Cyclopropane Ring Formation by Chromous Chloride Reduction. 5,9-Cyclo Steroids[1]

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Chromous chloride reduction of 9α-bromo-$\Delta^{1,4}$-3-keto steroids and the 1,2-dihydro analogs has been shown to give 5,9-cyclo steroids. Evidence is presented to support the structures assigned to these latter compounds. Structures are proposed for spiro steroids isolated in the course of the work.

The conversion of steroidal vicinal 1,2-dihalides[3] and halohydrins[4] in particular, and a variety of α-substituted halo compounds[5] in general, to olefins through the action of chromous chloride is well documented. In the course of dehalogenation studies we treated the 9α-bromo-11β-acetoxy-$\Delta^{1,4}$-3-keto steroid[6] (**1a**, Chart I) with chromous chloride[7] in acetone. The product of this reaction was not, however, the expected $\Delta^{1,4,9(11)}$-3-ketone **4** but proved to be a new halogen-free compound showing the correct analysis for reductive loss of bromine from **1a**. This new compound is formulated as the 5,9-cyclo steroid **2a** on the basis of its spectroscopic properties and reactions.

The infrared spectrum of **2a** showed a single strong absorption band at 6.1 μ instead of the three absorptions between 6.0 and 6.2 μ characteristic of the 1,4-dien-3-one system. Furthermore, the ultraviolet absorption at 272 mμ (ε 4900) was unusual and similar to that [269 mμ (ε 8700)] shown by the 9,10-cyclo-Δ^1-3-keto system in cycloartenone.[8] In addition to the resonances due to the 21-acetoxy-20-keto side chain, the nmr spectrum of **2a** showed resonances at δ 1.95 (methyl of C-11 acetate) and (4.80 hydrogen at C-11) as well as two doublets (J = 10 cps in each case) centered on 5.85 (C-2 hydrogen) and 6.65 (C-1 hydrogen), due to the vinyl hydrogens of the Δ^1-3-keto system. Resonances at δ 0.82 and 1.35 were attributed to the angular methyl groups at C-18 and C-19, respectively. These data provide good evidence for the postulated structure of **2a**, but confirmatory evidence was sought by chemical means, as follows.

When treated with hydrogen chloride in chloroform, at room temperature, the 5,9-cyclo steroid **2a** generated the known $\Delta^{1,4,9(11)}$-triene[9] **4**. Furthermore, **2a** on hydrogenation in ethyl acetate, over palladium–calcium carbonate catalyst, gave a dihydro compound formulated as **3**. This product showed no intense ultraviolet absorption above 220 mμ and no infrared absorption in the 6.0–6.1-μ region. The nmr spectrum of **3** showed no resonances due to vinyl protons, the C-11 acetate was still present as judged by its methyl resonance at δ 2.0, and the C-19 methyl resonance now appeared at 1.18. When the dihydro **3** was treated with hydrogen chloride in chloroform, the known[4] $\Delta^{4,9(11)}$-diene **5** was formed.

Having provided both chemical and spectroscopic evidence in support of structure **2a** for the chromous chloride product, we explored the action of chromous chloride on related systems. Under the same conditions that effected the transformation **1a** → **2a**, the 9α-fluoro[10] and 9α-chloro[6] analogs of **1a** were recovered unchanged, whereas the 9α-iodo analog[10] **1b** of **1a** gave the 5,9-cyclo steroid **2a**. The 9α-bromo-11β-formoxy steroid[6] **1c** also gave the corresponding 5,9-cyclo steroid **2b** on treatment with chromous chloride, in 70% yield.[11]

In connection with biological screening, we also prepared the 5,9-cyclo steroid **7** by the action of chromous chloride on 9α-bromo-11β-acetoxy-1(2)-dehydrotestosterone propionate. The spectroscopic properties of **7** and of its dihydro derivative **8**, and the acid-catalyzed conversion of **7** and **8** to the known[12,13] **9** and **10**, respectively, are in full accord with our previous observations based on **2a**.

Our attention was then turned to the bromohydrin system exemplified by the 9α-bromo-11β-hydroxy **1d**. When treated with chromous chloride in acetone this compound gave mainly the $\Delta^{1,4,9(11)}$-triene **4**. However, a small amount of a new product **6b** could be obtained by partition chromatography. This material showed no ultraviolet maxima, and the infrared spectrum showed no conjugated ketone absorption in the 6-μ region.

The same compound could also be prepared by a different route, namely the microbiological hydrolysis of the 5,9-cyclo steroid **2a** using *Flavobacterium dehydrogenans*,[14] which gave a deacetylated product formulated as **6a**. This compound showed no ultraviolet maxima, and the infrared spectrum showed loss of conjugated carbonyl and the presence of a new saturated carbonyl function at 5.86 μ. Acetylation of **6a** (pyridine–acetic anhydride at room temperature) gave the corresponding 21-acetate **6b**, identical with the product obtained from chromous chloride reduction of the 9,11-bromohydrin **1d**. When treated with hydrogen chloride in chloroform, **6b** gave the $\Delta^{1,4,9(11)}$-triene **4**.

(1) A preliminary account of this work has appeared earlier: C. H. Robinson, *et al.*, *Proc. Chem. Soc.*, 207 (1961).

(2) To whom inquiries should be addressed: Department of Pharmacology and Experimental Therapeutics, The Johns Hopkins School of Medicine, Baltimore, Md., 21205.

(3) P. L. Julian, W. Cole, A. Magnani, and E. W. Meyer, *J. Am. Chem. Soc.*, **67**, 1728 (1945).

(4) J. Fried and E. F. Sabo, *ibid.*, **79**, 1130 (1957).

(5) *Cf.* J. K. Kochi and P. E. Mocadlo, *J. Org. Chem.*, **30**, 1134 (1965).

(6) C. H. Robinson, L. Finckenor, M. Kirtley, D. Gould, and E. P. Oliveto, *J. Am. Chem. Soc.*, **81**, 2195 (1959).

