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Thiosteroids. XXII.[1] The Intramolecular Cyclization of 6-Acylthio-, Acyloxy-, and Acylamino-4-en-3-one Steroids. Pentacyclic Steroids

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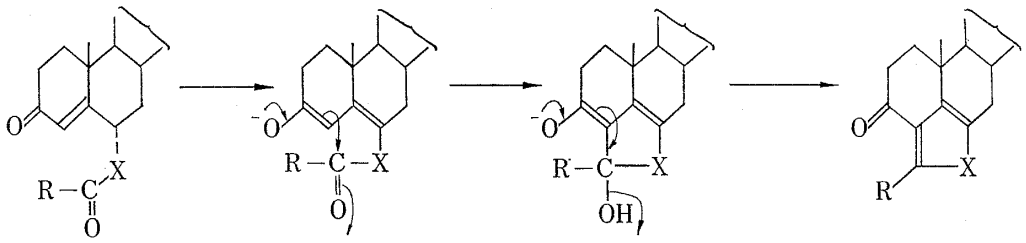
Extension on the cyclization reaction of a steroidal 6α-acetylthio-4-en-3-one by treatment of sodium hydride, giving a methyl thiophene fused at C_4, C_5, and C_6, was studied. Similar cyclization of 6α-acetoxy- and 6α-acetylamino-4-en-3-one, yielding a methylfuro- and a methylpyrrolo compound, respectively, was observed in considerable yield. The more facile cyclization was found in 6α-benzoyloxy- and 6α-benzoylthio-4-en-3-one. The structure of the former, 6-phenylfuro compound, was established chemically by the oxidation to an ene-dione (VI). In addition, benzenosteroids fused at C_4, C_5, and C_6 were also synthesized.

Among a large number of papers[3] dealing with biologically active steroids possessing a heteroaromatic ring fused in their flame work, only a few reported on the syntheses of pentacyclic steroids fused at C_4, C_5 and C_6.[4-7]

In 1963, we also published on the intramolecular Aldol condensation of 6-acetylthio-4-en-3-one to the 5′-methylthieno [4′,3′,2′-4,5,6]-5-en-3-one.[8] From the mechanism postulated in the article (*cf.* Chart 1), we expected that the reaction scheme would also be applicable to other systems, for instance, 6-acylthio-, 6-acyloxy-, and 6-acylamino-4-en-3-one as well as



X=S, O, NH, R=CH_3, Ph

Chart 1

1) Part XXI: T. Komeno, S. Ishihara, H. Itani, H. Iwakura, and K. Takeda, *Chem. Pharm. Bull.* (Tokyo), **17**, 2110 (1969).
2) Location: *Fukushima-ku, Osaka.*
3) Heteroaromatic steroids containing a nitrogen atom recently have been reviewed by M. M. Smith and M.F. Sugrue, *J. Pharm. Pharmacol.*, **16**, 569 (1964); Furosteroid fused at C_2 and C_3: J.C. Orr, M.L. Franco, A.D. Cross, and F. Sondheimer, *Steroids*, **3**, 1 (1964); H. Minato, and T. Nagasaki, *Chem. Ind.* (London), **1965**, 899; D.L. Storm and T.A. Spencer, *Tetrahedron Letters*, **1967**, 1865; Furosteroid fused at C_3 and C_4: S. Julia and C. Moutonnier, *Bull. Soc. Chim. France*, **1964**, 979; Pyrrolosteroid fused at C_2 and C_3: T.C. Miller and P.G. Christiansen, *J. Org. Chem.*, **29**, 3612 (1964).
4) For methylbenzenosteroid: J.M.H. Graves and H.J. Ringold, *Steroids*, **5** (Suppl. 1), 23 (1965).
5) For benzenosteroid: R. Gardi, P. Vitali, and P.P. Castelli, *Tetrahedron Letters*, **1966**, 3203.
6) For pyridinosteroid: R. Sciaky, U. Pallini, *Tetrahedron Letters*, **1964**, 1839; R. Sciaky, U. Pallini, and A. Consonni, *Gazz. Chim. Ital.*, **96**, 1284 (1966).
7) For isoxazolosteroid: J.T. Rinhey and E. Rizzardo, *Chem. Commun.*, **1965**, 362.
8) K. Takeda, T. Komeno, and S. Ishihara, *Chem. Pharm. Bull.* (Tokyo), **11**, 500 (1963); **12**, 1433 (1964).

6-acetylthio-4-en-3-one. The present paper describes the extension of this reaction; cyclization of 6-acetoxy, -benzoyloxy, -acetylamino, and -benzoylthio-4-en-3-one, as well as 6-(3′-acetoxy-1′-propenyl)-4-en-3-one.

Synthesis of 6-acetoxy-4-en-3-one has been fully investigated by Ehrenstein,[9] Bernstein,[10] and others,[11] but in no cases the formation of the furosteroid in problem has been mentioned. In fact, contrary to the facile formation of thienosteroid from 6-acetylthio-4-en-3-one with basic alumina, a similar treatment of 6α-acetoxyprogesterone (Ia) led mainly to recovery of starting material accompanied by a small amount of the hydrolysis product. Under the condition successful for cyclization of the acetylthio compound (heating under reflux in toluene with sodium hydride), 6α-acetoxyprogesterone (Ia) remained unchanged. However, replacement of toluene by boiling xylene and prolongation of the reaction time (20—50 hours) yielded 42% of 5′-methylfuro[4′,3′,2′-4,5,6]pregn-5-ene-3,20-dione (IIa). The structure of this compound was assigned on the basis of its analysis as well as absorption in the ultraviolet (UV) region (λ_{max} 228 and 298 mμ)[12] and in the infrared (IR) region (ν_{max} 1707, 1690, 1662, and 1582 cm^{-1}) but more particulary on the basis of its nuclear magnetic resonance (NMR) spectrum showing a singlet assigned to an aromatic methyl group at 7.47 τ and no olefinic protons. This compound was condensed with maleic anhydride to give a 1:1 adduct (III), treatment of which with base or acid regenerated the parent furo compound (IIa). The stereochemistry of this Diels–Alder adduct will be discussed in the following papers. In a similar manner the 5′-methylfuro[4′,3′,2′-4,5,6]-5-en-3-ones of testosterone acetate (IIb) and of 17,20,20,21-bismethylenedioxy (BMD) derivative of substance-S (IId) were prepared from the corresponding 6-acetoxyl compounds. In the last case, the fact that a considerable amount of substance-S BMD was obtained indicates that the reaction may be accompanied by hydrogenolysis of the allylic acetoxyl moiety. Treatment of the BMD derivative (IId) with 60% formic acid afforded 17α,21-dihydroxy-5′-methylfuro[4′,3′,2′-4,5,6]pregn-5-ene-3,20-dione without cleavage of the furan ring. It is well known that 6α-acetoxy-1,4-dien-3-one does not easily isomerize to 1-ene-3,6-dione with alkali. 6α-Acetoxypregna-1,4-diene-3,20-dione (Id) remained unchanged even after 70 hours reflux in xylene with sodium hydride. Recently cyclization of 17α-acetoxypregnenolone to 17-spirobutenolide with potassium tert-butoxide was reported by Lehman and Dyson.[13] But different from our reaction scheme the condensation have taken place between the methyl of the acetoxyl function and the carbonyl of the 17-acetyl group.

Reduction of 5α-hydroxy-6β-azido-3-ethylene ketal with lithium aluminum hydride followed by successive acetylation, hydrolysis of ketal, and dehydration with acid led to 6α-acetylamino-progesterone (XIIa) and -testosterone acetate (XIIb). Cyclization of these compounds with sodium hydride required a longer reaction time (50—90 hours) and afforded the pyrrolo compounds, (XIIIa) and (XIIIb), in low yield as a sole crystalline product, respectively. These compounds exhibited the absorption maxima at 256 and 310 mμ in the UV spectra and at 1655, 1620, and 1540 cm^{-1} in the IR spectra. Their NMR spectra showed a singlet due to a pyrrole methyl group at 7.50 τ, a multiplet (Wh/2=9.5 cps) integrating to one proton at 1.23 τ indicative of imino moiety, and no olefinic proton.

9) M. Ehrenstein and T.O. Stevens, *J. Org. Chem.*, **5**, 318 (1940); **6**, 908 (1941); M. Ehrenstein, *ibid.*, **6**, 626 (1941); **13**, 214 (1948); P. Th. Herzig and M. Ehrenstein, *ibid.*, **16**, 1050 (1951); C.P. Balant and M. Ehrenstein, *ibid.*, **17**, 1587 (1952).

10) S. Bernstein and R. Littel, *J. Org. Chem.*, **25**, 313 (1960); **27**, 2544 (1962); **28**, 92 (1963); S. Bernstein, W.S. Allen, C.E. Linden and J. Clemente, *J. Am. Chem. Soc.*, **77**, 6612 (1965).

11) J. Romo, G. Rosenkranz, C. Djerassi, and F. Sondheimer, *J. Org. Chem.*, **19**, 1509 (1954); F. Sondheimer, O. Mancera, and G. Rosenkranz, *J. Am. Chem. Soc.*, **76**, 5020 (1954); H. Mōri, *Chem. Pharm. Bull.* (Tokyo), **9**, 328 (1961); R. Sciaky and A. Consonni, *Gazz. Chim. Ital.*, **91**, 545 (1961); **92**, 547 (1962).

12) The UV absorption maximum of simple β-furyl ketones is observed at 251—255 mμ. T. Matsuura, K. Naya, N. Ichikawa, and T. Kubota, *Bull. Chem. Soc. Japan*, **35**, 1695 (1962).

13) H.G. Lehman, *Angew. Chem. Intern. Ed. Engl.*, **4**, 783 (1965); N.H. Dyson, J.A. Edwards and J.H. Fried, *Tetrahedron Letters*, **1966**, 1841.

