·76; H, 7·42%).

1-Vinyl-6-tetrahydropyranyloxytetralin (VI) was obtained from the ketone (III) and vinylmagnesium bromide. The reaction mixture was poured into a mixture of ice and ammonium chloride and extracted, and the extract was evaporated *in vacuo* (not above 30°), towards the end at 1 mm. The carbinal (VI) formed a viscous brownish liquid with n_D^{20} 1·5480.

Condensation of the carbinol (IV) *with methyldihydroresorcinol*

An alcoholic solution of Triton B (from 6 g benzyltrimethylammonium chloride, 1·8 g potassium hydroxide, and 25 ml alcohol) and 25 ml *p*-xylene was stirred in a flask fitted with a reflux condenser, water-separator, and stirrer, and the alcohol was distilled off through the water-separator on the water bath. To the catalyst was added 10 ml *p*-xylene and 28·6 g methyldihydroresorcinol. the mixture heated to boiling, and a solution of the freshly prepared carbinol (IV) in 200 ml *p*-xylene added with stirring during 1·5 hr. The mixture was boiled for 2 hr (bath temp 150–160°) and cooled, 300 ml ether added, and the methyldihydroresorcinol which had not reacted (8·5 g) filtered off. The ethereal solution was washed with 5% potassium hydroxide and water, and dried with magnesium sulphate. After filtration, evaporation and crystallization 35 g (50% of theory) 3-methoxy-$\Delta^{1,3,5(10),9(11)}$-8,14-seco-D-homo-oestratetraen-14,17a-dione (VII), m.p. 91–92° (from alcohol) was

obtained. IR spectrum: $\nu_{max}^{CHCl_3}$ cm^{-1} 1720, 1694 (cyclic β-diketone), 1601. UV spectrum: λ_{max}^{EtOH} mμ 267 (log ϵ 4·18). (Found: C, 76·97; H, 7·78. Calc. for $C_{20}H_{24}O_2$. C, 76·89; H, 7·74%).

Condensation of the carbinol (V) *with methyldihydroresorcinol*

The condensation was carried out in a manner similar to the condensation of the carbinol (IV) except that the unreacted methyldihydroresorinol was washed out with a saturated solution of

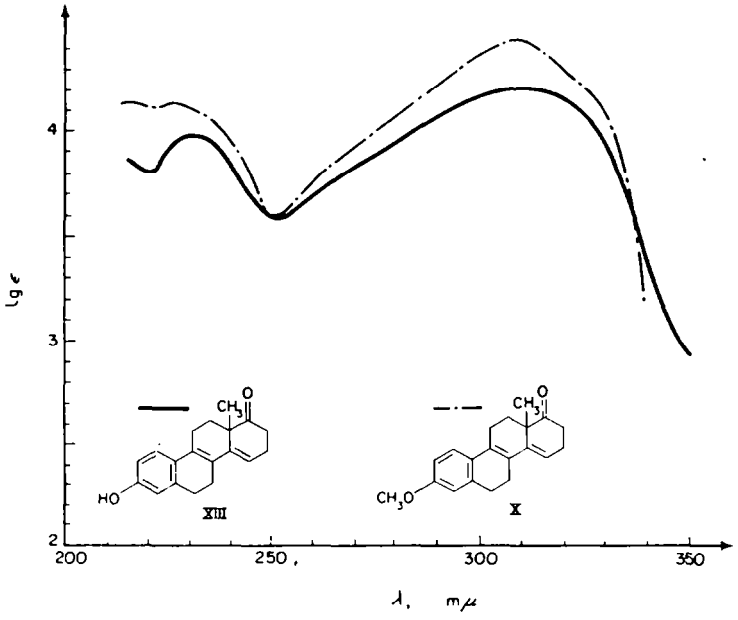


FIG. 1. Curves of the UV spectra (in alcohol) of the ketophenol (XIII) and its methyl ether (X).

sodium bicarbonate. The crude carbinol (from 10·5 g 6-hydroxytetralone) yielded (after crystallization from methanol and evaporation of the mother liquors) 4·2 g (21% of theory) $\Delta^{1,3,5(10),9(11)}$-8,14-seco-D-homo-oestratetraen-3-ol-14,17a-dione (VIII), m.p. 212°–213°. IR spectrum: ν_{max}^{nujol} cm^{-1} 1686 (cyclic β-diketone), 1606, 3262 (OH); UV spectrum: λ_{max}^{EtOH} mμ 262 (log ϵ 4·13). (Found: C,76·47-H, 7·43. Calc. for $C_{19}H_{22}O_2$: C, 76·48; H. 7·43%).