(7) Prepared by the procedure of G. Rosenkranz, O. Mancera, J. Gatica, and C. Djerassi, *ibid.*, **72**, 4077 (1950).

(8) D. S. Irvine, J. A. Henry, and F. S. Spring, *J. Chem. Soc.*, 1316 (1955).

(9) J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman, and F. M. Singer, *J. Am. Chem. Soc.*, **77**, 4181 (1955).

(10) Prepared by Elliott L. Shapiro of these laboratories.

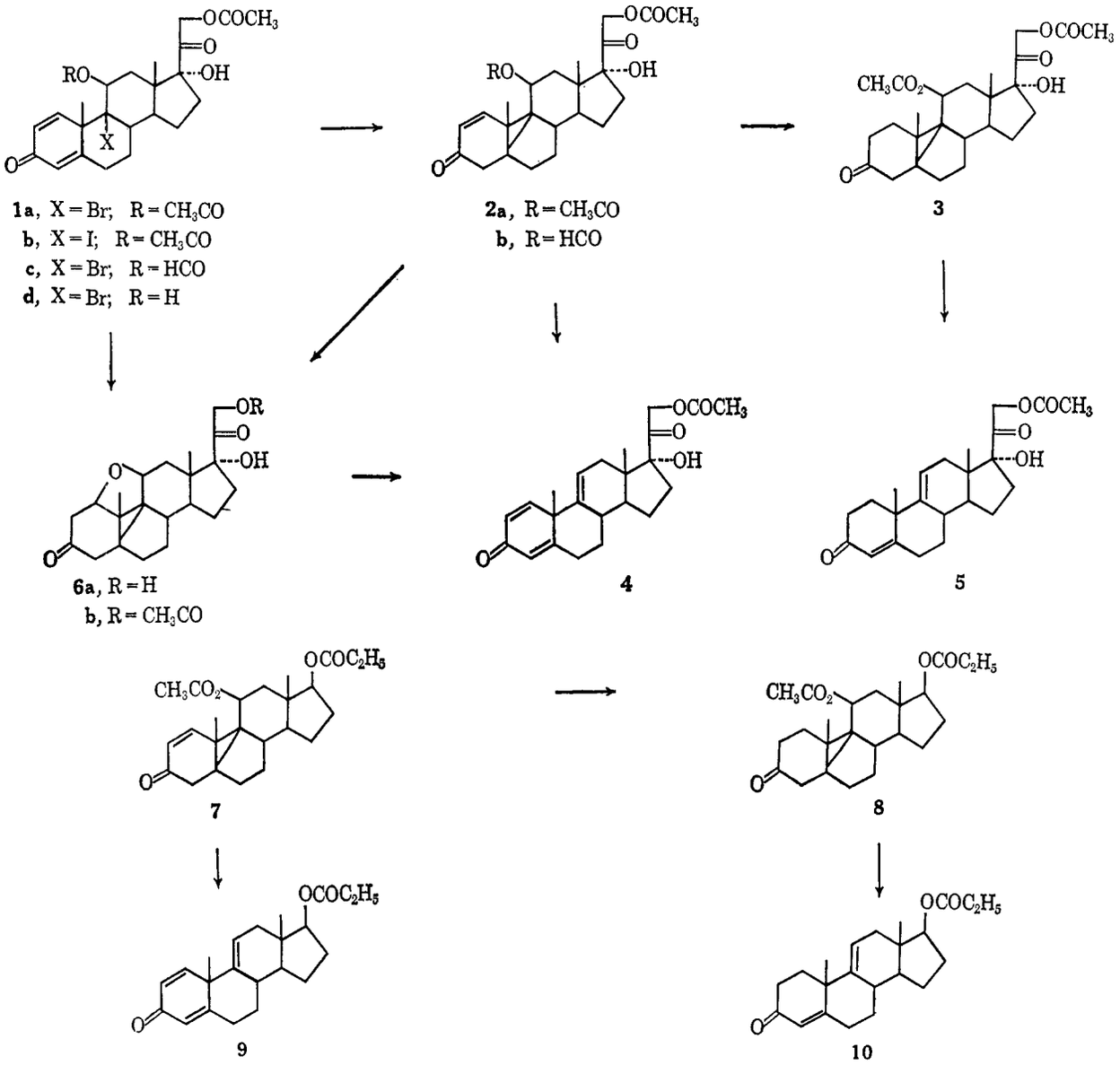
(11) The yields for the formation of the 5,9-cyclo steroids refer to analytically pure material and range from 40 to 70%. The crude products were, however, substantially pure as judged by spectroscopic and chromatographic analysis.

(12) C. H. Robinson, L. E. Finckenor, R. Tiberi, M. Eisler, R. Neri, A. Watnick, P. L. Perlman, P. Holroyd, W. Charney, and E. P. Oliveto, *J. Am. Chem. Soc.*, **82**, 4611 (1960).

(13) F. W. Heyl and M. E. Herr, *ibid.*, **77**, 488 (1955).

(14) W. Charney, L. Weber and E. P. Oliveto, *Arch. Biochem. Biophys.*, **79**, 402 (1959).

CHART I



On the basis of the spectroscopic and analytical data, and the acid-catalyzed transformation, we suggest that **6** contains the 1,11-oxido-5,9-cyclo system. The formation of this product can be accounted for by assuming initial formation of a 5,9-cyclo-11β-hydroxy-Δ^1-3-keto steroid, followed promptly by terminal addition of the 11-oxygen to the Δ^1-3-keto system. However, further study is clearly required before this structural assignment can be regarded as rigorously proved.

