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TOTALLY SYNTHETIC STEROID HORMONES—VI[1]

(±)-6α- AND β-METHYLESTRA-1,3,5(10)-TRIENES, (±)-13β-ETHYL-6β-METHYLGONA-1,3,5(10)-TRIENES, AND RELATED COMPOUNDS

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Abstract—(±)-6α and β-Methylestra-1,3,5(10)-trien-17β-ol (VII a and b; R = Me), and (±)-13β-ethyl-6β-methylgona-1,3,5(10)-trien-17β-ol (VIIb; R = Et) have been totally synthesized from 3-*m*-methoxyphenylbutyl bromide. The second compound has been converted to various (±)-13β-ethylgon-4-en-3-ones, the biological activities of which are reported.

THIS paper records the first direct total syntheses of 6-methylestrane and 13β-ethyl-6-methylgonane structures. The work was done because of the biologically interesting properties of various 6-methylsteroids, e.g. as myotrophic-androgenic[2] and progestational[3] agents, and their comparatively circuitous syntheses by attaching a carbon atom at the 6-position of a steroid nucleus.[4]

The total syntheses are extensions of ones[5,6] used earlier to make estrone and a variety of (±)-13β-alkylgona-1,3,5(10)-trienes, and related compounds[6] from 3-*m*-methoxyphenylpropyl bromide (I; R = H; X = Br). The 3-*m*-methoxyphenylbutyl bromide (I; R = Me; X = Br), required for the corresponding 6-methylsteroids, was made from 3-*m*-methoxyacetophenone by Reformatsky reaction with methyl bromacetate and hydrogenolysis of the resulting benzyl alcohol over Pd–C in acetic acid to methyl 3-*m*-methoxyphenylbutyrate, followed by successive reactions with LAH in ether, and phosphorus tribromide in benzene. The bromide was converted by sodium acetylide in liquid ammonia to the hexyne (I; R = Me; X = C≡CH) and transformed thence to the amine (I; R = Me; X = C≡C·CH_2NEt_2) by condensation with formaldehyde and diethylamine under Mannich conditions. Hydration of

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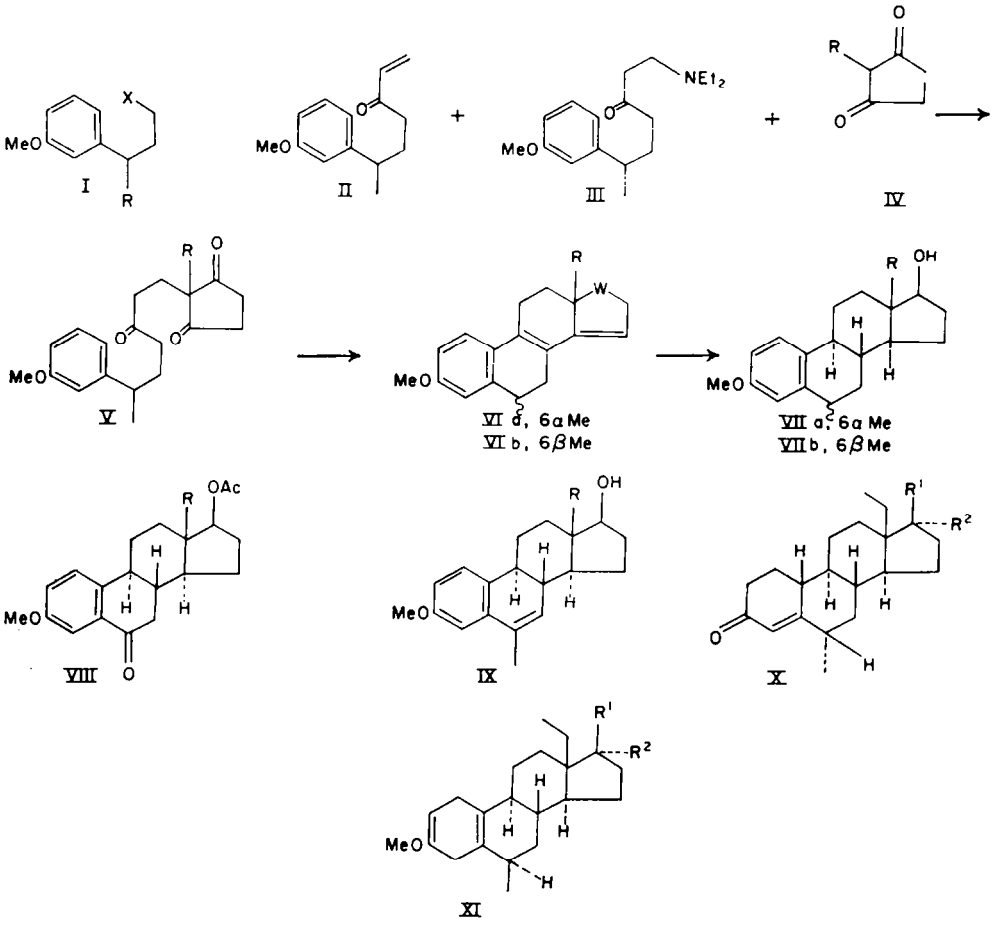
the amine and distillation gave a mixture of the ketones (II and III). For the preparation of 6-methylestrane derivatives this mixture was reacted with 2-methylcyclopentane-1,3-dione (IV; R = Me) in the presence of base to give the trione (V; R = Me). Cyclodehydration with toluene-*p*-sulfonic acid in benzene and distillation then gave a mixture of the 6-methylestrapentaenes which was separated by fractional