Condensation of the carbinol (VI) *with methyldihydroresorcinol*

The condensation was carried out in a manner similar to the condensation of the carbinol (IV); 42 g carbinol (VI) and 28 g methyldihydroresorcinol yielded 27·1 g (42%, with respect to the carbinol) 3-tetrahydropyranyloxy-$\Delta^{1,3,5(10),9(11)}$-8,14-seco-D-homo-oestratetraene-14,17a-dione (IX), white crystals, m.p. 106–107° (from methanol). IR spectrum: ν_{max}^{nujol} cm^{-1} 1728, 1694 (cyclic β-diketone), 1606. UV spectrum: λ_{max}^{EtOH} mμ 266 (log ϵ 4·26). (Found: C, 75·46; H, 7·96. Calc. for $C_{24}H_{30}O$: C, 75·36; H, 7·91%); 13·5 g of methyldihydroresorcinol was recovered unchanged.

Cyclization of the diketones IX and VIII

Hydrochloric acid (18%, 50 ml) was added to a solution of 25 g diketone (IX) in 150 ml tetrahydrofuran, and the mixture left for 1 day, the homogeneous solution gradually becoming orange. The solution was evaporated *in vacuo*, the residue extracted with ether, and the extract neutralized with sodium carbonate solution, washed with water, and evaporated, yield 18·1 g (98% of theory) $\Delta^{1,3,5(10),8,14}$-D-homo-oestrapentaen-3-ol-17a-one (XIII), orange plates, m.p. 208–209° (from methanol). The pure product m.p. 209–210°. IR spectrum: ν_{max}^{nujol} cm^{-1} 1690 (C=O), 1620, 1600 (C=C=$\varnothing$). UV spectrum: λ_{max}^{EtOH} mμ 231, 310 (log ϵ 3·98, 4·19). (Found: C, 81·68; H, 7·22. Calc. for $C_{19}H_{20}O_2$: C, 81·39; H, 7·19%). Similar cyclization of the diketone (VIII) gave the ketone (XIII), yield 98%, m.p. 206–208°.

Cyclization of the diketone (VII)

a. *With phosphoric anhydride.* A mixture of 21·3 g diketone (VII) and 0·21 g phosphoric anhydride was heated for 7 min at 115° and 100 mm. The reaction product was treated with sodium carbonate solution and extracted with chloroform, yielding 19 g (94% of theory) 3-methoxy-$\Delta^{1,3,5(10),8,14}$-D-homooestrapentaenone (X), m.p. 135–136° (from ethyl acetate). IR spectrum: $\nu_{max}^{CHCl_3}$ cm^{-1} 1699 (C=O), 1598 (C=C—Ø). UV spectrum: λ_{max}^{EtOH} mμ 230, 308 (log ε 3·18; 3·49). (Found: C, 81·67; H, 7·45. Calc. for $C_{20}H_{22}O_2$. C, 81·60; H, 7·53%).

b. *With* p-*toluenesulphonic acid.* A solution of 6·5 g diketone (VII) and 0·3 g *p*-toluenesulphonic acid in 100 ml benzene was boiled for 10 min. The benzene solution was washed with sodium carbonate solution and filtered, the solvent was distilled off and the residue crystallized from ethyl

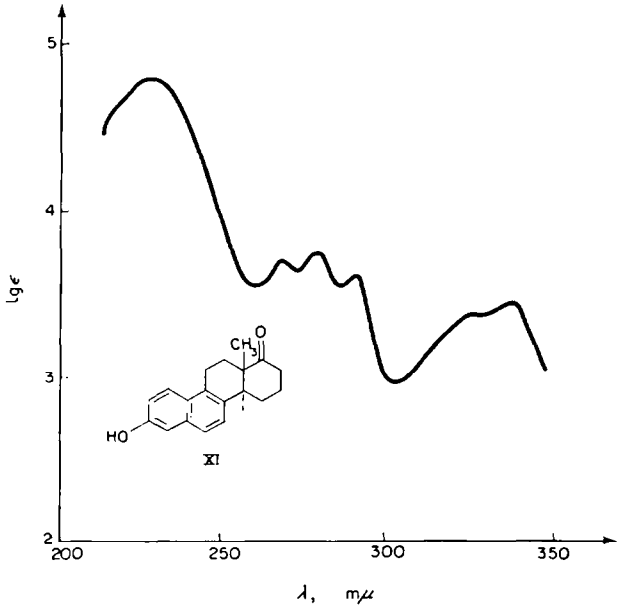


FIG. 2. Curve of the UV spectrum (in alcohol) of D-homoequilenin (XI).