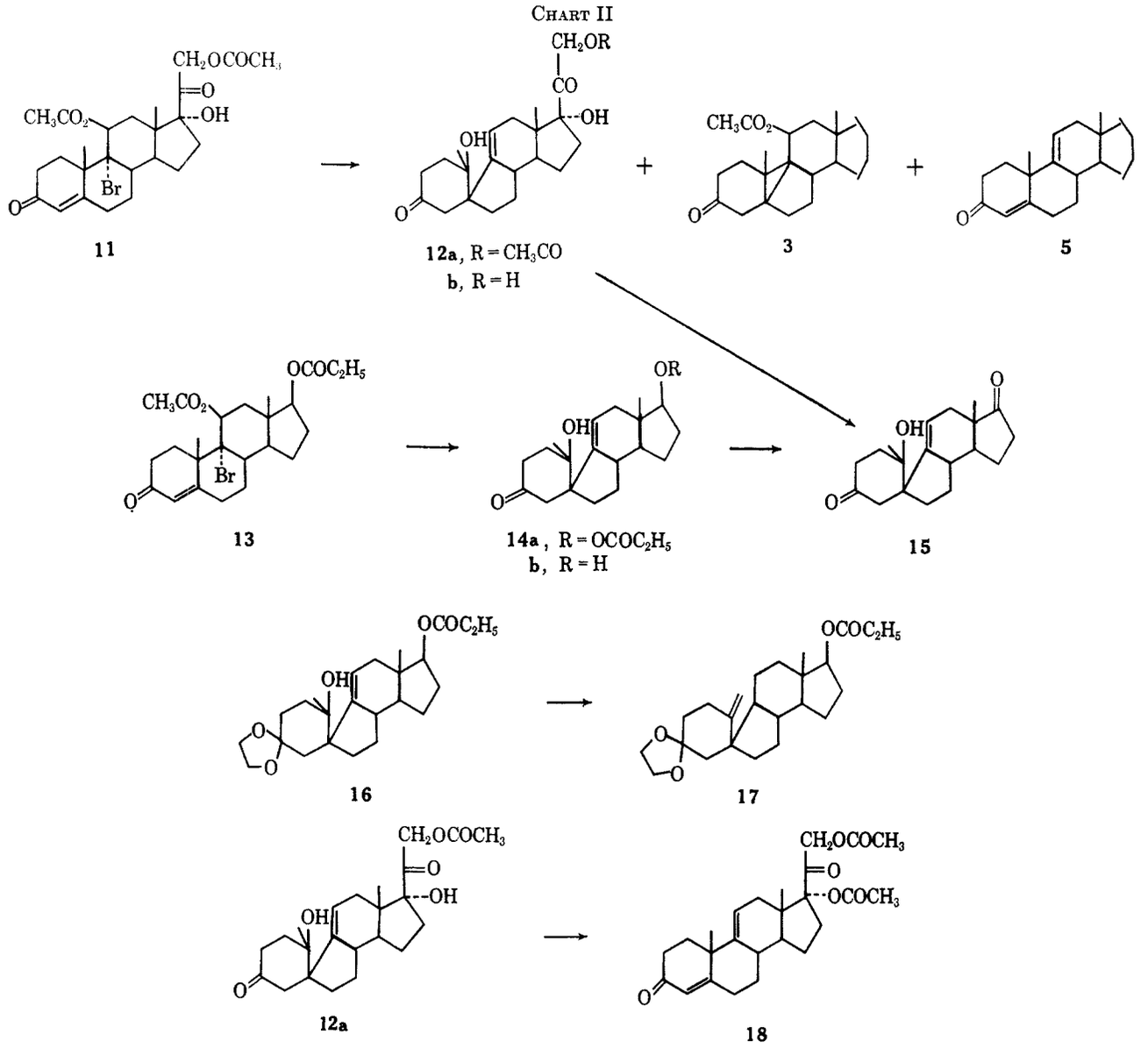
We then examined the action of chromous chloride on the 9α-bromo-11β-acetoxy-Δ^4-3-keto steroids **11** and **13** (Chart II), expecting to obtain the 1,2-dihydro-5,9-cyclo steroids **3** and **8** which had been prepared indirectly as described above. In contrast to the situation prevailing in the $\Delta^{1,4}$-3-ketone series, however, we obtained from **11** with chromous chloride a mixture of four products. These were the expected 5,9-cyclo steroid **3**, the $\Delta^{4,9(11)}$-diene **5**, and two new bromine-free products. The more abundant of the last two products, **12a**, contained no conjugated carbonyl function, as shown by its infrared and ultraviolet spectra. The nmr spectrum of **12a** showed, in addition to resonances due to the cortical side chain, absorptions at δ 0.62 (C-18), 1.29 (C-19), and 5.30 (multiplet, one vinyl hydrogen). Moreover, the original C-11 acetate function had clearly been lost.

Similarly the 9α-bromo-11β-acetoxy-Δ^4-3-keto androstene derivative **13** gave with chromous chloride a product **14a** analogous with the product **12a** which has just been described. The less complicated infrared spectrum of compound **14a** showed the presence of a six-membered ring carbonyl group (5.85 μ) and a hydroxyl group (2.85 μ). The nmr spectrum of **14a** showed resonances at δ 1.30 (C-19) and 5.27 (one vinyl hydrogen) in close analogy with those shown by **12a**.

These observations, namely that **12a** and **14a** contain a six-membered ring carbonyl function, an hydroxyl group, and a trisubstituted double bond, together with the requirement that the C-19 methyl group is attached to carbon bearing oxygen, can be satisfied by the 5,5′-spiro-10-hydroxy-$\Delta^{9(11)}$ system shown.