crystallization into two apparently pure isomers (VIa and b; R = Me; W = CO)[7] in yields of 1 and 25%, respectively. The composition of the distillate was not determined since we were unable to resolve its components by GLC (Experimental section) despite observing different retention times for the pure 6-methyl epimers when examined singly. Analogously, condensation of the mixture of ketones (II and III) with 2-ethylcyclopentane-1,3-dione (IV; R = Et)[6] and acid cyclodehydration of the resulting trione (V; R = Et) gave what is apparently a mixture of the ketones (VIa and b; R = Et; W = CO). Neither was obtained crystalline, but the mixture gave an apparently pure crystalline ethylene ketal (VIb; R = Et; W = $C_3H_4O_2$) in

[7] These and the other new compounds described later are racemates which are depicted by the enantiomorphs with the 13β-alkyl group.

40% yield. Evidence given later permits the 6β-methyl configuration to be assigned to the last compound and the major estrapentaenone (VIb; R = Me; W = CO).

The conversion of the pure ketones (VIa and b; R = Me; W = CO) and the ketal (VIb; R = Et; W = $C_3H_4O_2$) to the corresponding three alcohols (VIIa and b; R = Me and Et) followed procedures described in Parts I[5b] and II,[6b] and need not be further discussed. The stereochemistry at all of the asymmetric centers except C_6 in the foregoing alcohols was elucidated by their independent synthesis from the acetates of authentic (±)-3-methoxyestra-1,3,5(10)-trien-17β-ol,[5] or its 13-ethylgonane analog,[6] as appropriate. These syntheses proceeded by initial formation of the ketones (VIII; R = Me and Et), by oxidation with t-butyl chromate in carbon tetrachloride or sodium dichromate in acetic acid, and their transformation by methylmagnesium iodide and Hibbert dehydration[8] of the resulting 6,17-diols to the tetraenols (IX; R = Me and Et). Catalytic hydrogenation of these substances gave respectively, an estratrienol, identical with that made from the major isomer (VIb; R = Me; W = CO), and a corresponding gonatrienol, identical with that made from the ketal (VIb; R = Et; W = $C_3H_4O_2$). Accepting with previous workers[9] that the catalytic hydrogenation of a 6-methylestra-1,3,5(10),6-tetraene will occur by α-face adsorption, one can assign the 6β-methyl configuration to the estrapentaene (VIb; R = Me; W = CO) and, by extension, to the gonapentaene (VIb; R = Et; W = $C_3H_4O_2$).

The tetraenes (IX; R = Me and Et) were reduced, in turn, with lithium in liquid ammonia-aniline[5,6] to mixtures of the corresponding epimers (VIIa and b) which were fractionally crystallized. The former thus gave a low yield of the alcohol (VIIa; R = Me), identical with that made from the minor epimer (VIa; R = Me; W = CO), and the latter a 44% yield of the alcohol (VIIb; R = Et), identical with that made from the ketal (VIb; R = Et; W = $C_3H_4O_2$).