acetate, yielding 4·5 g ketone (X) m.p. 139–140° and 0·5 g m.p. 134–135°. The total yield amounted to 82% of theory.

c. *With pyridine hydrochloride.* A mixture of 0·4 g diketone (VII) and 10 g dry freshly prepared pyridine hydrochloride was heated for 40 min at 210–215° in an atmosphere of nitrogen. After cooling, the reaction product was stirred with 200 ml 5% potassium hydroxide; the mixture extracted with ether and the aqueous solution acidified to congo red, yielding 230 mg D-homoequilenin (XI), m.p. 203–205°, and pure product m.p. 234–235° after crystallization from alcohol. UV spectrum: $\lambda_{max}^{Et\,OH}$ mμ 230, 270, 281, 292, 326, 339 (log ε 4·80, 3·68, 3·74, 3·59, 3·33, 3·39). A mixed m.p. with a known sample* gave no depression.

d. *With dilute hydrochloric acid.* A solution of 5 g diketone (VII) in 40 ml tetrahydrofuran was mixed with 10 ml 2 N HCl and allowed to stand 2 days, and then neutralized with a saturated solution of sodium bicarbonate. The organic layer was separated and evaporated, and the yellow residue was crystallized from ethyl acetate. By repeated recrystallization, it was possible to isolate 1 g of the ketone (X), m.p. 135–137° and 0·7 g 3-methoxy-$\Delta^{1,3,5(10),9(11)}$-D-homo-oestratetraen-14-ol-17a-one (XIV), m.p. 213–215°. The pure ketone has m.p. 217–218° (from ethyl acetate). IR spectrum: ν_{max}^{nujol} cm^{-1} 1682 (C=O); 3445(OH). UV spectrum: λ_{max}^{EtOH} mμ 265, 300 (log ε 4·34, 3·58). (Found: C, 77·06; H, 7·99. Calc. for $C_{20}H_{24}O_3$. C, 76·89; H, 7·74%. Found by Zerevitinov's method: 0·32% active H, calc. 0·32%).

* Kindly provided by Professor Chang Chin of Pekin.

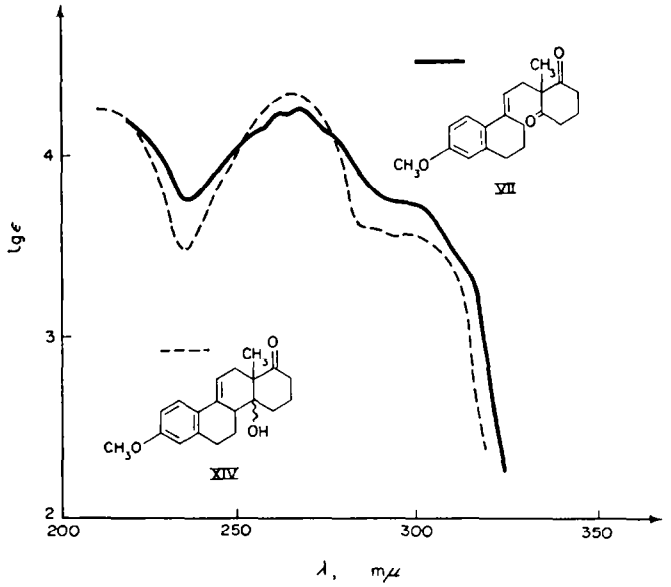


FIG. 3. Curves of the UV spectra (in alcohol) of the diketone (VII) and the ketol (XIV).

Selective hydrogenation of the ketone (XIII)

Ketone (XIII, 1·8g) in 20 ml tetrahydrofuran was hydrogenated in the presence of 0·5 g palladium on calcium carbonate until 1 mole of hydrogen had been absorbed. After filtration, evaporation