We now describe chemical evidence in support of this formulation. First of all, **12a** and **14a** were interrelated by the following sequence of reactions. Hydrolysis of the 21-acetate group in **12a** was carried out by the methanol–perchloric acid method.[4] The result-

CHART II



ing 21-alcohol **12b** was reacetylated (pyridine–acetic anhydride at room temperature) with regeneration of **12a**, thus precluding rearrangement during the acid hydrolysis. Sodium bismuthate degradation[15] of the cortical side chain in **12b** gave the 17-ketone **15**, which had the expected spectroscopic properties and gave the correct molecular weight by mass spectroscopy. The same 17-ketone was also obtained from **14a** as follows. Hydrolysis of the 17β-propionate function in **14a** by methanolic potassium hydroxide gave the 17β-alcohol **14b**, repropionylation of which (propionic anhydride–pyridine at room temperature) gave back the starting 17β-propionate **14a**. Oxidation of the 17β-alcohol **14b** with the Sarett reagent[16] gave the 17-ketone **15** identical in all respects with the compound derived from sodium bismuthate degradation of **12a**.

Control experiments with the 17β-propionate **14a** showed that the hydroxyl group was indeed tertiary, as evidenced by the recovery of unchanged **14a** from attempted acetylation and chromic acid oxidation reactions. The attempted oxidation experiment also satisfied us that no other reaction (or rearrangement) had occurred during the oxidation of the 17-alcohol **14b** to the 17-ketone **15**.

We then attempted to dehydrate the tertiary hydroxy system in these spiro compounds to give an exocyclic methylene group (as in **17**). To render the task easier, the 3-ethylene ketal **16** was prepared from **14a** under the usual conditions. This ketal showed the correct analytical data, and the infrared spectrum confirmed the presence of the tertiary hydroxyl group and the absence of the 3-ketone. The nmr spectrum of **16** confirmed the presence of the ethylene ketal grouping (δ 3.93; four hydrogens, OCH_2CH_2O) and testified to the unchanged situation elsewhere by the C-19 methyl resonance at δ 1.27 and the C-11 vinyl hydrogen absorption at 5.37.

The 3-ketal **16** was then treated with phosphorus oxychloride in pyridine at room temperature for 48 hr, to give unchanged material. Treatment of **16** with the same reagents under reflux for 2 hr gave a complex mixture as did the action of thionyl chloride in pyridine.

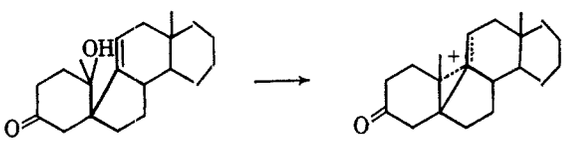
When the 3-ketal **16** was treated with oxalyl chloride in dimethylformamide at 0°, and the oily product was subjected to partition chromatography, fractions were

(15) C. J. W. Brooks and J. K. Norymberski, *Biochem. J.*, **55**, 371 (1953).
(16) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

obtained which appeared to be homogeneous by paper chromatography, but could not be crystallized. The nmr spectrum of this material showed absorption at δ 4.58, attributable to an exocyclic methylene group.

Finally we note that under strongly acidic conditions it proved possible to transform the spiro steroid **12a** back to a pregnane derivative **18**, although in modest yield. Thus, when **12a** was treated with an acetic acid–acetic anhydride–*p*-toluenesulfonic acid mixture, the 17,21-diacetate **18** was obtained. This compound was also secured from the known $\Delta^{4,9(11)}$-diene **5** by the use of the same reaction conditions. In addition to the expected infrared and ultraviolet absorption characteristics, **18** showed nmr resonances at δ 0.70 (C-18 methyl), 1.33 (C-19 methyl), 2.07 (methyl of C-17 acetate), 2.15 (methyl of C-21 acetate), 4.72 and 4.80 (C-21 methylene group), 5.5 (C-11 vinyl hydrogen), and 5.73 (C-4 vinyl hydrogen).

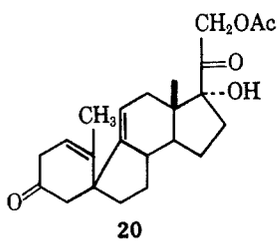
The conversion of the spiro steroid **12a** to **18** may involve **19** as an intermediate. This can then give an 11-



12a **19**

acetoxy-5,9-cyclo steroid by capture of acetate at C-11, followed by acid-catalyzed collapse of the 5,9-cyclo steroid to give the $\Delta^{4,9(11)}$-steroid **18**.

It will be recalled that we had referred earlier to a compound which accompanied **12a** as a minor product in the chromous chloride reduction of **11**. Lack of material prevented further study of this substance. However, the nmr spectrum, which showed two vinyl hydrogens at δ 5.40 and a doublet (J = 1.5 cps) at 1.65 attributed to the C-19 methyl, suggests that this compound is the endocyclic olefin **20** derived from **12a**.

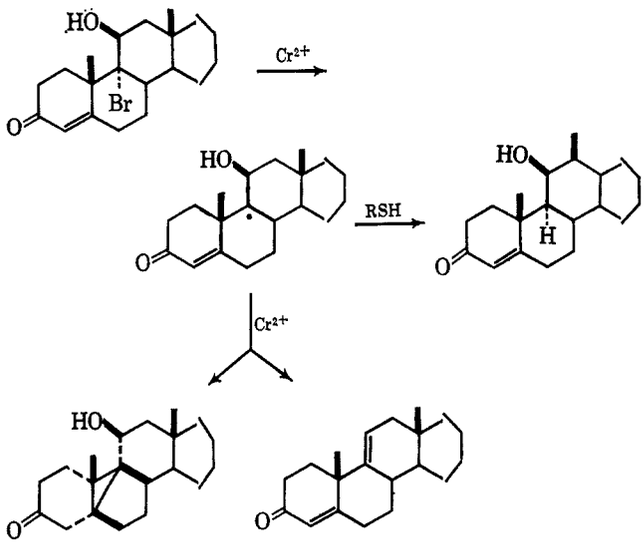


20

It now remains to account for the products of the chromous chloride reactions in mechanistic terms. We first note that the 5,9-cyclo steroid system can be constructed using Dreiding models, but only with the stereochemistry shown as in Chart III. Inversion at C-9 would not permit formation of the 5,9 bond, and any mechanism must take this into account. Recent work[17–19] suggests that the cleavage of carbon–halogen bonds with chromous salts involves a one-electron transfer to give a carbon radical, followed by a second one-electron transfer from Cr^{2+} to give an organochromium intermediate as opposed to a "bare" carbanion.