An analysis of the proton NMR spectra of the alcohols (VIIa and b; R = Me and VIIb; R = Et) based upon the corresponding Dreiding models provides support for the stereochemistry assigned to the C_6-positions. The 6-methyl and C_6-methine protons in the alcohols (VIIa and b; R = Me) resonate at closely similar chemical shifts (8·69 and 8·72 τ for the former protons, and 7·12 and 7·07 τ for the latter, respectively) and we conclude that the spectra are to be interpreted in terms of conformations having the flexible B ring in a halfchair form. With this arrangement, the plane of the aromatic ring makes approximately equal dihedral angles with the 6α and β-bonds so providing a similar magnetic environment for the C_6-methyl protons and the C_6-methine proton in each epimer; with ring B in a half-boat form, the same angles have appreciably different values. Accepting the foregoing conformations, the patterns of the C_6-methine proton resonances appear consistent with the assigned stereochemistry. Thus, the signal for the 6α-proton in (VIIb; R = Me) is less complex than that for the 6β-proton in the epimer, in accord with a dihedral angle of approximately 90° between the 6α and 7β-protons which should suppress coupling between them. Irradiation at 165 c/s upfield from the 6α-proton, sharpened its signal to a broad singlet. The more complex signal from the 6β-proton in (VIIa; R = Me) seems consistent with dihedral angles of approximately 30 and 150° between it and the 7β and 7α-protons, respectively. Irradiation at 160 c/s upfield sharpened this signal without abolishing its multiplicity. Notably, the C_4 aromatic proton in VIIa

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(R = Me) resonates at 0·17 ppm downfield from that in the epimer. This is probably due to a difference in the long range shielding effect arising in each compound from the diamagnetic anisotropy of the C_6-methyl bond (cf.[10]), and presumably reflects the sensitivity of the effect to slight changes in the conformation of the A and B rings. Finally, the C_4-aromatic and C_6-methine protons showed almost identical patterns of resonances in the spectra of the alcohols (VIIb; R = Me and Et) which were quite distinct from those shown for the corresponding protons in the alcohols (VIIa; R = Me), thus demonstrating an analogous stereochemistry at C_6 in the first pair. No long range coupling between the C_4- and C_6-protons (cf.[11]) could be detected in the spectrum of any of the three foregoing alcohols.

The biologically interesting properties found for various (±)-13β-ethylgon-4-en-3-ones[6,12] prompted us to prepare the gonenones (X; R^1 = OH; R^2 = H and C≡CH) from the 6β-methylgonatriene (VIIb; R = Et). The first ketone was made by Birch reduction and acid hydrolysis of the intermediate alcohol (XI; R^1 = OH; R^2 = H), and the second by Oppenauer oxidation of the latter compound to the ketone (XI; $R^1 + R^2$ = O), followed by interaction with lithium acetylide, and acid hydrolysis of the resulting alcohol (XI; R^1 = OH; R^2 = C≡CH). The stereochemistry at C_{10} and C_{17} in the ketones (X; R = H and C≡CH) was assigned by analogy with the stereochemical course demonstrated for analogous reaction sequences in the 13-ethylgonane series,[6] and that at C_6 on the assumption that, as has been observed previously,[13] the acidic conditions of the final stage in each synthesis epimerizes any of the less stable 6β-methyl isomer through the 3,5-dien-3-ol. The proton NMR spectrum of the dione (X; $R^1 + R^2$ = O), made by Jones oxidation[14] of the alcohol (X; R^1 = OH; R^2 = H), favors the 6α-methyl configuration for the latter, and, by analogy for the alcohol (X; R^1 = OH; R^2 = C≡CH). In this spectrum the C_4-proton signal, a broad unresolved multiplet, at 4·13 τ (average line width 4·2 c/s), is closely similar in shape to that at 4·27 τ (average line width 4·3 c/s) produced through the strong coupling of the axial 6β and 10β-protons to the C_4-proton in the spectra of various Δ^4-3-ketonic 19-norsteroids, and is quite different from the sharp doublet at 4·13 τ reported for the C_4-proton in 6β-methyl-19-norandrost-4-en-3-one.[15]