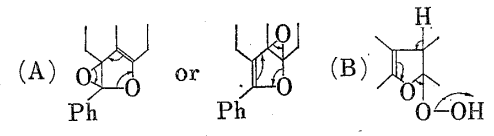
On the other hand, 6α-benzoyloxy-progesterone (Ie) and -androstenedione (If) were cyclized more easily and in a better yield to 5′-phenylfuro compounds, (IIf) and (IIj), respectively. The reaction of 6α-benzoyloxyprogesterone (Ie) with sodium hydride in boiling xylene for only 5 hours afforded a mixture of 17-*n*- and 17-iso-phenylfuro compounds, (IIf) and (IIg), total yield of 60.3%, which was separated by chromatography. In the latter compound (IIg) the structure of 17α-acetyl side chain was deduced from the large levorotatory contribution to the M_D ($\Delta M_{D(17\alpha-17\beta)} = -255$)[14] and the change in the chemical shift of the 18-methyl group in the NMR spectra ($\Delta\tau_{(17\alpha-17\beta)} = -0.28$ ppm) and was, in addition, established chemically by conversion to the 17-*n*-compound (IIf) with base. The biaryl nature of these compounds is reflected in their UV spectra (λ_{max} 225.5 and 348 mμ). The reaction of 5′-phenylfuroprogesterone (IIf) with ethanedithiol gave the monothioketal (IIh), which was desulfurized by Raney nickel to the 20-desoxo compound (IIi). Huang–Minlon reduction of IIf and IIj yielded 3-desoxo compound, (IVa) and (IVb), respectively. In contrast to no reaction with IIf, the 3-desoxo compound (IVa) was treated with maleic anhydride to give a 1:1 adduct (V). It is interesting to note that the 3-desoxo compound (IVb) was unstable in an atomosphere of air and slowly oxidized to give a compound, which was assigned to 4-benzoyl-4-en-6-one (VI) from the following results. The identical compound was also obtained by oxidation of IIb with an equivalent of *m*-chloroperbenzoic acid.[15] Baeyer–Villiger reaction of VI by treatment with an additional equivalent of peracid afforded 4,6-dione 4-enolbenzoate (VII) having a negative CD curve ($[\theta]_{333}$ −14190).[16] Reduction of VII with lithium aluminum hydride gave a mixture of 5-en-4α-ol (VIII) and 4-en-6α-ol (IX),[17] which was easily separated by means of preparative thin-layer chromatography (TLC). The structure of these allyl alcohols was assumed by their NMR spectra and was established by direct comparison with the authentic samples.

The cyclization of the other acylates of 6α-hydroxyprogesterone; *m*-dinitrobenzoate (Ig), *p*-nitrobenzoate (Ih), formate (Ii), and trifluoroacetate (Ij) was attempted, but in no cases the formation of the furo compounds was not observed. Similarly, 6α-benzoylaminotestosterone (XIIc) could not be converted to the phenylpyrrolo compound, but instead gave a complex mixture.

6α-Benzoylthioandrost-4-en-3-one was prepared on two different routes. Treatment of 17β-acetoxy-5α,6α-epoxyandrostan-3-ethyleneketal with thiocyanic acid in ether gave 5α,17β-dihydroxy-6β-thiocyanatoandrostan-3-ethyleneketal 17-acetate without affecting the 3-ketal moiety as previously observed by us[18] in the case of the reaction of 5α,6α-epoxypregnane-3,20-bisethyleneketal with thiocyanic acid (which results in the oxide-fission and partial hydrolysis of the 20-ketal). Reduction of the thiocyanatohydrin ketal with lithium aluminum hydride, followed by benzoylation and hydrolysis, afforded 27% of 5α,17β-dihydroxy-6β-mercaptoandrostan-3-one 6,17-dibenzoate and 7.2% of the desulfurized product, 5α,17β-dihydroxyandrostan-3-one 17-benzoate. The former compound was dehydrated with hydrochloric acid in chloroform to give 6α-benzoylthiotestosterone (XIVa). Alternatively, 6α-benzoylthioandrosta-4,9(11)-diene-3,17-dione (XIVb) was obtained more easily by treatment of 6β-

14) 17-Iso-20-oxopregnanes were reviewed by M.B. Rubin, *Steroids*, **2**, 561 (1963).

15) This oxidation with peracid was also observed in the 3-oxo compound (IIk) (see Experimental) and may be explained by the following mechanism (A). Autooxidation of the 3-desoxo compound (IVb) probably proceeds *via* an intermediate such as (B).



16) It is described that the CD curves of cholest-4-en-6-one is negative whereas that of cholest-5-en-4-one is positive. *cf.* C. Djerassi "Optical Rotatory Dispersion," McGraw-Hill Co., 1960, p. 68.

17) Reduction of cholest-4-en-6-one with $LiAlH_4$ gives preferably 4-en-6α-ol. E.J. Becker and E. Walls, *J. Org. Chem.*, **20**, 353 (1955); D.N. Jones, J.R. Lewis, C.W. Shoppee, and G.H. R. Summer, *J. Chem Soc.*, **1955**, 2876.

18) K. Takeda, T. Komeno, S. Ishihara, and H. Itani, *Chem. Pharm. Bull.* (Tokyo), **14**, 1096 (1966).

bromoandrostadienedione with potassium thiolbenzoate. The most facile cyclization of these benzoylthio compound, (XIVa) and (XIVb), was achieved by heating with sodium hydride in boiling toluene for 1—2 hours, whereby the phenylthieno compounds, (XVa) and (XVd), were obtained in 82 and 58% yield, respectively. Huang-Minlon reduction of (XVa) gave the 3-desoxo compound (XVI), which shows the absorption maximum at 294 mμ in the UV spectrum.

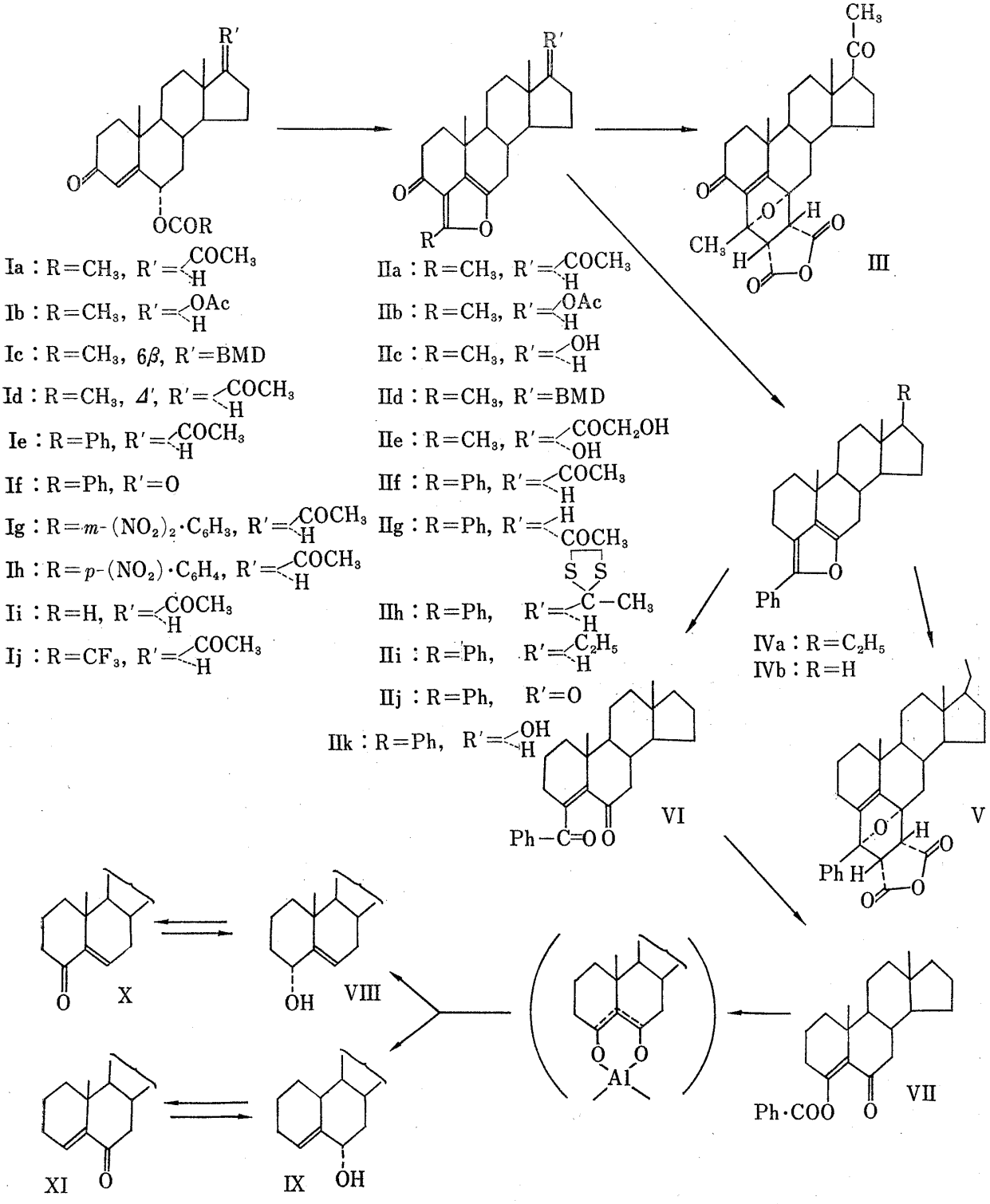


Chart 2 (continued)