(17) F. A. L. Anet and E. LeBlanc, *J. Am. Chem. Soc.*, **79**, 2649 (1952).
(18) C. E. Castro and W. C. Kray, *ibid.*, **85**, 2768 (1963).
(19) J. K. Kochi and D. D. Davis, *ibid.*, **86**, 5264 (1964).

CHART III



Indeed, it has now been shown[20,21] in the 9α-bromo-11β-hydroxy steroid system that the proposed radical intermediate can be trapped to give the 11β-alcohol. In the absence of trapping agents, the reaction can proceed further, presumably *via* the organochromium derivative, to give 5,9-cyclo steroid or olefin. The formation of the 5,9-cyclo steroids, which is considered to proceed with retention of stereochemistry at C-9 (see above), is not in disagreement with this sequence.

Experimental Section[22]

5,9-Cyclopregn-1-ene-11β,17α,21-triol-3,20-dione 11β,21-Diacetate (2a).—(a) To a solution of 9α-bromopregna-1,4-diene-11β,17α,21-triol-3,20-dione 11β,21-diacetate (**1a**, 7.6 g) in acetone (600 ml) at 25° was added chromous chloride solution[7] (228 ml) in three separate 76-ml portions over 45 min. A slow stream of carbon dioxide was bubbled through the reaction mixture during the whole operation. The reaction mixture was then diluted with water and filtered, and the precipitate was washed with water and dried. The crude product [showing λ_{max}^{MeOH} 272 mμ (ϵ 4700)] was crystallized several times from ethyl acetate–methanol to give analytically pure **2a** (2.82 g): mp 186–191°; $[\alpha]D$ +254°; λ_{max}^{MeOH} 272 mμ (ϵ 4900); λ_{max}^{Nujol} 3.00, 5.70, 5.78, 6.10, and 8.15 μ.

Anal. Calcd for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.85; H, 7.25.

(b) A solution of 9α-iodopregna-1,4-diene-11β,17α,21-triol-3,20-dione 11β,21-diacetate[10] (**1b**, 300 mg) in acetone (30 ml) was treated with chromous chloride solution (9 ml) in exactly the manner described in part a. The crude product (180 mg) was crystallized from methanol–ethyl acetate to give the pure 5,9-cyclo steroid (**2a**, 113 mg), identical in all respects with material prepared as in part a above.

5,9-Cyclopregn-1-ene-11β,17α-21-triol-3,20-dione 11β-Formate 21-Acetate (2b).—A solution of 9α-bromopregna-1,4-diene-11β,-17α,21-triol-3,20-dione-11β-formate 21-acetate (1.0 g) in acetone (100 ml) was treated with chromous chloride solution (30 ml) exactly as described for the preparation of **2a**. The crude prod-

(20) D. H. R. Barton and N. K. Basu, *Tetrahedron Letters*, 3151 (1964).
(21) D. H. R. Barton, N. K. Basu, R. H. Hesse, F. S. Morehouse, and M. M. Pechet, *J. Am. Chem. Soc.*, **31**, 3016 (1966).
(22) Melting points were determined on the Kofler block. Optical rotations were measured in dioxane solution, and infrared spectra refer to Nujol mulls unless otherwise specified. Ultraviolet spectra were recorded using methanol solutions. The Chromosorb W used in partition chromatography was 80–100 mesh, acid washed, supplied by the Johns-Manville Co. We are indebted to the Physical Chemistry Department, Schering Corp., for the physical measurements. Microanalyses were carried out by Mr. M. Conner, Microanalytical Laboratory, Schering Corp. Nmr spectra were recorded on Varian A-60 or HR-100 spectrometers, for deuteriochloroform solutions. Chemical shifts are given in parts per million on the δ scale (tetramethylsilane = 0).

uct obtained by water precipitation and filtration was crystallized from acetone to give the 5,9-cyclo steroid **2b** (582 mg): mp 189–193°; $[\alpha]D$ +254°; λ_{max}^{MeOH} 272 mμ (ε 5000); λ_{max}^{Nujol} 2.94, 5.75, 5.80, 5.84, 6.05, 8.15, and 8.6 μ.

Anal. Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02. Found: C, 66.88; H, 6.89.

5,9-Cyclopregnane-11β,17α,21-triol-3,20-dione 11β,21-Diacetate (3).—5,9-Cyclo-pregn-1-ene-11β,17α,21-triol-3,20-dione 11β,21-diacetate (**2a**, 1.00 g) was hydrogenated in ethyl acetate (170 ml) containing 15% palladium on calcium carbonate catalyst (1.0 g) at 25°, and atmospheric pressure. After 14 min, when the equivalent of 1 mole of hydrogen/mole of steroid had been absorbed, the mixture was filtered and the solvent was removed *in vacuo*. The residue was crystallized from acetone–hexane to give the 5,9-cyclo steroid **3** (846 mg): mp 163–164°; $[\alpha]D$ −59°; no high intensity ultraviolet absorption between 220 and 350 mμ; λ_{max}^{Nujol} 2.85, 5.70, 5.78–5.83, 8.05, and 8.14 mμ.

Anal. Calcd for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67. Found: C, 67.23; H, 7.75.

Pregna-1,4,9(11)-triene-17α,21-diol-3,20-dione 21-Acetate (4) from the 5,9-Cyclo Steroids 2a and b.—(1) A brisk stream of dry hydrogen chloride was bubbled through a solution of the 5,9-cyclo steroid **2a** (50 mg) in chloroform (10 ml) at 25° for 30 min. The solvent was then evaporated *in vacuo*, and the residue was crystallized from acetone–hexane, giving the triene **4** (15 mg), mp 209–215°, λ_{max}^{MeOH} 239 mμ (ε 14,800), identical in all respects with authentic material (melting point, mixture melting point, ultraviolet and infrared spectrum).