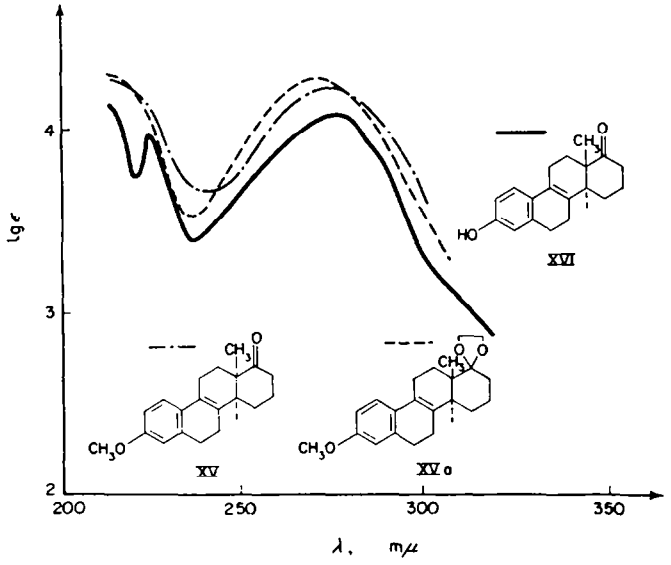


FIG. 4. Curves of the UV spectra (in alcohol) of the ketophenol (XVI), and its methyl ether (XV) and ketal (XVa).

and crystallization from methanol, 1·45 g $\Delta^{1,3,5(10),8}$-D-homo-oestratetraen-3-ol-17a-one (XVI) was obtained in the form of white microcrystals m.p. 214–215° (from methanol). UV spectrum: λ_{max}^{EtOH} mμ 277, (log ε 4·04). (Found: C, 80·86; H, 7·93. Calc. for $C_{19}H_{22}O_2$: C, 80·81; H, 7·85%).

In other similar hydrogenation experiments, sometimes, in addition to the ketone (XVI), the product of its further hydrogenation—8-iso-D-homo-oestrone (XVII), m.p. 262–263° (from ethyl acetate)

could be isolated (in small yield). UV spectrum: λ_{max}^{EtOH} mμ 228, 280, 286 (log ε 4·13, 3·63, 3·55). (Found: C, 80·26; H, 8·57. Calc. for $C_{19}H_{24}O_2$. C, 80·24; H, 8·51%).

Acetylation of the ketol (XVI) using acetic anhydride in pyridine (boiling, 4 hr) yielded the acetate, m.p. 155–156° (from methanol). UV spectrum: λ_{max}^{EtOH} mμ 220, 272 (log ε 4·23. 4·18). (Found: C, 77·85; H, 7·61. Calc. for $C_{21}H_{24}O_3$. C, 77·75; H, 7·46%).

Selective hydrogenation of the ketone (X)

The hydrogenation was carried out in a manner similar to the hydrogenation of ketone (XIII). 3-Methoxy-$\Delta^{1,3,5(10),8}$-D-homooestratetraen-17a-one (XV)[9] m.p. 125–127° (from alcohol-ethyl acetate) was obtained in a yield of 75–81%. UV spectrum: λ_{max}^{EtOH} mμ 276 (log ε 4·21). (Found: C, 81·06; H, 8·33; Calc. for $C_{20}H_{24}O_2$. C, 81·04; H, 8·16%).

Exhaustive hydrogenation of the ketone (X)

Ketone (X 2·5 g) in 24 ml benzene and 12 ml alcohol was hydrogenated in the presence of 0·6 g 30% palladium on strontium carbonate until 2 moles of hydrogen had been absorbed. After crystallization from ethyl acetate, 1·43 g (57% of theory) methyl ether of 8-iso-D-homooestrone (XVII) m.p. 123–125° was obtained. The pure ketone has m.p. 128–128·5°. UV spectrum: λ_{max}^{EtOH} mμ 279, 286 (log ε 3·32, 3·29). (Found: C, 80·55; H, 8·77. Calc. for $C_{20}H_{26}O_2$. C, 80·49; H, 8·78%).

Methylation of the ketols (XIII) and (XVIII).

Dimethyl sulphate (3 ml) was added to a solution of 200 mg ketol (XIII) and 3 g potassium hydroxide in 10 ml methanol and the mixture boiled for 5 hr and poured an eight-fold excess water. The reaction products were extracted with ether, the extract washed with water and evaporated, and the residue crystallized from alcohol, yielding 100 mg ketone (X) m.p. 138–139°, and giving no depression of mixed m.p. with the sample described above.

Similarly, 200 mg ketol (XVIII) yielded 180 mg ketone (XVII) m.p. 126–127°, and no depression of mixed m.p. with the sample described above.

Production of the ketal of the ketone (XV).

