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# NEW SYNTHESES OF ESTRONE, d,l-8-ISO-OESTRONE AND d,l-19-NORTESTOSTERONE[x)]

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EARLIER[1] we carried out the syntheses of D-homosteroids (d,l-D-homo-oestrone and d,l-19-homo-D-homotestosterone) by condensing 1-vinyl-6-methoxytetralol (I) with methylhydroresorcinol. At present we have extended this reaction to other cyclic 1,3-diketones and have prepared d,l-oestrone (II), d,l-8-isooestrone (III) and d,l-19-nortestosterone (IV), starting with the carbinol (I) and 2-methylcyclopentane-1,3-dione (V)[2]. On condensation of I with V in the presence of Triton B, 3-methoxy-$\Delta^{1,3,5(10),9(11)}$-8,14-secooestratetraene-14,17-dione (VI) was obtained in 50% yield; m.p. 79-80° (from $CH_3OH$); $\lambda_{max}$ (in alcohol) 264 mμ (lg ε 4.27); infrared bands (in nujol) 1610, 1728cm$^{-1}$; (Found: C 76.48; H 7.38; $C_{19}H_{22}O_3$ requires : C 76,48; H 7,43).

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[x)] The methods described in the present communication have been patented in USSR patent 778652/31-16, May 18, 1962. The Synthesis of d,l-oestrone was reported by I.V.Torgov in a paper on the "Achievements in the Total Synthesis of Steroids" read at the International Symposium on the Chemistry of Natural Products, Prague (August 1962).

[1] S.N.Ananchenko, V.Ye.Limanov, V.N.Leonov, V.N.Rzhezhnikov, I.V.Torgov, Tetrahedron, **18**, 1355 (1962).

[2] J.J.Panouse, C.Sannié, Bull., 1937 (1956).

Similar condensation of 1-vinyl-6-hydroxy-1-tetralol (VII) with V yields $\Delta^{1,3,5(10),9(11)}$-oestratetraene-3,14-diol-17-one (VIII); m.p.235-237° (from alcohol-ethyl acetate); $\lambda_{max}$ (in alcohol) 270 mμ (lg ε 4.18); infrared bands (in nujol) 1581, 1616, 1728, 3251, 3474 $cm^{-1}$; (Found: C 76.31; H 7.05. $C_{18}H_{20}O_3$ requires: C 76.03; H 7.09; active H-2.1).

Cyclization of VI with p-toluenesulfonic acid in benzene gives 3-methoxy-$\Delta^{1,3,5(10),8,14}$-oestrapentaen-17-one (IX) in 85% yield; m.p.108-109° (from alcohol); $\lambda_{max}$ (in alcohol) 312 mμ (lg ε 4.50); infrared bands (in nujol) 1140, 1252, 1570, 1590, 1610, 1740 $cm^{-1}$; (Found: C 81.35; H 7.16; $C_{19}H_{20}O_2$ requires: C 81.39; H 7.19). Dehydration of VII with the aid of p-toluenesulfonic acid in benzene forms $\Delta^{1,3,5(10),8,14}$-oestrapentaen-3-ol-17-one (X). Selective hydrogenation of (IX) in tetrahydrofuran in the presence of 10% Pd/$CaCO_3$ (or Raney Ni) leads to 3-methoxy-$\Delta^{1,3,5(10),8}$-oestratetraen-17-one (XI); m.p.120-121° (frommethyl acetate); $\lambda_{max}$ (in alcohol) 277 mμ (lg ε 4.34); infrared bands (in nujol) 1140, 1252, 1570, 1610, 1740 $cm^{-1}$; (Found C 80.93; H 7.76. $C_{19}H_{22}O_2$ requires: C 80.81; H 7.85).