(2) The 5,9-cyclo steroid **2b** (100 mg) in chloroform (20 ml) was treated with hydrogen chloride exactly as described in 1 above. The crude product crystallized from acetone–hexane to give the triene **4** (46 mg), identical in all respects with authentic material.

Pregna-4,9(11)-diene-17α,21-diol-3,20-dione 21-Acetate (5) from the 5,9-Cyclo Steroid 3.—A solution of the 5,9-cyclo steroid **3** (300 mg) in chloroform (60 ml) was treated with hydrogen chloride exactly as described above, to give after evaporation of solvent and crystallization from ethyl acetate, the diene **5** (62 mg), mp 230–235°, λ_{max}^{MeOH} 238 mμ (ε 16,200), identical in all respects with authentic material.

5,9-Cyclo-1,11-oxidopregnane-17α,21-diol-3,20-dione (6a).—*F. dehydrogenans*[14] was grown in a 1% Difco yeast buffered solution (10 g of Difco yeast, 4.68 g of $Na_2HPO_4 \cdot 7H_2O$, and 4.48 g of KH_2PO_4/l.) with shaking and light for 22 hr at 26–28°. The 5,9-cyclo steroid **2a** (3.0 g) in 80% aqueous ethanol (2 l.) was added and the transformation was allowed to proceed for 72 hr with shaking and light. Extraction with chloroform and evaporation gave the crude product which was subjected to partition chromatography on a Chromosorb W column (toluene–propylene glycol system, 300 g of Chromosorb W). A series of crystalline fractions was combined and crystallized from acetone–ether–hexane to give the 1,11-oxido compound **6a** (811 mg): mp 200–206°; $[\alpha]D$ −14°; no high-intensity ultraviolet absorption between 220 and 350 mμ; λ_{max}^{Nujol} 2.96, 5.82, and 5.86 μ.

Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 69.98; H, 7.85.

5,9-Cyclo-1,11-oxidopregnane-17α,21-diol-3,20-dione 21-Acetate (6b). A. From the 1,11-Oxido 21-Alcohol 6a.—The 1,11-oxido steroid **6a** (75 mg) from the previous experiment was acetylated using pyridine–acetic anhydride at 25° for 18 hr. The usual work-up and crystallization from acetone–ether–hexane gave the 21-acetate **6b** (51 mg): mp 177–180°; $[\alpha]D$ +11°; no high-intensity ultraviolet absorption between 220 and 350 mμ; λ_{max}^{Nujol} 2.95, 5.72, 5.76, 5.84, and 8.12 μ.

Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.64; H, 7.51. Found: C, 68.98; H, 7.55.

B. From 9α-Bromopregna-1,4-diene-11β,17α,21-triol-3,20-dione 21-Acetate (1d) by Chromous Chloride Reduction.—A solution of 9α-bromopregna-1,4-diene-11β,17α,21-triol-3,20-dione 21-acetate (1.00 g) in acetone (100 ml) was treated with chromous chloride solution (30 ml) exactly as described for the previous chromous chloride reductions. Work-up by ether extraction, after dilution of the reaction mixture with water, gave a noncrystalline product which was subjected to partition chromatography on Chromosorb W (150 g, toluene–propylene glycol system). Some early fractions contained crystalline material, which showed mp 157–167° after crystallization from acetone–hexane. In spite of the wide melting range this product migrated as one spot on paper chromatography (toluene–propylene glycol) with the same R_f as **6b** prepared as in A above. Identity of the two samples was confirmed by infrared comparison.

Pregna-1,4,9(11)-triene-17α,21-diol-3,20-dione 21-Acetate (4) from the 1,11-Oxido Steroid 6b.—Hydrogen chloride gas was bubbled through a solution of the 1,11-oxido **6b** (111 mg) in chloroform (25 ml) for 30 min at 25°. The solvent was removed *in vacuo*, and the residue was crystallized from acetone–ether–hexane to give the triene **4** (50 mg), identical in all respects with authentic material.

5,9-Cycloandrost-1-ene-11β,17β-diol-3-one 11-Acetate 17-Propionate (7).—A solution of 9α-bromoandrosta-1,4-diene-11β,17β-diol-3-one 11-acetate 17-propionate (1.0 g) in acetone (100 ml) was treated with chromous chloride solution (30 ml) exactly as in the chromous chloride reactions described previously. Water precipitation and crystallization of the crude product from ether–pentane gave the 5,9-cyclo steroid **7** (403 mg): mp 138–143°; $[\alpha]D$ +184°; λ_{max}^{MeOH} 272 mμ (ε 4900); λ_{max}^{Nujol} 5.78, 6.02, 6.18, 8.04, and 8.45 μ.

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.04; H, 8.13.

5,9-Cycloandrostane-11β,17β-diol-3-one 11-Acetate 17-Propionate (8).—The 5,9-cyclo Δ^1-steroid **7** (1.0 g) from the foregoing experiment was hydrogenated (at 25° and atmospheric pressure) in ethanol (120 ml) with 15% palladized calcium carbonate catalyst (1.0 g). When the equivalent of 1 mole of hydrogen/mole of steroid had been absorbed (17 min) the mixture was worked up in the usual way, and the product was crystallized from ether–pentane, giving the dihydro **8** (703 mg): mp 124–126°; $[\alpha]D$ −150°; no high-intensity ultraviolet absorption between 220 and 350 mμ; λ_{max}^{Nujol} 5.79 (br), 8.02, and 8.42 μ.

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.48; H, 8.40.