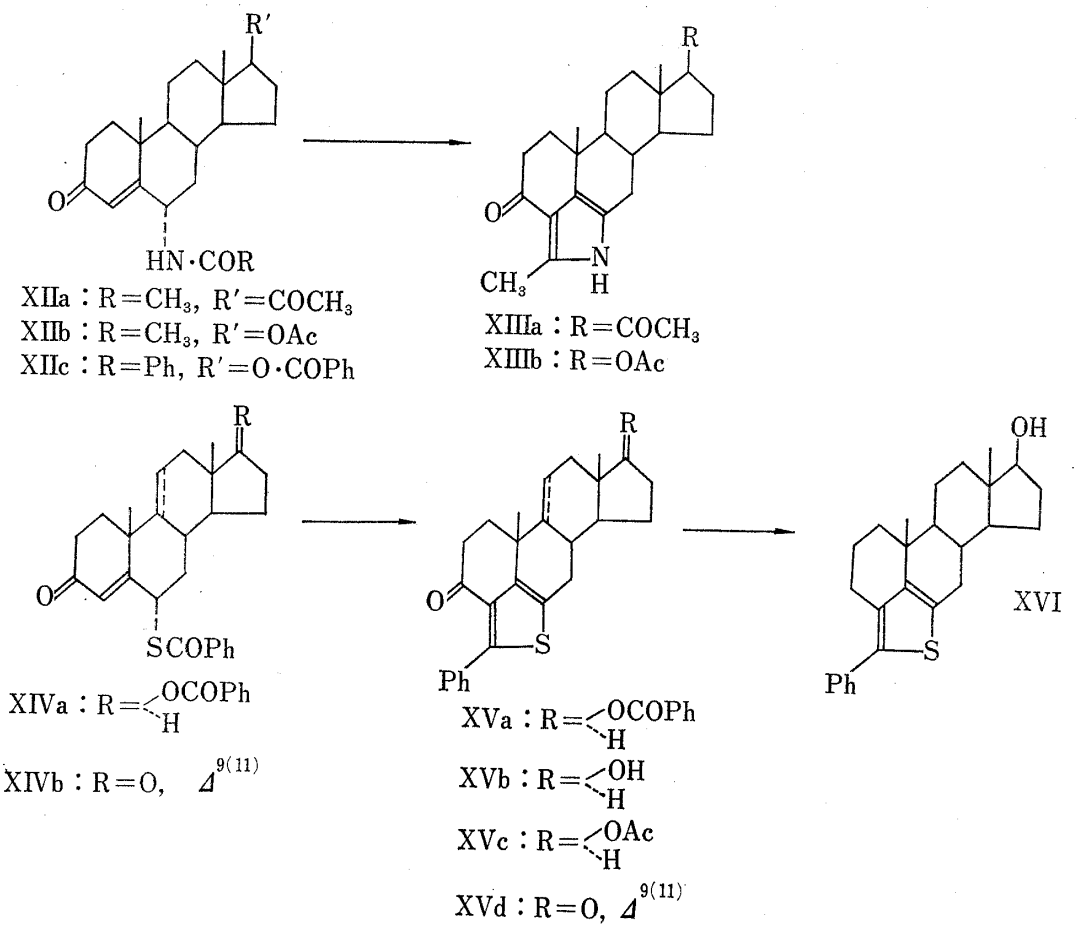


Chart 2

Finally, synthesis of the benzenosteroid was attempted following the same idea, namely intramolecular attack by the enolate anion and subsequent elimination of water. We chose 6-(3′-acetoxy-1′-propenyl)progesterone (XXIII) as substrate. Treatment of 5α,6α-epoxypregnane-3,20-bisethyleneketal (XVII) with 3-tetrahydropyranyloxyprop-1-yne magnesium bromide, followed by hydrolysis with aqueous acetic acid, gave 6β-(3′-hydroxyprop-1′-ynyl)-5α-hydroxypregnane-3,20-dione (XXa) in 80% yield. While hydrogenation of the acetate (XXb) over palladium–charcoal gave 6β-propyl-5α-hydroxypregnane-3,20-dione (XXI), with Lindlar catalyst the *cis*-allyl alcohol (XXII) was obtained, the structure of which was clarified by the NMR spectrum showing two olefinic protons at 3.8—4.65 τ as multiplet. Dehydration of XXII with thionyl chloride–pyridine, followed by treatment with sodium hydride in boiling xylene for 18 hours and chromatography over alumina, gave 17.6% of the benzenosteroid (XXIV) accompanied by a small amount of the dienone (XXV) (UV λ_{max} 294.5 mμ). The structure of the former product (XXIV) was established by the NMR spectrum which exhibits two protons centered at 2.77 τ and one proton centered at 2.15 τ assigned to the benzene protons and by the UV spectrum which is similar to that of the thieno compounds. The physical constants of XXIV were in accord with those reported by Gardi.[5] Formation of XXIV indicates that dehydrogenation occurs during the reaction. This observation led us to carry out the reaction of 6-exomethylenetestosterone (XXVIa) and -progesterone (XXVIb)[19] with dimethyl acetylene dicarboxylate, which gave the benzenosteroid, (XXVIIa) and (XXVIIc),

19) D. Burn, B. Ellis, P. Feather, D.N. Kirk, and V. Petrow, *Chem. Ind.* (London), **1962**, 1907; D. Burn, G. Cooley, M.T. Davies, J.W. Ducker, B. Ellis, P. Feather, A.K. Hiscock, D.N. Kirk, A.P. Leftwick, V. Petrow, and D.M. Williamson, *Tetrahedron*, **20**, 597 (1964).

respectively in good yield. However, decarboxylation of the free acid (XXVIIc) with lead tetraacetate was unsuccessful.

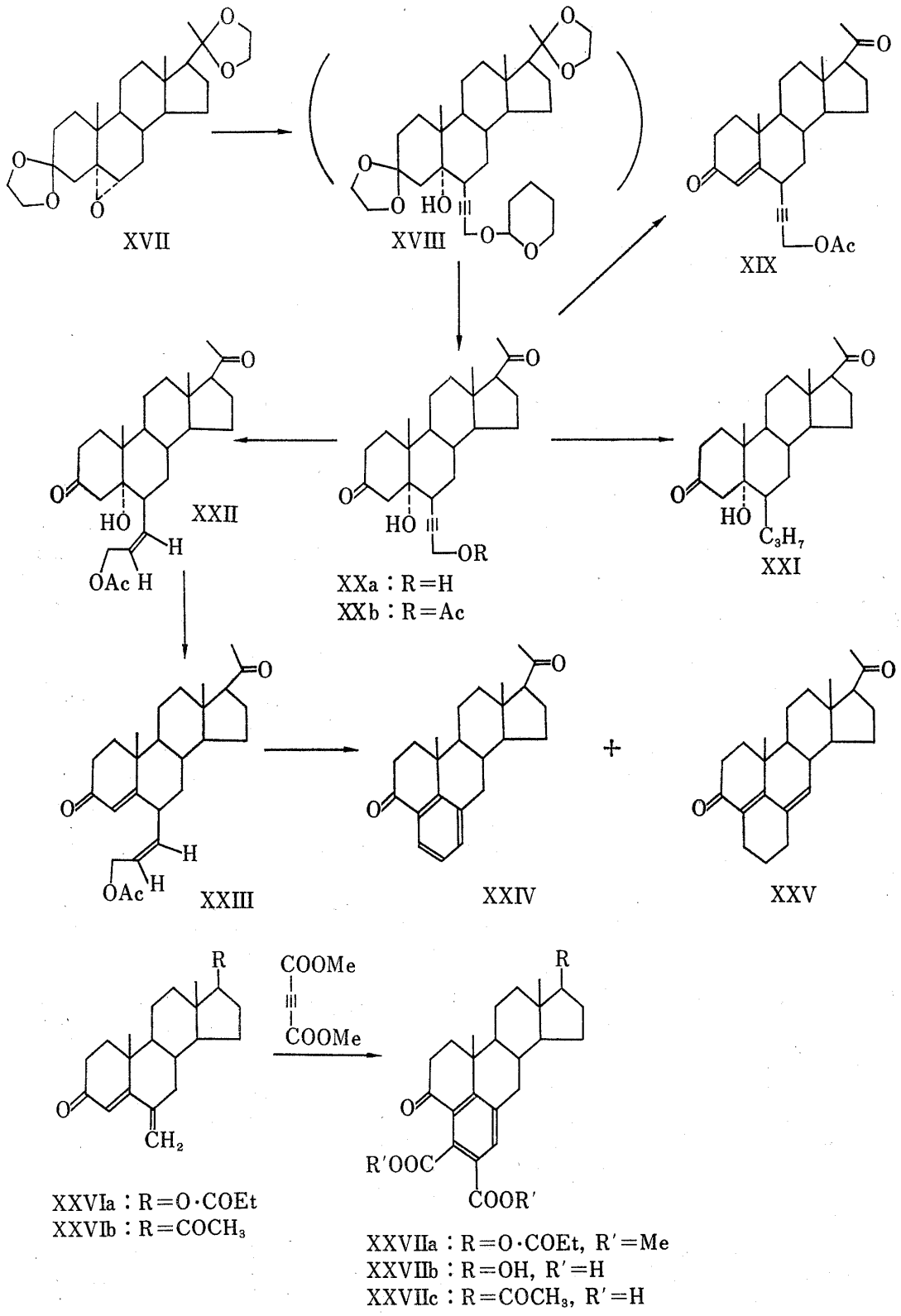


Chart 3

Experimental[20]

5′-Methylfuro[4′,3′,2′-4,5,6]pregn-5-ene-3,20-dione (IIa)——To a solition of 4.9 g of 6α-acetoxyprogesterone (Ia)[9] in 200 ml of xylene 3.2 g of NaH was added and the resulting mixture was refluxed with stirring for 88 hr. After cooling the excess of NaH and the precipitates were removed by filtration and washed with benzene. The combined filtrates were evaporated to dryness under reduced pressure. The residue was chromatographed over 125 g of standardized Al_2O_3. The fractions (2.718 g) eluted with pet ether–benzene (2:1, 1:1) and benzene were crystallized from ether to afford 1.973 g (42.3%) of IIa, which was further recrystallized from CH_2Cl_2–MeOH to give the pure sample, mp 161—162°, $[\alpha]_D^{26.5}$ −46.3±2° (c=1.028). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1707, 1690, 1662, 1582. UV λ_{max} mμ (ε): 208.5 (16000), 298.5 (3260). NMR (τ): (18-H) 9.28, (19-H) 8.82, (21-H) 7.86, (furan–Me) 7.47. *Anal.* Calcd. for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 78.23; H, 8.58.