Biological activities. Both ketones (X; R^1 = OH; R^2 = H and C≡CH) are highly potent steroid hormones. The former has 150% of the anabolic, and 18% of the androgenic activity of testosterone propionate in the Hershberger test,[16] and the latter 8500% of the progestational activity of 17α-ethynyl-17β-hydroxyestra-4-en-3-one[17] in the Clauberg Test.[18]

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EXPERIMENTAL

General directions are as for Part I.[5b] Proton NMR spectra were measured using 5–10% solutions in $CDCl_3$ containing tetramethysilane (TMS) as internal reference standard. Chemical shifts are expressed in τ units measured downfield from the reference, and coupling constants, J, in c/s. The former should be accurate to ± 1 ppm, the latter to $\pm 0{\cdot}5$ c/s. The spectra at 100 and 60 Mc were measured on the Varian HR-100 and A-60 Spectrometers, respectively.

(±)-3-*Methoxy*-6-*methylestra*-1,3,5(10),6-*tetraen*-17β-ol (IX; R = Me). (±)-3-Methoxyestra-1,-3,5(10)-trien-17β-ol[5] (67 g) was kept overnight in acetic anhydride (70 ml)-pyridine (150 ml)-acetyl chloride (25 ml) to give the corresponding acetate (70 g). The ester (10 g) was refluxed for 4 hr with t-butyl chromate (57 g) in CCl_4 (600 ml)–acetic anhydride (150 ml), cooled, then stirred with aqueous oxalic acid to destroy the excess of reagent. The product crystallized from MeOH to give (±)-17β-acetoxy-3-methoxyestra-1,3,5(10)-trien-6-one (0·95 g). The ketone (0·8 g) was refluxed for 5 min in tetrahydrofuran (50 ml)–ether (10 ml) containing MeMgBr (from the metal, 0·73 g). On cooling, sat. NH_4Claq was added and the mixture extracted with ether. The gummy product, after dehydration by refluxing for 4 hr in benzene (50 ml) containing a crystal of I_2 (Dean–Stark water separator), was filtered in benzene through Florex to give the *tetraenol* (0·3 g), m.p. 123–126° (from acetonitrile, λ_{max} 262 and 305 mμ (ε 5,500 and 2,200). (Found: C, 80·3; H, 8·7 $C_{20}H_{26}O_2$ requires: C, 80·5; H, 8·8%.)

(±)-17β-*Acetoxy*-13β-*ethyl*-3-*methoxygona*-1,3,5(10)-*trien*-6-*one* (VIII; R = Et). (±)-13β-Ethyl-3-methoxygona-1,3,5(10)-trien-17β-ol[6] (10 g) was kept for 2·5 days in pyridine (50 ml)–acetic anhydride (10 ml). The acetate (2·0 g), m.p. 131–132° (from MeOH), was kept for 6 hr at 60–70° with sodium dichromate (1·7 g of the dihydrate) in acetic acid (40 ml)–acetic anhydride (20 ml). The cooled mixture was poured into water and extracted with ether, and the ether solution was washed with 1N NaOH. Chromatography of the gummy product on Florex gave the *trienone* (0·75 g), m.p. 161–163° (from MeOH), λ_{max} 256 and 325 mμ (ε 7,800 and 2,700). (Found: C, 73·6; H,. 7·9 $C_{22}H_{28}O_4$ requires: C, 74·1; H, 7·9%.)

(±)-13β-*Ethyl*-3-*methoxy*-6-*methylgona*-1,3,5(10),6-*tetraen*-17β-*ol* (IX; R = Et). The foregoing ketone (0·75 g) was refluxed for 1 hr in tetrahydrofuran (50 ml)–ether (20 ml) containing MeMgBr (from the metal, 1·46 g). The product was refluxed for 7 hr in benzene containing a crystal of I_2 and the resulting crystals were filtered, in ether–benzene (1:9), through Florex to give the *tetraene* (0·425 g) m.p. 128–130°, (from ether–hexane), λ_{max} 262 and 305 mμ (ε 7,100 and 2,450). (Found: C, 80·38; H, 8·8 $C_{21}H_{28}O_2$ requires: C, 80·73; H, 9·0%.)