A mixture of 11·5 g ketone (XV), 85 ml ethylene glycol, and 0·46 g *p*-toluenesulphonic acid in 575 ml toluene was boiled with removal of the water and toluene by distillation after 5 hr. After cooling, the mixture was washed with sodium carbonate solution, the solvent distilled off *in vacuo* and the residue crystallized from ethyl acetate, yielding 10·2 g (77% of theory) ketal (XVa) m.p. 145–146°. UV spectrum: λ_{max}^{EtOH} mμ 274 (log ε 4·24). (Found: C, 77·73; H, 8·32. Calc. for $C_{22}H_{28}O_3$: C, 77·61; H, 8·29%).

Preparation of the methyl ether of (±)-D-*homo-oestrone* (XIX) *and the methyl ether of* (±)-*oestrone*

a. Potassium (4·2 g) was added during 3 min to a solution of 2 g ketal (XVa) in 50 ml absolute tetrahydrofuran, 300 ml absolute ether, and 300 ml liquid ammonia, cooled to −40°, and the mixture stirred for 40 min after which time the blue colour disappeared; 11 g dry ammonium chloride was added to the reaction mixture, the ammonia allowed to evaporate, and 400 ml water added in drops at 0°. The organic layer was separated, and the aqueous layer was extracted twice with ether. The combined extract was neutralized, washed with 20 ml water, and dried with sodium sulphate. After filtration, removal of the solvent, and crystallization of the residue from ethyl acetate, yielding 1·24 g (62% of theory) ketal of XIX m.p. 136–138°, giving no depression of mixed m.p. with a known sample.[9]

Hydrolysis of the ketal by a known method[9] yielded the methyl ether of (±)-homo-oestrone (XIX), m.p. 162–163° (from ethyl acetate). UV spectrum: λ_{max}^{EtOH} mμ 278 (log ε 3·35). (Found: C, 80·45; H, 8·79. Calc. for $C_{20}H_{26}O_2$: C, 80·49; H, 8·78%).

b. Potassium (4·7 g) was added during 1 hr to a solution of 3 g ketone (XV) in 200 ml absolute tetrahydrofuran and 300 ml liquid ammonia cooled to −70°, the mixture was stirred for 2 hr, 9 g ammonium chloride added, and the product isolated as in the preceding experiment. After crystallization from alcohol, 1·26 g (42% of theory) ketone (XIX) m.p. 152–157° was obtained. Recrystallization gave a product with m.p. 158–160°, giving no depression of mixed m.p. with the previous sample.

By Johnson's method,[8] the ketone (XIX) yielded[9] the methyl ester of (±)-oestrone (XX), identical in all respects with Johnson's sample.

Reduction of the ketone (X).

A solution of 10 g ketone (X) in 50 ml absolute tetrahydrofuran was added in drops during 1 hr to a stirred suspension of 1 g lithium aluminium hydride in 10 ml tetrahydrofuran, the mixture was then stirred for a further 1 hr and decomposed, 10 ml ethyl acetate, 70 ml water, and 5 ml hydrochloric acid being added successively. The aqueous layer was extracted with ether, the extract combined with the organic layer and dried with magnesium sulphate. After filtration and evaporation, the residual yellow oil was crystallized by trituration with alcohol, and 8·9 g (88% of theory) 3-methoxy-$\Delta^{1,3,5(10),8,14}$-D-homo-oestrapentaen-17a-ol (XXII) m.p. 115–117° (from alcohol) was obtained. UV spectrum: λ_{max}^{EtOH} mμ 232·5, 307 (log ϵ 4·16, 4·48). (Found: C, 80·72; H, 8·08. Calc. for $C_{20}H_{24}O_2$. C, 81·04; H, 8·16%).