Addition of Maleic Anhydride to 5′-Methylfuro[4′,3′,2′-4,5,6]pregn-5-ene-3,20-dione (IIa)——A solution of 194 mg of IIa and 70 mg of maleic anhydride in 3 ml of benzene was refluxed for 8 hr. After cooling, the appeared precipitate was collected by filtration and washed with a small amount of benzene. Recrystallization from CH_2Cl_2–benzene afforded 156 mg of the adduct III, mp 154—156° (decomp.), $[\alpha]_D^{23.5}$ +35.8±2° (c =1.069). IR ν_{max} cm^{-1}: 1892, 1889, 1777, 1703, 1663, 1235, 1095, 927. UV λ_{max} mμ (ε): 250.5 (11070). NMR (τ): (18-H) 9.28, (19-H) 8.82, (21-H) 7.88, (Me) 8.14, (CO–O–COCH) 6.77s (2H). *Anal.* Calcd. for C_{27}-$H_{32}O_6$: C, 71.66; H, 7.13; O, 21.21. Found: C, 71.83; H, 7.15; O, 21.13.

A solution of 150 mg of the adduct (III) in 5 ml of AcOH and 0.5 ml of 48% HBr was heated on a steam bath for 2 hr, poured into water, and extracted with ether. The ethereal solution was evaporated and the residue was crystallized from ether yielding 110 mg of the parent furan (IIa).

17β-Acetoxy-5′-methylfuro[4′,3′,2′-4,5,6]androst-5-en-3-one (IIb)——A mixture of 2.015 g of 6α,17β-diacetoxyandrost-4-en-3-one (Ib), 750 mg of NaH, and 60 ml of xylene was heated under reflux for 17 hr. The product was chromatographed over 36 g of Al_2O_3. The fractions (1.01 g) eluted with pet ether–benzene (4:1—1:1) were recrystallized from aq. MeOH to afford 512 mg (26.6%) of IIb, mp 128—130°, $[\alpha]_D^{25.5}$ −116.3 ±2° (c=0.982). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740, 1250, 1689, 1664, 1582. UV λ_{max} mμ (ε): 211 (15070), 297.5 (3300). NMR (τ): (18-H) 9.12, (19-H) 8.82, (AcO) 7.95, (furan–Me) 7.48, (17α-H) 5.35t. *Anal.* Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.84; H, 8.27. Treatment of IIb with 10% K_2CO_3–aq. MeOH at room temperature overnight afforded IIc, which was recrystallized from acetone–hexane, mp 196—198°, $[\alpha]_D^{27}$ −120.0± 2° (c=0.982). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3644, 1690, 1664, 1583. UV λ_{max} mμ (ε): 208.5 (15120), 230inf (7460), 296 (3190). *Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.68; H, 8.63.

17α,21-Dihydroxy-5′-methylfuro[4′,3′,2′-4,5,6]pregn-5-ene-3,20-dione (IIe)——According to the method described by Bernstein[10] 8.474 g of 3-ethoxy-17α,20,20,21-bismethylenedioxypregna-3,5-diene was oxidized with monoperphthalic acid. The product was crystallized from ether to give 4.533 g of 6β-hydroxy-4-en-3-one, which on acetylation with pyridine–Ac_2O in the usual manner afforded 4.642 g of Ic, mp 174—175°, $[\alpha]_D^{25}$ −55.6±2° (c=1.051). IR ν_{max} cm^{-1}: 1738, 1680, 1625. *Anal.* Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68. Found: C, 67.41; H, 7.74.

A mixture of 5.859 g of Ic, 1.9 g of NaH, and 300 ml of xylene was refluxed for 20 hr. The crude product was chromatographed over 180 g of Al_2O_3. The fractions eluted with pet ether–benzene (2:1) gave 530 mg of crystals, which upon recrystallization from acetone afforded 450 mg of IId, mp 220—222°, $[\alpha]_D^{24}$ −182.4±2° (c=1.049). IR ν_{max} cm^{-1}: 1688, 1662, 1586, 1095, 1079, 939. UV λ_{max} mμ (ε): 210 (14030), 230inf (7550), 297 (3190). *Anal.* Cacld. for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found: C, 70.32; H, 7.59. The fractions eluted with pet ether–benzene and benzene were crystallized from ether to yield 270 mg of 17α, 20,20,21-bismethylenedioxypregn-4-en-3-one, mp 246—247°, which was identified with the authentic sample by a mixed mp and comparison of the IR spectrum.

A mixture of 339 mg of IId, 20 ml of 60% HCO_2H, and 10 ml of ethylene glycol was heated to 100° with stirring for 1 hr. After cooling the mixture was poured into water and extracted with CH_2Cl_2. The organic solution was washed with 5% Na_2CO_3, dried, and evaporated to dryness *in vacuo*. The residue was crystallized from ether to yield 184 g of IIe, which was further recrystallized from CH_2Cl_2–MeOH affording the pure sample (132 mg), mp 245—248° (decomp.), $[\alpha]_D^{24.5}$ −101.0±2° (c=0.996). IR ν_{max} cm^{-1}: 3466, 1702, 1684, 1652,

20) All melting points were measured on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined in 1% EtOH–$CHCl_3$ with a Perkin-Elmer Polarimeter, type 141. Unless otherwise stated UV spectra were recorded in 95% EtOH with a Hitachi EPS-2 spectrophotometer and IR spectra in Nujol mulls by use of a Koken DS-201B spectrophotometer. All NMR spectra were taken on $CDCl_3$ solutions with a Varian A-60 spectrometer, tetramethylsilane serving as internal standard. For preparative TLC silica gel G (E. Merck Co.) was used as an adsorbent. Usually a weighed amount of sodium hydride (50% mineral oil dispersion: Metal Hydrides, Inc.), washed three times with dry pet-ether, was used for the cyclization reaction.

1570. UV λ_{max} mμ (ε): 209.5 (15,090), 230inf (7220), 297 (3350). *Anal.* Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.28; H, 7.83.

6α-Acetylaminotestosterone Acetate (XIIb)——A solution of 2.552 g of 5α,6α-epoxy-3,3-ethylenedioxy-androstan-17β-ol acetate and 2.55 g of NaN_3 in 24 ml of 40% dioxane was heated to 140° in a sealed tube for 92 hr. After working up in the usual manner the product was recrystallized from acetone–hexane to give 2.347 g of 3,3-ethylenedioxy-5α,17β-dihydroxy-5α-androstan-6β-azide, mp 126—127°, $[\alpha]_D^{25}$ −109.2±2° (c =1.071). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3640, 3487, 2089, 1112, 1085. *Anal.* Calcd. for $C_{21}H_{33}O_4N_3$: C, 64.42; H, 8.50; N, 10.73. Found: C, 64.63; H, 8.55; N, 10.69.

A solution of 2.310 g of the azide in 100 ml of dry tetrahydrofuran was added to a suspension of 2.24 g of $LiAlH_4$ in 100 ml of dry ether with stirring during 30 min. The resulting mixture was agitated for 3.5 hr. After working up in the usual manner the product was acetylated with pyridine–Ac_2O. The product was recrystallized from acetone–hexane yielding 2.076 g of 6β-acetylamino-5α,17β-dihydroxy-3-ketal 17-acetate, mp 220.5—221.5°, $[\alpha]_D^{25}$ −59.4±2° (c=1.003). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470, 1725, 1675, 1506, 1111, 1083. *Anal.* Calcd. for $C_{25}H_{39}O_6N$: C, 66.79; H, 8.74; N, 3.16. Found: C, 66.52; H, 8.47; N, 3.09.

A solution of 2.023 g of the above ketal in 45 ml of 65% AcOH was heated on a steam-bath for 1 hr. After working up, a gentle stream of HCl was bubbled into a solution of the isolated product in 25 ml of AcOH during 4 hr. The resulting mixture was poured into water, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with 10% Na_2CO_3 and water, dried, and evaporated. The residue was recrystallized from MeOH to afford 1.225 g of (XIIb), mp 133—136°, $[\alpha]_D^{25.5}$ +46.0±2° (c=1.021). IR ν_{max} cm^{-1}: 3578, 3245, 3055, 1731, 1678, 1646, 1618, 1546, 1254. NMR (τ): (18-H) 9.15, (19-H) 8.72, (Ac) 7.98, 7.96, (4-H) 4.15, (6β-H, 17α-H) 4.9—5.7m, (NH) 3.41d ($J\approx$9.0). *Anal.* Calcd. for $C_{23}H_{33}O_4N\cdot CH_3OH$: C, 68.70; H, 8.89; N, 3.34. Found: C, 68.85; H, 8.89; N, 3.35.