3-m-*Methoxyphenylbutan*-1-*ol* (I; R = Me; X = OH). *m*-Methoxyacetophenone (100 g) in benzene (450 ml)–methyl bromacetate (153 g) was added dropwise to a vigorously reacting mixture of methyl bromacetate (5 ml) in benzene (20 ml) containing Zn turnings (67 g, previously activated by washing with 3N HCl) and a crystal of I_2, so as to maintain gentle refluxing. The mixture was refluxed for 1 hr, cooled, and added to 2N H_2SO_4 containing crushed ice. Distillation of the product gave a forerun of the reactants, then methyl 3-hydroxy-3-*m*-methoxyphenylbutanoate (116 g) b.p. 140°/0·65 mm. The ester, in acetic acid (1 l.) containing 10% Pd–C (20 g), was shaken with H_2 at atm. press. until uptake of H_2 ceased (12·5 l.). The product was distilled to give methyl 3-*m*-methoxyphenylbutanoate (112 g) b.p. 139–142°/5 mm n_D^{21} 1·5060, which was reduced with LAH (40 g) in ether (1 l.) to give the *alcohol*, b.p. 118–121°/0·4 mm, n_D^{21} 1·5260, λ_{max} 274 and 285 mμ (ε 1,800 and 1,650). (Found: C, 73·0; H, 9·1 $C_{11}H_{16}O_2$ requires: C, 73·3; H, 8·95%.)

3-m-*Methoxyphenylbutyl bromide* (I; R = Me; X = Br). PBr_3 (55 g) in benzene (100 ml) was added with stirring to the foregoing alcohol (84 g) in benzene (125 ml) at 0–5° and the mixture was heated at 60° for 3 hr, cooled, then added to crushed ice. The *bromide* (92·8 g) had b.p. 100–104°/0·15 mm. (Found: C, 54·5; H, 6·4; Br, 32·6 $C_{11}H_{15}BrO$ requires: C, 54·4; H, 6·2; Br, 32·85%.)

5-m-*Methoxyphenylhex*-1-*yne* (I; R = Me; X = C$\equiv$CH). The foregoing bromide (84 g) was stirred for 24 hr with sodium acetylide (from the metal, 11·5 g) in liquid ammonia (750 ml). The *hexyne* (56·6 g) had b.p. 84–95°/0·45 mm. (Found: C, 82·8; H, 8·3 $C_{13}H_{16}O$ requires: C, 83·0; H, 8·6%.)

1-*Diethylamino*-6-m-*methoxyphenylhept*-2-*yne* (I; R = Me; X = C$\equiv$CH_2NEt_2). The foregoing hexyne (56·6 g) was kept at 70° for 16 hr under N_2 in dioxan (175 ml)–diethylamine (40 ml)–40% formalin (38·5 ml)–acetic acid (19 ml) containing CuCl (1 g). The *diethylaminoheptyne* (79·5 g) had b.p. 135–140°/0·2 mm, n_D^{25} 1·5116. (Found: C, 79·0; H, 9·7 $C_{18}H_{27}NO$ requires: C, 79·1; H, 9·95%.)

(±)-3-*Methoxy*-6α *and* β-*methylestra*-1,3,5(10),8,14-*pentaen*-17-*one* (VIa and b; R = Me; W = CO). The foregoing amine (63 g) was stirred at 70–80° for 2 hr under N_2 in H_2SO_4 (17·5 ml)–water (177 ml) containing $HgSO_4$ (3·15 g). Distillation of the product gave a mixture of 1-diethylamino-6-*m*-methoxyphenylheptan-3-one and 6-*m*-methoxyphenylhept-1-en-3-one (43 g), b.p. 135°/0·2 mm, n_D^{24} 1·5212. (Found: N, 0·8%), which was refluxed for 12 hr with 2-methylcyclopentane-1,3-dione (30 g) in MeOH (90 ml) containing a trace of KOH. The resulting trione (V; R = Me; 60 g) was refluxed for 1 hr in benzene (750 ml) containing toluene-*p*-sulfonic acid (from the monohydrate, 20 g; Dean–Stark water separator) to give a gum (43 g) b.p. 200–220° (bath)/0·1 mm which crystallized from MeOH to give a mixture of (±)-3-methoxy-6α and β-methylestra-1,3,5(10),8,14-pentaen-17-one (23 g) m.p. 75–90°. Six recrystallizations from MeOH gave the 6β-*methyl epimer* (11 g) m.p. 112–115°, λ_{max} 314 mμ (ε 27,000). (Found: C, 81·1; H, 7·5 $C_{20}H_{22}O_2$ requires: C, 81·4; H, 7·2%.) The material contained in the mother liquors of the first recrystallization, after 4 recrystallizations from MeOH, gave the 6α-*methyl epimer* (0·2 g) m.p. 109–111°, depressed on admixture with the first epimer, λ_{max} 316 mμ (ε 25,000). (Found: C, 81·2; H, 7·6%.)