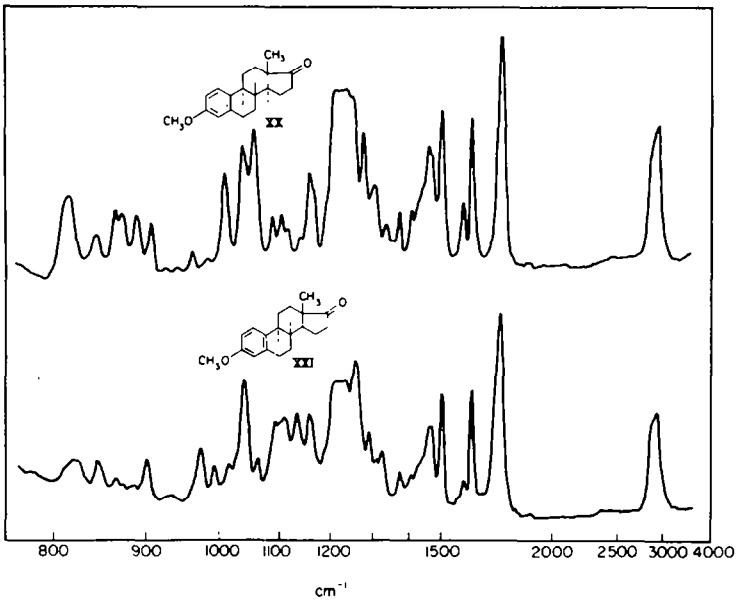


FIG. 5. Curves of the IR spectra (in chloroform) of the methyl ether of (±)-oestrone (XX) and its 8-epimer (XXI).

Acetylation of the carbinol (XXII) with acetic anhydride in pyridine (20°, 12 hr) yielded 70% acetate m.p. 172–174° (from ethyl acetate). (Found: C, 78·04; H, 7·79. Calc. for $C_{22}H_{26}O_3$. C, 78·07; H, 7·74%).

Hydrogenation of the carbinol (XXII).

Carbinol (XXII, 5·2 g) in 50 ml absolute tetrahydrofuran was hydrogenated in the presence of 0·3 g 10% palladium on calcium carbonate until 1 mole hydrogen had been absorbed. The solution was filtered, the filtrate evaporated, and the residue crystallized by trituration with alcohol, yielding 4·6 g (88% of theory) 3-methoxy-$\Delta^{1,3,5(10),8}$-D-homo-oestratetraen-17a-ol (XXIII) m.p. 116–117° (from alcohol). UV spectrum: λ_{max}^{EtOH} mμ 274 (log ϵ 4·21). (Found: C, 80·35; H, 8·97. Calc. for $C_{20}H_{26}O_2$: C, 80·49; H, 8·78%).

The acetate (obtained in a manner similar to the acetate of XXII) had m.p. 154–155° (from alcohol). (Found: C, 77·43; H, 8·31. Calc. for $C_{22}H_{28}O_3$: C, 77·61; H, 8·29%).

Reduction of the carbinol (XXIII).

Carbinol (XXIII, 1 g) in a mixture of 100 ml absolute tetrahydrofuran and 100 ml absolute ether was added to 200 ml liquid ammonia, and 1·6 g potassium was added at −40°. After 10 min,

160 ml absolute alcohol was added dropwise during 20 min, followed by 100 ml ammonia and 42 g lithium. The ammonia was evaporated and the mixture decomposed with water. The aqueous layer was extracted with ether, the combined extracts neutralized with carbon dioxide, washed with water, and dried with magnesium sulphate. The solvent was evaporated and the oily residue crystallized by trituration with alcohol yielding 0·7 g (69% of theory 3-methoxy-$\Delta^{2,5(10)}$-D-homo-oestradiene-17aβ-ol (XXIV) m.p. 134–138°. The pure carbinol had m.p. 141–142° (from alcohol). UV spectrum: λ_{max}^{EtOH} mμ: 278 (log ; 2·21). (Found: C, 79·46; H, 9·90. Calc. for $C_{20}H_{30}O_2$: C, 79·42; H, 10·00%).

Propionylation of the carbinol (XXIV) with propionic anhydride in pyridine (20°, 24 hr; checked by chromatogram) yielded about 70% of the propionate m.p. 123–124 (from alcohol). (Found: C, 76·60; H, 9·48. Calc. for $C_{23}H_{34}O_3$: C, 77·05; H, 9·56%).

Production of 19-*nor*-D-*homotestosterone* (XXV).

A mixture of a solution of 4·34 g carbinol (XXIV) in 45 ml tetrahydrofuran, 130 ml alcohol, and 100 ml hydrochloric acid (1:2) was boiled for 15 min, cooled and poured into water. The precipitate was filtered off and washed with water and ether, yielding 3·64 g (88% of theory) ketone (XXV) m.p. 138–140°. The pure ketone had m.p. 140–141° (from benzene–pet ether). IR spectrum: $\nu_{max}^{CHCl_3}$ cm^{-1} 1669 (C=C—C=O); ν_{max}^{nujol} cm^{-1} 1608, 1658 (C=C—CO), 3330, 3420 (OH). UV spectrum: λ_{max}^{EtOH} mμ 241 (log ϵ 4·21). (Found: C, 79·02; H, 9·80. Calc. for $C_{19}H_{28}O_2$: C, 79·12; H, 9·79 %).