Androsta-1,4,9(11)-triene-17β-ol-3-one 17-Propionate (9) from the 5,9-Cyclo Steroid 7.—Hydrogen chloride was bubbled through a solution of the 5,9-cyclo Δ^1-steroid **7** (100 mg) in chloroform (20 ml) at room temperature for 30 min. Evaporation *in vacuo* and crystallization of the residue from acetone–hexane gave pure triene **9** (15 mg): mp 131–135°; λ_{max}^{MeOH} 239 mμ (ε 15,000).

Androsta-4,9(11)-dien-17β-ol-3-one 17-Propionate (10) from the 5,9-Cyclo Steroid 8.—A solution of the 5,9-cyclo steroid **8** (100 mg) in chloroform (20 ml) was treated with hydrogen chloride for 30 min at room temperature. Evaporation *in vacuo* and crystallization from acetone–hexane gave pure diene **10** (10 mg): mp 104–110°; λ_{max}^{MeOH} 240 mμ (ε 16,000).

9α-Bromopregn-4-ene-11β,17α,21-triol-3,20-dione 11β,21-Diacetate (11).—A solution of pregna-4,9(11)-diene-17α,21-diol-3,20-dione 21-acetate (**5**, 2.5 g) in glacial acetic acid (100 ml) containing lithium acetate (10 g) and N-bromosuccinimide (0.987 g) was stirred at room temperature for 18 hr. The reaction mixture was then diluted with water, filtered, and the precipitate was washed with water and dried. Crystallization from acetone–hexane gave the 9α-bromo **11** (1.54 g): mp 278–283° dec; $[\alpha]D$ +162°; λ_{max}^{MeOH} 240 mμ (ε 16,200); λ_{max}^{Nujol} 2.94, 5.69, 5.73, 5.78, 6.06, 6.14, and 8.03 μ.

Anal. Calcd for $C_{25}H_{33}BrO_7$: C, 57.14; H, 6.33; Br, 15.21. Found: C, 57.07; H, 6.08; Br, 15.20.

The Reaction of 9α-Bromopregn-4-ene-11β,17α,21-triol 3,20-dione 11β,21-Diacetate (11) with Chromous Chloride.—A solution of the 9α-bromo **11** (3.5 g) in acetone (300 ml) was treated at room temperature with chromous chloride solution (105 ml) as described for the other chromous chloride reductions in this paper. Water was added, and the mixture was filtered.

Thin layer chromatography of the crude product (chloroform–ethyl acetate, 1:1) showed the presence of four products, two of which corresponded in R_f to the 4,9(11)-pregnadiene (**5**) and the 5,9-cyclo steroid **3**. On further standing, the aqueous filtrate from the reaction mixture deposited more solid, which by thin layer chromatography corresponded to only one of the four products mentioned above, namely, **12a**.

Crystallization of this latter material from acetone–hexane gave the spiro **12a**: mp 215–222°; $[\alpha]D$ +39°; no high-intensity ultraviolet absorption between 220 and 350 mμ; λ_{max}^{Nujol} 2.87, 5.85, 8.08, and 9.62 μ.

Anal. Calcd for $C_{23}H_{32}O_6$; C, 68.29; H, 7.97. Found: C, 68.40; H, 8.23.

Chromatography of the original precipitate on silica gel gave, on elution with chloroform–ethyl acetate (1:1), more spiro **12a**, total yield 332 mg.

In addition, a further product was isolated in small yield (25 mg), showing mp 155–162° (from acetone–hexane); $[\alpha]D$ +39°; no selective high-intensity ultraviolet absorption between 220 and 350 mμ; λ_{max}^{Nujol} 2.92, 5.76, 5.82, and 8.01 μ. Consistent

analyses could not be obtained for this substance, and in view of the small amount available it was not studied further.

Finally, as column chromatography gave only the above two products in pure form, preparative tlc was employed to isolate the 5,9-cyclo steroid **3**. Using the chloroform–ethyl acetate (1:1) system, 100 mg of the original crude precipitate was separated to give, after crystallization from acetone–hexane, the pure 5,9-cyclo steroid **3** (13 mg), identified by melting point, mixture melting point, $[\alpha]D$, and infrared comparison.

Hydrolysis of the 21-Acetoxyspiro Steroid 12a to the 21-Alcohol 12b.—A solution of the spiro steroid **12a** (200 mg) in methanol (19.5 ml) and 60% perchloric acid (0.5 ml) was stirred at room temperature for 24 hr. The mixture was diluted with water and extracted with methylene chloride; the organic extract was washed with water, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (25 g) when elution with chloroform–ethyl acetate gave the 21-alcohol **12b**. Recrystallization from acetone–hexane gave analytically pure material (30 mg): mp 200–210°; $[\alpha]D$ +27°; λ_{max}^{Nujol} 2.95, 5.75, and 5.84 μ. Reactylation of **12b** (pyidine–acetic anhydride, room temperature for 18 hr.) gave back quantitatively the 21-acetate **12a**.

Anal. Calcd for $C_{21}H_{30}O_5$: C, 69.59; H, 8.34. Found: C, 69.26; H, 8.75.

Side-Chain Degradation of the 21-Alcohol 12b to Give the 17-Ketone 15.—A solution of the 21-alcohol (**12b** (300 mg) in 50% aqueous acetic acid (30 ml) containing sodium bismuthate (5.1 g) was stirred at room temperature for 5 hr. The mixture was filtered, and the filtrate was neutralized with 10% aqueous sodium bicarbonate and was then extracted with methylene chloride. The extract was washed with water, dried (Na_2SO_4), and evaporated, and the residue was subjected to partition chromatography on Chromosorb W (50 g). A series of crystalline fractions resulted, giving the pure 17-ketone **15** (62 mg): mp 142–143° (from acetone–hexane); $[\alpha]D$ +108°; λ_{max}^{Nujol} 2.9, 3.0, 5.72, and 5.90 μ.

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.24; H, 8.63.