Gas chromatography was done on the distillate mixture of epimers using the Perkin–Elmer Vapor Fractometer Model 154-C, but no resolution into components was observed on running a sample in CH_2Cl_2 at a flow rate of 62 ml/min of He on a 2 meter column (external diameter 0·25 in) at 220° packed with Celite containing 3% w/w fluorosilicone QF-1 as stationary phase. Under the same conditions the pure 6α and 6β-methyl epimers had retention times of 103 and 135 min, respectively.

(±)-3-*Methoxy*-6β-*methylestra*-1,3,5(10),8-*tetraen*-17-*one*. The foregoing 6β-methyl epimer (0·5 g) was hydrogenated in benzene (12 ml) over 2% Pd–$CaCO_3$ (0·17 g) to afford the 6β-*methylestratetraene* (0·3 g) m.p. 88–91° (from MeOH, λ_{max} 281 mμ (ε 15,800). (Found: C, 80·75; H, 8·3 $C_{20}H_{24}O_2$ requires: C, 81·05; H, 8·2%.)

(±)-3-*Methoxy*-6β-*methylestra*-1,3,5(10),8-*tetraen*-17β-*ol*, prepared from the foregoing tetraene (3 g) by reduction with $NaBH_4$ in MeOH, formed crystals (2·45 g) m.p. 130–132° (from acetonitrile), λ_{max} 281 mμ (ε 15,500). (Found: C, 80·4; H, 8·65 $C_{20}H_{26}O_2$ requires: C, 80·5; H, 8·8%.)

(±)-3-*Methoxy*-6β-*methylestra*-1,3,5(10)-*trien*-17β-*ol* (VIIb; R = Me). (a) Li was added piecemeal to the foregoing tetraenol (2 g) in liquid ammonia (120 ml)–aniline (10 ml) until a permanent blue color was formed. After 1 hr acetone was added, then dil. acetic acid, and the mixture was extracted with ether. Recrystallization of the product from ether gave the *trienol* (0·2 g) m.p. 138–141° λ_{max} 286 mμ (ε 2,900), NMR (100 Mc): 3-proton doublet 8·72 τ, J 8 c/s (6β-Me); 1-proton multiplet 7·07 τ (C_6–H); and 1-proton doublet 3·34 τ, J 3 c/s (C_4–H). (Found: C, 79·6; H, 9·2 $C_{20}H_{28}O_2$ requires: C, 79·95; H, 9·4%.) (b) (±)-3-Methoxy-6-methylestra-1,3,5(10),6-tetraen-17β-ol (0·1 g) in benzene (10 ml) containing Pd–$CaCO_3$ (0·02 g) was shaken with H_2 at atm. pressure until uptake of gas ceased. Recrystallization of the product from ether gave the *triene* (0·05 g) m.p. 137–139°, undepressed by, and having UV and IR absorption spectra identical to, material prepared as in (a).