The propionate (obtained in a manner similar to the propionate of XXIV) had m.p. 111–112° (from benzene–pet. ether). (Found: C, 76·63; H, 9·48. Calc. for $C_{22}H_{32}O_3$: C, 76·70; H, 9·36%).

Acylation of the carbinol (XXV) with β-phenylpropionic acid chloride in pyridine (20°, 24 hr; checked by chromatogram) gave a yield of about 40% of the β-phenylpropionate (XXVb) m.p. 141–143° (from benzene–pet. ether). (Found: C, 80·24; H, 8·70. Calc. for $C_{28}H_{36}O_3$: C, 79·96; H, 8·63%).

Preparation of the ketol (XXVa)

A solution of 1·38 g oxalic acid in 6 ml water was added to a solution of 1 g carbinol (XXIV) in 50 ml methanol and 30 ml tetrahydrofuran. The mixture was stirred for 1 hr, poured into ice water and extracted with ether. The extract was carefully neutralized with 5% sodium carbonate solution, dried with magnesium sulphate, evaporated and the residual oil crystallized by trituration with pet. ether, yielding 0·56 g (59% of theory) $\Delta^{5(10)}$-19-nor-D-homoandrosten-17aβ-ol-3-one (XXVa) m.p. 120–122°. The pure ketol has, mp. 122·5–123·5°. IR spectrum: ν_{max}^{nujol} cm^{-1} 1657, 1703 (unconjugated CO), 3371, 3497 (OH). (Found: C, 79·19; H, 9·93. Calc. for $C_{19}H_{28}O_2$: C, 79·12; H, 9·79%).

Preparation of the carbinols (XXVI *and* XXVIa).

A solution of 6·2 g ketone (XV) in a mixture of 45 ml absolute tetrahydrofuran and 100 ml ether was added during 25 min to a solution of methylmagnesium iodide (from 2 g of Mg, 16 g of CH_3I and 70 ml of ether) cooled to 0°, and the mixture stirred for 2 hr and boiled for 30 min. The solution was cooled with ice, decomposed with 5% hydrochloric acid, the aqueous layer extracted with ether, and the combined extract neutralized with sodium carbonate and evaporated. The reaction product (7·7 g of a brown oil) was dissolved in 100 ml of a mixture of ether and benzene (7:3) 40 g alumina (activity III) was added to the solution, the mixture stirred for 2 hr, and transferred to a column with 240 g of alumina. Elution with pet. ether and mixtures of it with benzene (up to a ratio of 6:4) yielded 3·04 g crystals, recrystallization from benzene gave 2·25 g (39% of theory) 17a-methyl-3-methoxy-$\Delta^{1,3,5(10),8}$-oestratetraen-17a-ol (XXVI), m.p. 112–114°. The pure carbinol had m.p. 114–115°. (Found: C, 80·88; H, 9·00. Calc. for $C_{21}H_{28}O_2$. C, 80·73; H, 9·03%).

Further elution with mixtures of pet. ether and benzene (from 3:7 and above), benzene, and a mixture of benzene and ether (9:1) gave 3·40 g crystals, recrystallization of which from benzene yielded 2·82 g (43% of theory) of the epimer of XXVI (XXVIa) m.p. 117–119°. A pure sample had m.p. 126–127°. (Found: C, 80·70; H, 9·13. Calc. for $C_{21}H_{28}O_2$. C, 80·73; H, 9·03%).

Preparation of 17a-*methyl*-19-*nor*-D-*homotestosterone* (XXVII) *and its epimer* (XXVII*a*)

Potassium (4·3 g) was added during 10 min at −60 to −70° to a mixture of 500 ml liquid ammonia and a solution of 2·3 g carbinol (XXVI) in 70 ml absolute tetrahydrofuran and 150 ml absolute ether, the mixture was left for 1 hr, 400 ml absolute alcohol was added during 50 min, and then 9·35 g lithium during 1 hr. The mixture was kept at −60 to −70° for 2·5 hr, 300 ml ether added,

the ammonia allowed to evaporate, and decomposition carried out by the addition of 400 ml water with cooling. The organic layer was separated and the aqueous layer extracted with ether. The combined extract was neutralized and evaporated *in vacuo*, the residue (2·35 g) dissolved in 70 ml methanol, 5 ml acetic acid and 20 ml of 10% hydrochloric acid added, the mixture allowed to stand for 1 hr and then boiled for 5 min, poured into water with ice, and extracted with ether. The extract was neutralized with 10% sodium carbonate solution and evaporated, and, after crystallization of the residue from benzene, 0·86 g (39% of theory) 17a-methyl-19-nor-D-homotestosterone (XXVII) m.p. 168–170° was obtained. The pure ketol had m.p 171–173°. IR spectrum: ν_{max}^{nujol} cm ^{1} 1670 (C=C—C=O). (Found: C, 79·44; H, 9·91. Calc. for $C_{20}H_{30}O_2$. C, 79·42; H, 10·00%).