5′-Methylpyrrolo[4′,3′,2′-4,5,6]pregn-5-ene-3,20-dione (XIIIa)——A mixture of 1.191 g of XIIa,[21] 635 mg of NaH, and 50 ml of xylene was refluxed for 48 hr. The product (835 mg) was chromatographed over 15 g of neutral Al_2O_3 (grade II). The fractions eluted with benzene and benzene–CH_2Cl_2 (9:1—2:1) were recrystallized from acetone–hexane yielding 185 mg (15.4%) of XIIIa, mp 277—280° (decomp.), $[\alpha]_D^{24.5}$ −28.7±2° (c=1.014). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3448, 3288, 1698, 1656, 1619, 1537. UV λ_{max} mμ (ε): 209.5 (11770), 256 (11440), 310 (4110). NMR (τ): (18-H) 9.30, (19-H) 8.83, (21-H) 7.86, (pyrrole-Me) 7.50, (NH) 1.23. *Anal.* Calcd. for $C_{23}H_{31}O_2N$: C, 78.14; H, 8.84; N, 3.96. Found: C, 78.09; H, 9.05; N, 4.04.

17β-Acetoxy-5′-methylpyrrolo[4′,3′,2′-4,5,6]androst-5-en-3-one (XIIIb)——A mixture of 3.729 g of XIIb, 1.38 g of NaH and 280 ml of a mixture of xylene and toluene (1:1) was refluxed for 49 hr. The isolated product was chromatographed over 75 g of silicagel. The fractions eluted with CH_2Cl_2 was further purified by means of preparative TLC using benzene–MeOH (9:1) as developing solvent. Crystallization from ether afforded 718 mg (19.7%) of XIIIb, which was twice recrystallized from AcOEt affording 585 mg of the pure sample, mp 267—269°, $[\alpha]_D^{23}$ −87.5±2° (c=1.047). IR ν_{max} cm^{-1}: 3185, 3060, 1735, 1652, 1615, 1538, 1253. UV λ_{max} mμ (ε): 209 (11830), 257 (11470), 310 (4120). *Anal.* Calcd. for $C_{23}H_{31}O_3N$: C, 74.76; H, 8.46; N, 3.79. Found: C, 74.87; H, 8.51; N, 4.01.

5′-Phenylfuro[4′,3′,2′-4,5,6]pregn-5-en-3,20-dione (IIf)——A mixture of 6.914 g of the oily benzoate (Ie), 3.3 g of NaH, and 200 ml of xylene was refluxed for 5 hr. The product was chromatographed over 100 g of neutral Al_2O_3 (grade II). The fractions eluted with pet. ether–benzene (1:1) afforded 106 mg of the solid, which upon recrystallization from acetone gave 69 mg (1.1%) of the 17-iso compound (II g), mp 203—205.5°, $[\alpha]_D^{24}$ −228.4±2° (c=0.991). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3075, 1708, 1688, 1653, 1603, 1582, 1164, 688. UV λ_{max} mμ (ε): 225.5 (20290), 245inf (9900), 349 (13440). *Anal.* Calcd. for $C_{28}H_{32}O_3$: C, 80.73; H, 7.74. Found: C, 80.92; H, 7.80. This compound was treated with 5% KOH–MeOH affording the 17-*n*-compound (IIf).

The fractions eluted with pet. ether–benzene (1:2) yielded 1.440 g of a mixture of IIf and IIg, which was treated with 5% KOH–MeOH. The product was recrystallized from CH_2Cl_2–acetone yielding 1.052 g (17.6%) of the 17-*n*-compound (IIf), mp 203—205°, $[\alpha]_D^{25.5}$ −167.1±2° (c=1.015). IR ν_{max} cm^{-1}: 3060, 1694, 1680, 1648, 1600, 1580, 778, 741, 696. UV λ_{max} mμ (ε): 225.5 (20150), 245inf (9770), 348 (13340). NMR (τ): (18-H) 9.28, (19-H) 8.79, (21-H) 7.86, (Ph–H)2.62m (3H), 1.68 (2H). *Anal.* Calcd. for $C_{28}H_{32}O_3$: C, 80.73; H, 7.74. Found: C, 80.92; H, 7.77. The eluates with pet. ether–benzene (1:3) and benzene were recrystallized from CH_2Cl_2–acetone to give an additional 2.478 g (41.6%) of IIf. Combined yield of IIf: 59.2%.

5′-Phenylfuro[4′,3′,2′-4,5,6]pregn-5-en-3-one (IIi)——To a solution of 500 mg of IIf and 0.5 ml of ethanedithiol in 18 ml of AcOH 0.5 ml of $BF_3\cdot OEt_2$ was added and the resulting mixture was allowed to stand at room temperature for 2 days. The appeared precipitate was filtered off, washed with cold MeOH, and the solid was recrystallized from CH_2Cl_2–MeOH affording 533 mg (90.2%) of the thioketal (IIh), mp 231—232° (decomp.), $[\alpha]_D^{24}$ −172.0±2° (c=1.049). IR ν_{max} cm^{-1}: 1674, 1647, 1595, 1578, 1525, 1062, 976, 775, 738, 691. *Anal.* Calcd. for $C_{30}H_{36}O_2S_2$: C, 73.13; H, 7.36; S, 13.01. Found: C, 72.88; H, 7.60; S, 13.18.

The thioketal (497 mg) was desulfurized by heating with Raney nickel in dioxane for 2 hr. Recrystallization from acetone gave 260 mg of (IIi), mp 144—145°, $[\alpha]_D^{25.5}$ −209.1±2° (c=0.971). IR ν_{max} cm^{-1}: 3069,

21) This compound was prepared by Dr. K. Sasaki in this laboratory: unpublished data.

1680, 1647, 1601, 1581, 1531, 1065, 974, 775, 742, 692. *Anal.* Calcd. for $C_{28}H_{32}O_2$: C, 83.75; H, 8.51. Found: C, 83.50; H, 8.34.

5′-Phenylfuro[4′,3′,2′-4,5,6]pregn-5-en (IVa)——A mixture of 800 mg of IIf, 800 mg of NaOH, 6 ml of 80% NH_2–NH_2–H_2O, and 30 ml of diethylene glycol was heated to 120° for 5 hr, then distilled off until the inner temperature rose to 190°, and the remained mixture was heated to the same temperature for 5.5 hr. After cooling the mixture was poured into water and extracted with ether. The product, dissolved in pet. ether, was chromatographed over 15 g of neutral Al_2O_3 (grade II). The fractions eluted with pet. ether and pet. ether–benzene (9:1) were recrystallized from acetone to give 349 mg (46.8%) of IVa, mp 115—117°, $[\alpha]_D^{24}$ −52.9±2° (c=1.054). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1652, 1606, 1494, 1262, 689. UV λ_{max} mμ (ε): 226 (8020), 233inf (6580), 300 (26210), 312inf (22390). NMR (τ): (18-H) 9.36, (19-H) 8.87, (Ph-H) 2.93. *Anal.* Calcd. for $C_{28}H_{36}O$: C, 86.54; H, 9.34. Found: C, 86.54; H, 9.20.

5′-Phenylfuro[4′,3′,2′-4,5,6]androst-5-ene-3,17-dione (IIj)——A mixture of 14.4 g of the oily benzoate (If), 8.5 g of NaH, and 430 ml of xylene was refluxed for 70 hr. The product was crystallized from ether yielding 8.3 g of IIj, which upon recrystallization from CH_2Cl_2–MeOH afforded 8.165 g (64.0%) of the pure sample, mp 243—245°, $[\alpha]_D^{24}$ −137.6±1.6° (c=1.041). IR ν_{max} cm^{-1}: 1743, 1685, 1582, 1528, 690. NMR (τ): (18-H) 9.03, (19-H) 8.76, (Ph–H) 2.58m (3H), 1.64m (2H). *Anal.* Calcd. for $C_{26}H_{28}O_3 \cdot CH_3COCH_3$: C, 77.99; H, 7.67. Found: C, 78.28; H, 7.44.

17β-Hydroxy-5′-phenylfuro[4′,3′,2′-4,5,6]androst-5-en-3-one (IIk)——To a suspension of 8.00 g of IIj in 280 ml of MeOH 2.0 g of $NaBH_4$ was added portionwise. The resulting mixture was stirred for 1.5 hr and poured into ice water. The formed 3,17-diol was collected by filtration, washed with water, and dried. A mixture of the diol (7.5 g) and 4.40 g of dichlorodicyanobenzoquinone (DDQ) in 200 ml of dioxane was allowed to stand with stirring for 30 min. The precipitates were removed by filtration and washed with CH_2Cl_2. The organic solution was several times washed with 5% NaOH and water, dried, and evaporated to dryness under reduced pressur e. The residue was crystallized from ether to give 5.352 g of IIk. Recrystallization from CH_2Cl_2–acetone afforde d 4.069 g of the pure sample, mp 225—227°, $[\alpha]_D^{24}$ −225.7±2.5° (c=1.117), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3606, 3456, 1681, 1648, 1603, 1580, 1533. UV λ_{max} mμ (ε): 225.5 (18400), 249inf (9300), 348 (12600). NMR (τ): (18-H) 9.16, (19-H) 8.77, (Ph–H) 2.56m (3H), 1.64m (2H). *Anal.* Calcd. for $C_{26}H_{30}O_3$: C, 79.96; H, 7.74. Found: C, 79.99; H, 7.79.

Addition of Maleic Anhydride to 5′-Phenylfuro[4′,3′,2′-4,5,6]pregn-5-ene (IVa)——A solution of 101 mg of IVa and 51 mg of maleic anhydride in 2 ml of dry ether was allowed to stand for 1 hr. The appeared precipitate was filtered off, washed with a small amount of dry ether. Recrystallization from acetone–hexane afforded 55 mg of the adduct (V), mp 101—103°, $[\alpha]_D^{25}$ −44.5±2° (c=1.068). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1857, 1785, 1606, 1494, 1086, 1056, 891, 841. NMR (τ): (18-H) 9.34, (19-H) 8.87, (21-H) 8.98t ($J \approx 10.0$), (CO–O–CO–C(–H)–) 6.71d, 6.44d ($J_{AB} \approx 6.5$), (Ph–H) 2.63 (5H). *Anal.* Calcd. for $C_{32}H_{38}O_4$: C, 78.98; H, 7.87. Found: C, 78.80; H, 7.98.