Hydrogenation of XI in tetrahydrofuran in the presence of Pd/$SrCO_3$ in which two moles of $H_2$ are absorbed leads to the methyl ether of III (IIIa); m.p.151-152° [3]. Similar hydrogenation of X in the presence of Pd/$CaCO_3$ yields III;

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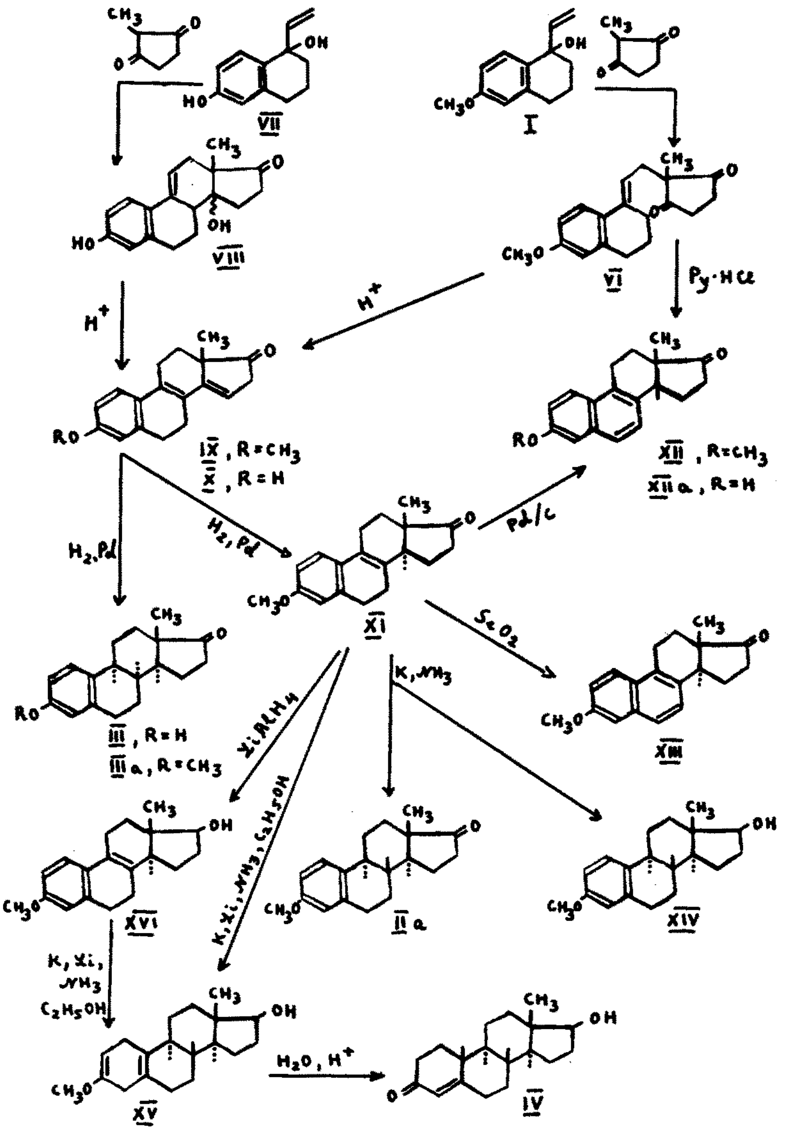
[3] V.N.Leonov, S.N.Ananchenko, I.V.Torgov, Dokl.Akad.Nauk SSSR, 138, 384 (1961).


VII
I
VIII
VI
H+
H+
Py·HCl
IX, R=CH3
X, R=H
XII, R=CH3
XIIa, R=H
H2,Pd
H2,Pd
Pd/C
XI
SeO2
III, R=H
IIIa, R=CH3
XIII
Li,AlH4
K,Li,NH3,C2H5OH
K,NH3
XVI
IIa
XIV
K,Li,
NH3
C2H5OH
XV
H2O, H+
IV

m.p.251-252° (from acetone)[3,4]. Methylation of III then gives IIIa.