In a similar manner, 1·85 g carbinol (XXVIa) yielded 1·02 g of a product giving a single spot on a chromatogram, crystallization of which gave 0·5 g or the pure epimer (XXVIIa) m.p. 161–162° (from cyclohexane–ethyl acetate). IR spectrum: ν_{max}^{nujol} cm^{-1} 1660 (C=C—C=O), 3520 (OH). (Found: C, 79·46; H, 10·05. Calc. for $C_{20}H_{30}O_2$. C, 79·42; H, 10·0%).

Preparation of the carbinol (XXVIII)

Acetylene (5–6 l.) were passed into 400 ml liquid ammonia cooled to −70°, and 0·75 g lithium added. To the colourless solution of lithium acetylide, a solution of 7·8 g ketone (XV) in a mixture of 100 ml absolute tetrahydrofuran and 100 ml absolute ether was added over 1·5 hr, the mixture kept for a further 2 hr at −70°, with passage of acetylene, decomposed by the addition of 20 g ammonium chloride and 200 ml water, and extracted with ether. After evaporation and crystallization from methanol, 6·1 g (72% of theory) 17a-ethinyl-3-methoxy-$\Delta^{1,3,5(10),8}$-D-homo-oestratraen-17a-ol (XXVIII) m.p. 152–153° was obtained. The pure carbinol had m.p. 155–156°. (Found: C, 81·87; H, 8·09. Calc. for $C_{22}H_{26}O_2$. C, 81·95; H, 8·13%).

Preparation of the carbinols (XXIX *and* XXIXa)

a. Carbinol (XXVIII, 1 g) was hydrogenated in 40 ml absolute tetrahydrofuran over 10% palladium on calcium carbonate. After the absorption of 900 ml hydrogen (728 mm, 18°; 95% of the theoretical H_2), hydrogenation practically ceased. After filtration, evaporation and crystallization from methanol, 4·9 g (80% of theory) 17a-ethyl-3-methoxy-$\Delta^{1,3,5(10),8}$-D-homo-oestratetraen-17a-ol (XXIX) m.p. 176–178° was obtained. The pure carbinol had m.p. 181–182°. UV spectrum: λ_{max}^{EtOH} mμ 274 (log ϵ 4·20). (Found: C, 80·61; H, 9·43. Calc. for $C_{22}H_{30}O_2$: C, 80·93; H, 9·26%).

b. A solution of 1·5 g ketone (XV) in 10 ml absolute tetrahydrofuran was added during 5 min to a solution of ethylmagnesium bromide (from 1·2 g Mg, 6 g ethyl bromide, and 20 ml of ether), cooled to 0° (a precipitate separated). The mixture was stirred for 2 hr, boiled for 30 min, and treated as in the preparation of the carbinol (XXVI). Crystallization of the reaction product from methanol yielded about 100 mg carbinol (XXIX) m.p. 181–182°, identical (mixed m.p.) with the sample obtained earlier, and 156 mg of the epimer of the carbinol (XXIXa) m.p. 158–159·5°. (Found: C, 80·83; H, 9·24. Calc. for $C_{22}H_{30}O_2$: C, 80·93; H, 9·26%).

The mother liquors were found (on a chromatogram) to contain the carbinol (XXIII), formed by the reduction of the ketone (XV), as is sometimes observed in the Grignard reaction.[11]

Preparation of the ketol (XXX)

In a manner similar to the preparation of the ketols (XXVII and XXVIIa), 1·7 g carbinol (XXIX) yielded 0·87 g (53% of theory) 17a-ethyl-D-homotestosterone (XXX) m.p. 148–151°. The pure ketol had m.p. 153–154° (from cyclohexane–CCl_4). IR spectrum; $\nu_{max}^{CHCl_3}$ cm^{-1} 1667 (C=C—C=O). UV spectrum: ν_{max}^{EtOH} mμ 241 (log ϵ 4·23). (Found; C, 79·49; H, 10·17. Calc. for $C_{21}H_{32}O_2$: C, 79·70; H, 10·19%).

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