5′-Phenylfuro[4′,3′,2′-4,5,6]androst-5-ene (IVb)——3,17-Dione (IIj) (2.7 g) was submitted to Huang-Minlon reduction under a similar condition as described before. Recrystallization from acetone gave 1.263 g (50.3%) of IVb, mp 152—154°, $[\alpha]_D^{24}$ −73.6±1° (c=0.990). IR ν_{max} cm^{-1}: 1652, 1605, 1558, 1491, 763, 692. *Anal.* Calcd. for $C_{26}H_{32}O$: C, 86.61; H, 8.95. Found: C, 86.64; H, 8.93.

The mother liquor of repeated recrystallization gave the compound which showed a more polar spot on TLC. This compound, mp 164—166°, was also obtained in 40% yield by treatment of IVb with 70% AcOH–dioxane overnight, followed by preparative TLC using cyclohexane–AcOEt (3:1) as developing solvent. This was identical with the following compound (VI) in a mixed mp and the IR sepctrum.

4-Benzoylandrost-4-en-6-one (VI)——A mixture of 530 mg (IVb), 308 mg of *m*-chloroperbenzoic acid, and 15 ml of $CHCl_3$ was kept standing at room temperature overnight. After working up in the usual way recrystallization from ether–pet. ether afforded 184 mg of VI. The mother liquor was subjected to preparative TLC, using cyclohexane–AcOEt (5:1) as developing solvent. The more moblie fraction gave 85 mg of VII. The less mobile fraction was recrystallized from ether–pet. ether yielding 75 mg of VI. Combined yield of VI: 259 mg, mp 168—169°, $[\alpha]_D^{24}$ +65.0±0.9° (c=1.086). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3070, 3026, 1688, 1675, 1620, 1600, 1583, 1452, 1284, 1255, 702. UV λ_{max} mμ (ε): 249 (14700). CD ($CHCl_3$) $[\theta]_{333m\mu}^{max}$ −14190, $[\theta]_{300m\mu}^{max}$ −3590. NMR (τ): (18-H) 9.26, (19-H) 8.92, (Ph–H) 2.58m (3H), 2.25m (2H). *Anal.* Calcd. for $C_{26}H_{32}O_2$: C, 82.94; H, 8.57. Found: C, 82.92: H, 8.50.

4-Benzoyloxyandrost-4-en-6-one (VII)——The enedion (VI) (100 mg) was treated with 50 mg of *m*-chloroperbenzoic acid in 3 ml of CH_2Cl_2 as above. Recrystallization from ether–pentane afforded 85 mg of VII, mp 129—131°, $[\alpha]_D^{25}$ +3.7±0.3° (c=1.095). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1738, 1699, 1658, 1605, 1587, 1268, 1165, 705. UV λ_{max} mμ (ε): 233.5 (17200). CD (dioxane) $[\theta]_{324m\mu}^{max}$ −2540, $[\theta]_{290m\mu}^{max}$ mμ −310. NMR ((τ): (18-H) 9.25, (19-H) 8.95. (Ph-H) 2.55m (3H), 1.87m (2H). *Anal.* Calcd. for $C_{26}H_{32}O_3$: C, 79.55; H, 8.22. Found: C, 79.35; H, 8.28.

Reduction of 4-Benzoyloxyandrost-4-en-6-one (VII)——The enol benzoate (VII) (704 mg) was reduced with 180 mg of $LiAlH_4$ in 60 ml of dry ether for 1.5 hr. After working up in the usual manner the product was subjected to preparative TLC using cyclohexane–AcOEt (3:1) as developing solvent.

a) The more mobile fraction was recrystallized from aq. acetone yielding 156 mg (31.7%) of 4-en-6α-ol (IXa), mp 109—111°, $[\alpha]_D^{24}$ +60.1±0.8° (c=1.021). IR ν_{max} cm^{-1}: 3305, 3037, 1661, 1065. NMR (τ): (18-H) 9.27, (19-H) 9.00, (6β-H) 5.81, (4-H) 4.32. *Anal.* Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.28; H, 10.88. This compound was identified by comparison with the $LiAlH_4$ reduction product of androst-4-en-6-one prepared according to the method described by R. Reugelmans[22a] (Photoisomerization of 3α,5α-cycloandrostan-6-one). Acetylation of IXa with pyridine-Ac_2O in the usual manner afforded the acetate (IXb), mp 65—67° (from EtOH), $[\alpha]_D^{24}$ +78.5±1° (c=1.003). IR ν_{max} cm^{-1}: 1735, 1653, 1245. CD (MeOH) $[\theta]^{max}_{220m\mu}$ −426. NMR (τ): (18-H) 9.27, (19-H) 8.94, (AcO) 7.92, (6β-H) 4.65, (4-H) 4.53. *Anal.* Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.76; H, 10.22. Jones oxidation of IXa gave 4-en-6-one (XI), mp 134—136° (from MeOH), $[\alpha]_D^{24}$ +23.9±0.5° (c=1.094) (reported[22a] mp 135°, $[\alpha]_D$ +24°). IR ν_{max} cm^{-1}: 1684, 1625. UV $\lambda^{isooctane}_{max}$ mμ (ε): 231.5 (7770). CD (dioxane) $[\theta]^{max}$ mμ −6010. NMR (τ): (18-H) 9.25, (19-H) 9.03, (4-H) 3.62t-d (J≈3.4, 1.0). *Anal.* Calcd. for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.79; H, 10.44.

b) The less mobile fraction was recrystallized from aq acetone to give 223 mg (45.2%) of 5-en-4α-ol (VIIIa), mp 138.5—140°, $[\alpha]_D^{24}$ −94.2±1.2° (c=1.017). IR ν_{max} cm^{-1}: 3322, 3058, 1068. NMR (τ):(18-H) 9.28, (19-H) 9.00, (4β-H) 5.77, (6-H) 4.30. *Anal.* Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.43; H, 10.87. This compound was identified by comparison with the $LiAlH_4$ reduction product of androst-5-en-4-one, prepared according to a similar method as described by Butenandt.[23] Acetylation of VIIIa afforded the acetate (VIIIb), mp 111.5—113° (from MeOH), $[\alpha]_D^{24}$ −69.9±0.9° (c=1.048). IR ν_{max} cm^{-1}: 1742, 1669, 1250. CD (MeOH) $[\theta]^{max}_{230m\mu}$ +2650, $[\theta]^{max}_{220m\mu}$ +6010. NMR (τ): (18-H) 9.28, (19-H) 8.96, (AcO) 7.92, (6-H) 4.54t-d (J≈5.5, 2.0), (4β-H) 4.57. *Anal.* Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.92; H, 10.01. Jones oxidation of VIIIa in acetone yielded androst-5-en-4-one (X), mp 83—85° (from MeOH), $[\alpha]_D^{24}$ −79.4±1° (c=1.154). IR ν_{max} cm^{-1}: 1688, 1640, 1377. UV $\lambda^{isooctane}_{max}$ mμ (ε): 233 (6900). CD (isooctane) $[\theta]^{max}_{335m\mu}$ +3530. *Anal.* Calcd. for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.55; H, 10.49.

Oxidation of 17β-Hydroxy-5′-phenylfuro[4′,3′,2′-4,5,6]androst-5-en-3-one (IIk)——A mixture of 167 mg of IIk, 96 mg of *m*-chloroperbenzoic acid, and 6 ml of CH_2Cl_2 was allowed to stand for 2 hr. After working up recrystallization from MeOH afforded 155 mg (89.1%) of 17β-hydroxy-4-benzoylandrost-4-ene-3,6-dione, mp 196.5—198.5°, $[\alpha]_D^{24}$ +40.1±0.6° (c=1.111). IR ν_{max} cm^{-1}: 3506, 1695, 1672, 1600, 1588, 1232, 688. UV λ_{max} mμ (ε): 249.5 (19500). Acetylation of this compound with pyridine–Ac_2O at room temperature yielded 4-benzoyl-6,17β-diacetoxyandosta-4,6-dien-3-one, mp 184—186° (from ether-pet ether), $[\alpha]_D^{21}$ +56.5±0.8° (c=1.121). IR ν_{max} cm^{-1}: 1765, 1739, 1684, 1662, 1628, 1599, 1575, 1255, 1172, 693. UV λ_{max} mμ (ε): 249.5 (15800), 291.5 (21900). NMR (τ): (18-H) 9.10, (19-H) 8.64, (AcO) 7.96, (17α-H) 5.37, (7-H) 4.25d (J≈2.9), (Ph-H) 2.53m (3H), 2.21m (2H). *Anal.* Calcd. for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99. Found: C, 73.33; H, 7.01.

Attempted Cyclization of Other 6α-Acyloxyprogesterone——a) A mixture of 2.974 g of Id[24] prepared by dehydrogenation of Ia with DDQ, 1.65 g of NaH, and 100 ml of xylene was refluxed for 70 hr. After working up 2.75 g of Id was recovered unchanged (UV λ_{max} 244 mμ).

b) A mixture of 395 mg of Ig, 156 mg of NaH, and 15 ml of xylene was refluxed for 25.5 hr. Working up afforded 288 mg of Ig.

c) A mixture of 1.325 g of Ih, 515 mg of NaH, and 50 ml of xylene was refluxed for 47 hr. Chromatography of the product over 24 g Al_2O_3 provided 466 mg of Ih and 56 mg of pregnane-3,6,20-trione.

d) A mixture of 267 mg of Ii, 155 mg of NaH, and 15 ml of xylene was refluxed for 42 hr. Chromatography of the product over 4 g of Al_2O_3 gave 60 mg of pregnane-3,6,20-trione.