(±)-3-*Methoxy*-6α-*methylestra*-1,3,5(10)-*trien*-17β-*ol* (VIIa; R = Me). (a) (±)-3-Methoxy-6α-methylestra-1,3,5(10),8,14-pentaen-17-one (0·2 g) was hydrogenated in benzene (10 ml) containing 2% Pd–$CaCO_3$ (0·07 g) to a gum, λ_{max} 282 mμ, which was reduced successively with $NaBH_4$ (0·07 g) in MeOH (10 ml) and Li (0·020 g) in liquid ammonia (100 ml)–tetrahydrofuran (50 ml)–aniline (1 ml). The *triene* formed crystals (0·05 g) m.p. 171–175° (from ether). The analytical sample had m.p. 173–177°, NMR (100 Mc): 3-proton doublet 8·69 τ, J 8 c/s (6α-Me); 1-proton multiplet 7·12 τ (C_6–H); and 1-proton doublet 3·17 τ, J 3 c/s (C_4–H). (Found: C, 79·5; H, 9·2 $C_{20}H_{28}O_2$ requires: C, 79·95; H, 9·4%.) (b) Li (0·05 g) was added to (±)-3-methoxy-6-methylestra-1,3,5(10),6-tetraen-17β-ol (0·3 g) in liquid ammonia (100 ml)–tetrahydrofuran (50 ml)–aniline (1 ml). After 1 hr several drops of acetone were added followed by dil. acetic acid. Repeated recrystallization of the product from ether gave the *triene* (0·017 g), m.p. 173–176°, undepressed by the sample prepared as in (a), λ_{max} 286 mμ (ε 2,100).

(±)-13β-*Ethyl*-17,17-*ethylenedioxy*-3-*methoxy*-6β-*methylgona*-1,3,5(10),8,14-*pentaene* (VIb; R = Et; W = $C_2H_4O_2$). 1-Diethylamino-6-*m*-methoxyphenylheptan-3-one and 6-*m*-methoxyphenylhept-1-en-3-one [35·5 g, prepared from 1-diethylamino-6-*m*-methoxyphenylhept-2-yne (52·3 g) as before] was refluxed for 18 hr with 2-ethylcyclopentane-1,3-dione in MeOH (100 ml) containing a trace of KOH. The resulting *trione* (53·3 g) was refluxed for 20 min with toluene *p*-sulfonic acid (from the monohydrate, 15 g) in benzene (600 ml; Dean-Stark separator). The gummy product (38 g), had b.p. 180–200° (bath)/0·003 mm, λ_{max} 311 mμ (ε 27,200).

An aliquot (28·4 g) was refluxed for 16 hr with ethylene glycol (50 ml) and toluene *p*-sulfonic acid (from the dihydrate, 11 g) in benzene (500 ml; Dean-Stark water separator). Filtration of the product in hexane through Florex gave the *pentaene* (16·8 g), m.p. 116–119°. The analytical sample had m.p. 120–122°, λ_{max} 312 mμ (ε 29,400). (Found: C, 78·15; H, 8·0 $C_{23}H_{28}O_2$ requires: C, 78·4; H, 8·0%.)

(±)-13β-*Ethyl*-3-*methoxy*-6β-*methylgona*-1,3,5(10)-*trien*-17-*one*. The foregoing pentaene (15·3 g) was hydrogenated in benzene (400 ml) containing 2% Pd–$CaCO_3$ (5 g) until 1 mole gas had been absorbed (10 min). Recrystallization of the product from 95% EtOH gave (±)-13β-ethyl-17,17-ethylenedioxy-3-methoxy-6β-methylgona-1,3,5(10),8-tetraene (11·0 g) m.p. 122–124°, λ_{max} 280 mμ (ε 15,100), which was reduced with Li (0·6 g) in liquid ammonia (600 ml)–tetrahydrofuran (330 ml)–aniline (30 ml) to (±)-13β-ethyl-17,17-ethylenedioxy-3-methoxy-6β-methylgona-1,3,5(10)-triene (9·5 g), m.p. 130–131° (from propan-2-ol), λ_{max} 280 mμ (ε 2,000). This triene was refluxed for 15 min in MeOH (200 ml)-11N HCl (5 ml) to yield the ketone (7·29 g), m.p. 115–123°. The analytical sample had m.p. 123–127° (from MeOH), λ_{max} 280 mμ (ε 2,200). (Found: C, 80·4; H, 8·9 $C_{21}H_{28}O_2$ requires: C, 80·7; H, 9·0%.)