On heating ketone (XI) at 350° in the pressence of Pd/C, d,l-isoequilenin methyl ether (XII) is formed; m.p. 124-125° (from alcohol-ethyl acetate). In the presence of $SeO_2$ in tert.-$C_4H_9OH$ and pyridine solution the dehydrogenation reaction leads to equilênin methyl ether (XII) of m.p.185-185.5° [5]. Demethylation of diketone (VI) with pyridine hydrochloride at 210-230° gives d,l-isoequilenin (XIIa); m.p.218-220° [6]; $\lambda_{max}$ (in alcohol) 229, 265, 276, 322, 335 mμ (lg ε 3.77, 3.72, 3.74, 3.23, 3.30). Reduction of ketone (XI) by potassium in liquid ammonia (distilled over sodium) gives a 1:1 mixture of d,l-oestrone methyl ether (IIa); m.p.143-144° [7] and d,l-oestradiol methyl ether (XIV); m.p.130.0-130.5° (from alcohol-ethyl acetate); $\lambda_{max}$ (in alcohol) 279, 281 mμ (lg ε 3.36, 3.32); (Found: C 79.78; H 9.06. $C_{19}H_{26}O_2$ requires: C 79.68; H 9.15); XIV-acetate; m.p.148.5-149 (from alcohol); $\lambda_{max}$ (in alcohol) 280 mμ (lg ε 3.36). XIV is obtained in 72% yields on reducing ketone XI by potassium in liquid ammonia (without preliminary drying). Chromic anhydride oxidation of XIV in pyridine gives IIa,

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[4] W.S.Johnson, I.A.David, H.C.Dehn, R.J.Highet, E.W.Warnhoff, W.D.Wood, E.T.Jones, J.Amer.Chem.Soc., **80**, 661 (1958).

[5] G.H.Hughes, H.Smith, Chem.and Ind., 1022 (1960).

[6] W.E.Bachmann, W.Cole, A.L.Wilds, J.Amer.Chem.Soc., **61**, 974 (1939); **62**, 824 (1940).

[7] S.N.Ananchenko, V.N.Leonov, A.V.Platonova, I.V.Torgov, Doklad.Akad.Nauk SSSR, **135**, 73 (1960).

demethylation of which with the aid of pyridine hydrochloride gives II; m.p.250-251° (from acetone); $\lambda_{max}$ (in alcohol) 280 m$\mu$ (log $\varepsilon$ 3.34)[4].

Reduction of ketone XI with potassium and lithium in alcohol liquid ammonia under Johnson's conditions[8] affords 3-methoxy-$\Delta^{2,5(10)}$-oestradien-17$\beta$-ol (XV); m.p.118-119° (from alcohol); $\lambda_{max}$ (in alcohol) 276 m$\mu$ (lg $\varepsilon$ 1.48); infrared bands (in nujol) 1667, 1695, 3226, 3527 cm$^{-1}$; (Found 79.09; H 9.83; $C_{19}H_{28}O_2$ requires: C 79.12; H 9.78); Hydrolysis of XV with dilute HCl yields d,l-19-nortestosterone (IV), m.p.121-122° (from acetone); $\lambda_{max}$ (in alcohol) 240 m$\mu$ (lg $\varepsilon$ 4.32); infrared bands (in nujol) 1618, 1665, 3420 cm$^{-1}$; (Found C 78.46; H 9.69. $C_{18}H_{26}O_2$ requires: C 78.79; H 9.55); IV-acetate; m.p.108-109° (from light petroleum)[9]. Ana alternate route to IV has been investigated. $LiAlH_4$ reduction of XI gives 3-methoxy-$\Delta^{1,3,5(10),8}$-oestratetraen-17$\beta$-ol (XVI), m.p.130-132° (from alcohol); $\lambda_{max}$ (in alcohol) 274 m$\mu$ (lg $\varepsilon$ 4.30); infrared band (in nujol) 1134, 1247, 1496, 1574, 1611, 3405 cm$^{-1}$; (Found C 80.34; H 8.52. $C_{19}H_{24}O_2$ requires C 80.24; H 8.51). XVI-acetate; m.p.113-114° (from alcohol). Reduction of XVI with the aid of potassium and $NH_4Cl$ in liquid ammonia affords XIV whereas reduction with potassium and lithium + alcohol in liquid ammonia under Johnson's conditions leads to XV,

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[8] W.S.Johnson, W.A.Vredenburgh, J.E.Pike, J.Am.Chem.Soc., 82, 3409 (1960).

[9] L.J.Chinn, H.L.Dryden,Jr., J.Organ.Chem., 26, 3904 (1961).

which on hydrolysis with conc. HCl in $CHCl_3$[10] is converted into IV. Identification (and purity tests) of the products was carried out by means of thin layer binderless chromatography on $Al_2O_3$[11].

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[10] V.Pelc, *Coll.Czech.Chem.Comm.*, **27**, 2706 (1962).

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