6α-Benzoylaminotestosterone Benzoate (XIIc)——The method used here was virtually identical with that described for the acetylamino compound (XIIb) except that the acetylation step was replaced by benzoylation, and resulted XIIc in 22.4% overall yield from the azide, mp 238—240°, $[\alpha]_D^{22}$ +128.5±2° (c=1.081). IR ν_{max} cm^{-1}: 3337, 1712, 1662, 1608, 1582, 1282, 1125, 719. *Anal.* Calcd. for $C_{33}H_{37}O_4N$: C, 77.46; H, 7.29; N, 2.74. Found: C, 77.40; H, 7.35; N, 2.70.

17β-Hydroxy-5′-phenylthieno[4′,3′,2′-4,5,6]androst-5-en-3-one (XVb)——Treatment of 5.246 g of 5α,6α-epoxy-17β-acetoxyandrostan-3-ethyleneketal with HSCN–ether solution, followed by recrystallization of the product from acetone, gave 5.548 g (91.8%) of the 5α-hydroxy-6β-thiocyanate, mp 180—182°, $[\alpha]_D^{26}$ −102.3±2° (c=1.033). IR ν_{max} cm^{-1}: 3466, 2144, 1728, 1254, 1114. *Anal.* Calcd. for $C_{24}H_{35}O_5NS$: C, 64.11; H, 7.85; N, 3.12; S, 7.13. Found: C, 63.89; H, 7.84; N, 3.03; S, 7.07.

To a stirred suspension of 1.824 g of $LiAlH_4$ in 120 ml of ether a solution of 5.14 g of the above compound in 120 ml of tetrahydrofuran was added dropwise, the reaction mixture was agitated for an additional 2 hr,

22) *a*) R. Reugelmans, *Bull. Soc. Chim. France.*, **1967**, 244; *b*) C.H. Robinson, O. Gnoj, and F.E. Carlon, *Tetrahedron*, **21**, 2509 (1965).

23) A. Butenandt and A. Wolff, *Ber.*, **68**, 2091 (1935); A. Butenandt and R. Bauer, *Ber.*, **77**, 397 (1944); L.F. Fieser and M. Romero, *J. Am. Chem. Soc.*, **75**, 4716 (1953).

24) M. Tadra, *Folia Microbiol.* (Prague), **8**, 176 (1963); *Chem. Abstr.*, **59**, 10420 (1963).

and worked up in the usual way. The product was benzoylated with 20 ml of pyridine and 3.3 g of PhCOCl in the usual manner. The isolated product (2.7 g) was heated on a steam-bath in 25 ml of 70% AcOH for 30 min. After working up the product was chromatographed over 75 g of Florisil. The fractions (1.142 g) eluted with benzene–ether (19:1) were recrystallized from CH_2Cl_2·MeOH to yield 652 mg (26.7%) of 6β-mercapto-5α,17β-dihydroxyandrostan-3-one 6,17-dibenzoate, mp 215—217°, $[\alpha]_D^{24}$ −101.9±2° (c=1.029). IR ν_{max} cm^{-1}: 3366, 1705, 1678, 1610, 1585, 1299. UV λ_{max} mμ (ε): 233.5 (2430), 271.5 (1070). *Anal.* Calcd. for $C_{33}H_{38}O_5S$: C, 72.50; H, 7.01; S, 5.87. Found: C, 72.56; H, 7.10; S, 5.85. The fractions eluted with benzene–ether (19:1) afforded 266 mg of a mixture. The fractions (137 mg) eluted with benzene–ether (9:1) were recrystallized from CH_2Cl_2·MeOH yielding 120 mg of 5α,17β-dihydroxyandrostan-3-one 17-benzoate, mp 202—204°, IR ν_{max} cm^{-1}: 3370, 1718, 1272.

Into a solution of 690 mg of the 6-benzoylthio compound in 10 ml of 1% EtOH·$CHCl_3$ a gentle stream of HCl was babbled during 5 hr. Working up afforded a theoretical amount of XIVa as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1724, 1685. UV λ_{max} 237 mμ. A mixture of XIVa, 270 mg of NaH, and 20 ml of toluene was refluxed with stirring for 1.5 hr. The product was chromatographed over 14 g of neutral Al_2O_3 (grade II). The fractions eluted with pet ether–benzene (1:1) and benzene were recrystallized from acetone–hexane affording 529 mg of XVa, mp 173—175°, $[\alpha]_D^{25}$ −41.9±2° (c=1.024). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1709, 1669, 1600, 1585, 1573, 1501, 1285, 1129, 732, 722. UV λ_{max} mμ (ε): 231 (30480), 277 (9820), 333 (6540). *Anal.* Calcd. for $C_{33}H_{34}O_3S$: C, 77.61; H, 6.71; S, 6.28. Found: C, 77.57; H, 6.96; S, 6.36.

Hydrolysis of XVa with 5% KOH–MeOH gave XVb. Recrystallization from CH_2Cl_2–acetone, yielded the pure sample, mp 257—260° (decomp.), $[\alpha]_D^{24}$ −110.6±2° (c=1.039). IR ν_{max} cm^{-1}: 3539, 1668, 1598, 1565, 1505, 762, 700. UV λ_{max} mμ (ε): 232 (15020), 278 (9030), 333 (6400). *Anal.* Calcd. for $C_{26}H_{30}O_2S$: C, 76.81; H, 7.44; S, 7.89. Found: C, 76.99; H, 7.65; S, 7.90.

Acetylation of XVb with pyridine–Ac_2O, yielded the acetate (XVc), which was recrystallized from acetone–hexane, mp 183.5—185°, $[\alpha]_D^{24}$ −102.2±2° (c=0.984). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3064, 1742, 1688, 1600, 1564, 1503, 1246, 691. UV λ_{max} mμ (ε): 232 (15040), 238inf (14495), 278 (8940), 332 (6440). NMR (τ): (18-H) 9.12, (19-H) 8.77, (AcO) 7.95, (17α-H) 5.32t, (Ph-H) 2.53m (5H). *Anal.* Calcd. for $C_{28}H_{32}O_3S$: C, 74.96; H, 7.19; S, 7.15. Found: C, 74.73; H, 7.34; S, 7.33.

5′-Phenylthieno[4′,3′,2′-4,5,6]androst-5-en-17β-ol (XVI)——A mixture of 225 mg of XVa, 750 mg of KOH, 2 ml of 80% NH_2–NH_2–H_2O, and 15 ml of triethylene glycol was refluxed for 1 hr, then distilled until the inner temperature reached to 200°, and the remained mixture was heated to 200° for 2 hr. After working up in the usual way recrystallization from ether–MeOH afforded 160 mg (92.5%) of XVI, mp 144—146°, $[\alpha]_D^{23}$ +4.2±2° (c=1.004). IR ν_{max} cm^{-1}: 3396, 1597, 1505, 753, 698. UV λ_{max} mμ (ε): 294 (14500). NMR (τ): (18-H) 9.18, (19-H) 8.88, (17α-H) 6.32, (Ph-H) 2.68 (5H). *Anal.* Calcd. for $C_{26}H_{32}OS$: C, 79.54; H, 8.22; S, 8.17. Found: C, 79.36; H, 8.29; S, 8.21.

5′-Phenylthieno[4′,3′,2′-4,5,6]androsta-5,9(11)diene-3,17-dione (XVd)——To a solution of 5.779 g of 3-ethoxyandrosta-3,5,9(11)-trien-17-one in 100 ml of acetone a mixture of 3.81 g of anhydrous AcONa, 4 ml of AcOH, 5.95 g of N-bromosuccinimide, and 140 ml of 70% acetone was added portionwise with stirring during 15 min.[25] The reaction mixture was further agitated for 3 hr and poured into water. The appeared precipitate was filtered off, washed with water, and dried. The obtained crystals (5.710 g, 85.0%) were used for the next step without further purification. Recrystallization from acetone–hexane gave pure 6β-bromoandrosta-4,9(11)-diene-3,17-dione, mp 171—172°, $[\alpha]_D^{24}$ +99.9±2° (c=1.040). IR ν_{max} cm^{-1}: 1738, 1682, 1630, 1610. NMR (τ): (18-H) 9.04, (19-H) 8.30, (6α-H) 4.90t ($J\approx$3.0), (11-H) 4.36t-d, (4-H) 4.03. *Anal.* Calcd. for $C_{19}H_{23}O_2Br$: C, 62.81; H, 6.38; Br, 22.00. Found: C, 62.84; H, 6.50; Br, 22.24. A mixture of 5.850 g of the bromide and 4.225 g of freshly prepared Ph·COSK in 300 ml of acetone was allowed to stand with stirring for 4 hr, poured into water, and the mixture was extracted with ether. Working up in the usual way afforded 6.80 g of XIVb as an oil, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1741, 1670, 1610, 1580.

a) 6α-Thiolbenzoate (423 mg), dissolved in pet ether–benzene (2:1), was adsorbed on a column of standarized Al_2O_3 (12 g) and the column was allowed to stand overnight. Then the column was eluted with pet ether–benzene (1:1). After removal of the solvents the residue was recrystallized from MeOH yielding 217 mg (35%) of XVd, mp 206—208°. $[\alpha]_D^{24.5}$ −67.7±2° (c=1.082). IR $\nu_{max}^{CHCl_3}$cm^{-1}: 1737, 1674, 1599, 1566, 1503. UV λ_{max} mμ (ε): 231.5 (15500), 277.5 (8700), 331 (6580). NMR (τ): (18-H) 9.09, (19-H) 8.60, (11-H) 4.30t-d ($J\approx$3.5, 1.0), (Ph-H) 2.50m (5H). *Anal.* Calcd. for $C_{26}H_{26}O_2S$: C, 77.57; H, 6.51; S, 7.97. Found: C, 77.12; H, 6.67; S, 7.89.

b) A mixture of 6,870 g of XIVb, 3.50 g of NaH, and 140 ml of toluene was refluxed for 6 hr. After working up in a similar manner as described before recrystallization from CH_2Cl_2–MeOH afforded 4.663 g (71.0%) of XVd, mp 206—208°.