(±)-13β-*Ethyl*-3-*methoxy*-6β-*methylgona*-1,3,5(10)-*trien*-17β-*ol* (VIIb; R = Et). (a) The foregoing ketone (7 g) was reduced with $NaBH_4$ (3 g) in MeOH (300 ml) to give the *alcohol* (6·8 g), m.p. 158–160°, NMR (100 Mc): 3-proton doublet 8·69 τ, J 8 c/s (6β-Me); 1-proton multiplet 7·04 τ (C_6–H); 1-proton doublet 3·33 τ, J 3 c/s (C_4–H). (Found: C, 80·1; H, 9·4 $C_{21}H_{30}O_2$ requires: C, 80·2; H, 9·6%.)

(b) (±)-13β-Ethyl-3-methoxy-6-methylgona-1,3,5(10),6-tetraen-17β-ol (0·1 g) was hydrogenated in benzene (10 ml) over 10% Pd–C (0·05 g) to the *alcohol* (0·065 g), m.p. 158–160°, identical to that prepared as in (a).

(c) (±)-13β-Ethyl-3-methoxy-6-methylgona-1,3,5(10),6-tetraen-17β-ol (0·25 g) was reduced with Li (0·012 g) in liquid ammonia (100 ml)–tetrahydrofuran (40 ml)–aniline (2 ml). Recrystallization of the product from ether gave the alcohol (0·09 g), m.p. 152–155° raised to 155–158° on admixture with material prepared as in (a).

(±)-13β-*Ethyl*-17β-*hydroxy*-6α-*methylgon*-4-*en*-3-*one* (X; R^1 = OH; R^2 = H). (±)-13β-Ethyl-3-methoxy-6β-methylgona-1,3,5(10)-trien-17β-ol (6·8 g) was reduced with Li (3·5 g) and EtOH (50 ml) in liquid ammonia (800 ml)–tetrahydrofuran (250 ml) to (±)-13β-ethyl-3-methoxy-6β-methylgona-2,5(10)-dien-17β-ol, m.p. 176–182°. The foregoing alcohol (1 g) was stirred under N_2 in MeOH (50 ml)-11N HCl (6 ml)–water (40 ml) (cf.[68]) for 1·5 hr. Chromatography of the product on alumina gave the *gonenone* (0·3 g), m.p. 127–130° (from ether–hexane), λ_{max} 240 mμ (ε 16,500). (Found: C, 79·6; H, 9·9 $C_{20}H_{30}O_2$ requires: C, 79·4; H, 10·0%.)

(±)-13β-*Ethyl*-17α-*ethynyl*-17β-hydroxy-6α-*methylgon*-4-*en*-3-*one* (X; R^1 = OH; R^2 = C≡CH). (±)-13β-Ethyl-3-methoxy-6β-methylgona-2,5(10)-dien-17β-ol (5·5 g) was refluxed for 2·5 hr under N_2 in toluene (250 ml)–cyclohexanone (50 ml) containing aluminum isopropylate (4 g). The resulting (±)-13β-ethyl-6β-methylgona-2,5(10)-dien-17-one (3·5 g), m.p. 163–166° (from MeOH) was stirred for 4 hr under acetylene in dimethylacetamide (35 ml) containing lithium acetylide–ethylenediamine complex. The gummy product was stirred for 1 hr under N_2 in MeOH (90 ml)-11N HCl (6 ml)–water (4 ml). Chromatography of the product on Florex gave the gonenone (0·6 g), m.p. 148–151° (from ether–hexane), λ_{max} 240 mμ (ε 15,300). (Found: C, 81·0; H, 9·6 $C_{22}H_{30}O_2$ requires: C, 80·9; H, 9·3%.)

(±)-13β-*Ethyl*-6α-*methylgon*-4-*en*-3,17-*dione* (X; R^1 + R^2 = 0). (±)-13β-Ethyl-17β-hydroxygon-4-en-3-one (1·5 g) in acetone (40 ml) was oxidized for 10 min with 8N CrO_3[14] (2·5 ml) to give the *dione* (1·1 g), m.p. 160–162° (from ethyl acetate), NMR (60 Mc): 3-proton doublet 8·87 τ, J 7 c/s (6α-Me); and 1-proton multiplet 4·13 τ (6β-H). (Found: C, 80·00; H, 9·23 $C_{20}H_{28}O_2$ requires: C, 79·95; H, 9·39%.)

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