5α-Hydroxy-6β-(3′-acetoxyprop-1′-ynyl)pregnane-3,20-dione (XXb)——To a cooled solution of EtMgBr prepared from 5.74 g of Mg and 26.2 g of EtBr in 70 ml of dry ether, a solution of 40.2 g of pyranyl ether of propargy alcohol in 120 ml of tetrahydrofuran was added dropwise during 1.5 hr. The resulting solution warmed to 50° for 1.5 hr until evolution of gas ceased and then cooled with ice. To the solution 10.0 g of

25) L.H. Knox, J.A. Zderic, J.P. Ruelas, C. Djerassi, and H.J. Ringold, *J. Am. Chem. Soc.*, **82**, 1230 (1960).

3,3,20,20-bisethylenedioxypregnan-5α,6α-oxide (XVII) was added at once. The resulting mixture was allowed to stand with stirring at room temperature for 19 hr. Then, to the cooled mixture a saturated solution of NH_4Cl was added portionwise and extracted with ether. Working up in the usual way afforded 46 g of a dark red oil, which was chromatographed over 700 g of standardized Al_2O_3. The fractions eluted with pet ether and pet ether–benzene (1:1) gave 17.4 g of an oil, which was not studied. The fractions eluted with benzene and benzene–ether (9:1) afforded 9.642 g of XVIII as an oil, hydrolysis of which was effected by heating with 130 ml of 70% AcOH for 1 hr. After dilution with water the appeared precipitate was collected by filtration, washed with water, and dried. Recrystallization from CH_2Cl_2–MeOH gave 7.2 g (78.3%) of XXa, mp 260.5—262° (decomp.). IR ν_{max} cm^{-1}: 3460, 3360, 1706, 1698. *Anal.* Calcd. for $C_{24}H_{34}O_4 \cdot 1/4H_2O$: C, 73.72; H, 8.89. Found: C, 73.88; H, 9.01.

Acetylation of (XXa) with pyridine–Ac_2O in the usual manner yielded XXb, mp 183—185° (from aq MeOH), $[\alpha]_D^{22.5}$ +32.9±2° (c=1.108). IR ν_{max} cm^{-1}: 3341, 1747, 1695, 1245, 1220. *Anal.* Calcd. for $C_{26}H_{36}O_5$: C, 72.86; H, 8.47. Found: C, 72.81; H, 8.73.

6β-(3′-Acetoxyprop-1′-ynyl)progesterone (XIX)——To a stirred solution of 2.63 g of XXb in 50 ml of pyridine, cooled to −6°, 2.6 ml of $SOCl_2$ was added dropwise. After agitation at −5° for 10 min, ice water was added to the mixture. The appeared precipitate was filtered off, washed with water, and dried. Recrystallization from ether afforded 1.942 g (75.3%) of XIX, mp 99—101°, $[\alpha]_D^{22}$ +16.6±2° (c=1.053). IR ν_{max} cm^{-1}: 2278, 1745, 1677, 1620. UV λ_{max} mμ (ε): 238.5 (15510). *Anal.* Calcd. for $C_{26}H_{34}O_4 \cdot 1/4OEt_2$: C, 75.58; H, 8.57. Found: C, 75.45; H, 8.79.

5α-Hydroxy-6β-propylpregnane-3,20-dione (XXI)——A solution of 1.550 g of XXb in 30 ml of EtOH was hydrogenated over 1.5 g of pre-reduced 5% Pd–C until absorption of H_2 ceased. After working up, recrystallization from MeOH gave 1.00 g of XXI, mp 225.5—227.5°, $[\alpha]_D^{23}$ +35.1±2° (c=1.077). IR ν_{max} cm^{-1}: 3388, 1706, 1681. *Anal.* Calcd. for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 77.05; H, 10.08.

5α-Hydroxy-6β-(3′-acetoxyprop-1′-enyl)pregnane-3,20-dione (XXII)——The propargyl compound (XXb) (1.00 g), dissolved in 30 ml of abs EtOH, was hydrogenated over 1.0 g of freshly prepared Lindlar catalyst, until absorption of 1 equivalent of H_2 ceased (It required 9 hr). After working up recrystallization from aq MeOH yielded 702 mg of XXII, mp 186—188°, $[\alpha]_D^{22}$ +1.4±2° (c=1.017). IR ν_{max} cm^{-1}: 3420, 1737, 1710, 1685, 1230. NMR (τ): (18-H) 9.33, (19-H) 8.77, (Ac) 7.95, 7.88, (CH=CH-$\underline{CH_2}$-) 5.35m (2H), (-$\underline{CH}$=$\underline{CH}$-) 4.43d-t (J≈10.5, 6.0), 4.02d-d (J≈10.5). *Anal.* Calcd. for $C_{26}H_{38}O_5$: C, 72.52; H, 8.90. Found: C, 72.53; H, 8.93.

Cyclization of 6β(3′-Acetoxyprop-1′-enyl)progesterone (XXIII)——The above compound (XXII) (1.163 g), dissolved in 15 ml of pyridine, was treated with 1.00 g of $SOCl_2$ as described before. Extraction with ether afforded XXIII as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1748, 1700, 1685, 1610, 1229. A mixture of XXIII, 380 mg of NaH, and 30 ml of xylene was refluxed for 18 hr. After working up the product was chromatographed over 28 g of Al_2O_3. The fractions (281 mg) eluted with benzene were recrystallized from acetone–MeOH to give 175 mg (17.6%) of XXIV, mp 211—213°, $[\alpha]_D^{24}$ +70.8±2° (c=1.095). IR ν_{max} cm^{-1}: 1693, 1679, 1590, 1584, 790, 760. UV λ_{max} mμ (ε): 211 (22130), 260 (11410), 303 (2510). NMR (τ): (18-H) 9.28, (19-H) 8.78, (21-H) 7.85, (Ph-H) 2.77m (2H), 2.15m (1H). *Anal.* Calcd. for $C_{24}H_{30}O_2$: C, 82.24; H, 8.63. Found: C, 82.18; H, 8.70. (reported[5]) mp 214—215°, $[\alpha]_D$ +53°, UV λ_{max} mμ (ε): 219 (11420), 260 (10400), 303 (2260)).

The mother liquor obtained by repeated experiments was combined and separated by preparative TLC using *n*-hexane–AcOEt (1:1) as developing solvent. The more mobile fraction gave an additional XXIV. The less mobile fraction was recrystallized from acetone yielding XXV, mp 165—167°, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1710, 1671, 1615, 1582. UV λ_{max} mμ (ε): 294.5 (18100). *Anal.* Calcd. for $C_{24}H_{32}O_2$: C, 81.77; H, 9.15. Found: C, 81.51; H, 9.26.

Addition of Dimethyl Acetylene Dicarboxylate to 6-Exo-methylenetestosterone Propionate (XXVIa)——A solution of 204 mg of XXVIa[19] and 165 g of dimethyl acetylene dicarboxylate in 2 ml of dry benzene was refluxed for 8.5 hr, and evaporated to dryness *in vacuo*. The residue was chromatographed over 8 g of neutral Al_2O_3 (grade II). The fractions (225 mg) eluted with pet ether–benzene (2:1—1:1) and benzene gave a solid, which was recrystallized from ether–hexane yielding 200 mg of XXVIIa, mp 137.5—139.5°, $[\alpha]_D^{25.5}$ +34.3±2° (c=1.017). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740, 1695, 1593, 1560. UV λ_{max} mμ (ε): 230.5 (35710), 303inf (1500), 310 (1550). NMR (τ): (18-H) 9.11, (19-H) 8.78, [$\underline{CH_3}$-CH_2-] 8.84t (3H, J≈7.0), (COO$\underline{Me}$) 6.13, 6.03; (17α-H) 5.29t, (Ph-H) 2.08s (1H, $W_{h/2}$≈2.2). *Anal.* Calcd. for $C_{29}H_{36}O_7$: C, 70.14; H, 7.31. Found: C, 70.02; H, 7.52.

Hydrolysis of 116 mg of XXVIIa was carried out by heating with 1.5% KOH–MeOH for 1 hr. After working up recrystallization from acetone gave 50 mg of XXVIIb, which does not melt even at 300°, $[\alpha]_D^{24.5}$ +74.5±2° (c=1.066). IR ν_{max} cm^{-1}: 3400, 3000—2400, 1741, 1695, 1658, 1590, 1557. *Anal.* Calcd. for $C_{24}H_{28}O_6 \cdot 1/3H_2O$: C, 68.88; H, 6.90. Found: C, 68.98; H, 6.87.

Addition of Dimethyl Acetylene Dicarboxylate to 6-Exo-methyleneprogesterone (XXVIb)——A solution of 1.247 g of XXVIb[19] and 1.08 g of dimethyl acetylene dicarboxylate in 20 ml of dry benzene was refluxed for 32 hr and evaporated to dryness *in vacuo*. The residue was chromatographed over 34 g of Al_2O_3. The fractions eluted with benzene and benzene–CH_2Cl_2 (9:1—4:1) afforded 1.489 g of an oily product, which was

hydrolyzed by treatment with 20 ml of 5% KOH–MeOH overnight. After working up recrystallization from MeOH–AcOEt afforded 850 mg of XXVIIc, mp 219—221°, $[\alpha]_D^{24.5}$ +145.1±2° (c=1.105). IR ν_{max} cm^{-1}: 3000—2500, 1702, 1688, 1590, 1546. UV λ_{max} mμ (ε): 228.5 (28460), 306—310 (1650). *Anal.* Calcd. for $C_{26}H_{30}O_6 \cdot 1/3H_2O$: C, 70.25; H, 6.95. Found: C, 70.25; H, 7.04.

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