9α-Bromoandrost-4-ene-11β,17β-diol-3-one 11β-Acetate 17β-Propionate (13).—A solution of androsta-4,9(11)-diene-17β-ol-3-one 17β-propionate (5.62 g) in glacial acetic acid (225 ml) containing lithium acetate (22.5 g) and N-bromoacetamide (2.51 g) was stirred at room temperature for 18 hr. The mixture was diluted with water and filtered, and the precipitate was washed with water and dried. Crystallization from methylene chloride–hexane gave pure 9α-bromo **13** (5.31 g): mp 115–122° dec; $[\alpha]D$ +101°; λ_{max}^{MeOH} 240 mμ (ϵ 14,300); λ_{max}^{Nujol} 5.80, 6.01, 8.10, 8.15, and 8.5 μ.

Anal. Calcd for $C_{24}H_{33}BrO_5$: C, 59.88; H, 6.91; Br, 16.60. Found: C, 59.69; H, 7.11; Br, 16.72.

The Reaction of 9α-Bromoandrost-4-ene-11β,17β-diol-3-one 11β-Acetate 17β-Propionate (13) with Chromous Chloride.—A solution of the 9α-bromo **13** (5.0 g.) in acetone (100 ml) was treated with chromous chloride (150 ml) in the way described in other such experiments in this paper but the time interval before working up was unduly prolonged. Dilution with water and extraction with ether gave the crude product, which was chromatographed on silica gel (250 g). Elution with chloroform gave the spiro steroid **14a** (420 mg). The analytical sample showed mp 153–158° (from methylene chloride–ether–hexane); $[\alpha]D$ −17°; no high-intensity ultraviolet absorption between 220 and 350 mμ; λ_{max}^{Nujol} 2.85, 5.80–5.85, and 8.4 μ.

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 72.97; H, 8.80.

The above **14a** (200 mg) was hydrolyzed at C-17, using 10% methanolic potassium hydroxide solution under reflux for 0.5 hr. The crude product, isolated by methylene chloride extraction, was crystallized from methylene chloride–acetone–hexane to give the pure 17β-ol **14b** (85 mg): mp 150–152°; $[\alpha]D$ −12°; λ_{max}^{Nujol} 2.95 and 5.87 μ.

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.13; H, 9.24.

Treatment of the above 17β-ol **14b** (60 mg) with propionic anhydride–pyridine (room temperature, 18 hr) gave back the 17β-propionate **14a** (48 mg) after crystallization from methylene chloride–acetone–hexane. Identity was confirmed by melting point, mixture melting point, and infrared comparison.

Oxidation of the 17β-Hydroxy Spiro 14b to the 17-Ketone 15.—The 17β-ol **14b** (100 mg) was oxidized using chromium trioxide (200 mg) in pyridine (3 ml) at room temperature for 18 hr. The crude product was chromatographed on silica gel (3 g). Elution with ethyl acetate gave the 17-ketone **15**, and recrystallization from methylene chloride–ether–hexane gave material of mp 136–140°; $[\alpha]D$ +106°. This material was identical with the compound obtained by sodium bismuthate degradation of the spiro **12a** (see above).

Preparation of the 3-Dioxolane Derivative 16 of 14a.—The spiro steroid **14a** (100 mg) was treated for 5.5 hr with ethylene glycol (0.4 ml) in refluxing benzene (10 ml) containing *p*-toluenesulfonic acid (1.5 mg, Dean-Stark trap used). Pyridine (2 drops) was added to the cooled reaction mixture, and the mixture was then diluted with water. The organic phase was separated, washed with water, dried ($MgSO_4$), and evaporated at room temperature under nitrogen. The residue was crystallized from an ether–methylene chloride–hexane mixture, to give the 3-ethylene ketal **16** (40 mg): mp 115–117°; $[\alpha]D$ +23°; no high-intensity ultraviolet absorption; λ_{max}^{Nujol} 2.85, 5.80, and 8.4 μ.

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.26; H, 8.97. Found: C, 71.18; H, 9.05.

Dehydration Experiments with the 3-Dioxolane 16. A. Thionyl Chloride–Pyridine.—The 3-dioxolane **15** (45 mg) in pyridine (0.5 ml) at 0° was treated with thionyl chloride (2 drops) and left at 0° for 18 hr. The usual work-up gave an oily product which could not be crystallized. The nmr spectrum of the oil showed no absorption due to an exocylic methylene group.

B. Phosphorus Oxychloride–Pyridine.—(i) The 3-dioxolane **15** (45 mg) was treated with phosphorus oxychloride (0.07 ml) in pyridine (2 ml) at room temperature for 48 hr. The reaction mixture was then worked up to give unchanged starting material.

(ii) A solution of the 3-dioxolane **16** (45 mg) in pyridine (2 ml) and phosphorus oxychloride was refluxed under nitrogen for 2 hr. The crude oily product was shown, by tlc and paper chromatography, to contain four substances; two of these were ultraviolet absorbing.

C. Oxalyl Chloride–Dimethylformamide.—The 3-dioxolane **16** (200 mg) was added to a mixture of oxalyl chloride (0.2 ml) and dimethylformamide (3 ml) at 0°, and the reaction mixture was left at 5° for 18 hr. The crude product was an oil, which was subjected to partition chromatography on Chromosorb W (ligroin–propylene glycol system). A series of fractions resulted which were homogeneous by paper chromatography (ligroin–propylene glycol), and were combined. However, the combined fractions could not be crystallized. The nmr spectrum of this oily material showed absorption due to an exocyclic methylene group at δ 4.58.

Pregna-4,9(11)-diene-17α,21-diol-3,20-dione 17,21-Diacetate 18. A. From the Spiro Steroid 12a.—The spiro steroid, **12a** (1.20 g) was added to glacial acetic acid (20 ml), acetic anhydride (20 ml), and *p*-toluenesulfonic acid (0.24 g) and the mixture was stirred at 25° for 6 hr. Water was then added, and the mixture was filtered. The washed and dried precipitate was subjected to partition chromatography on Chromosorb W (ligroin–propylene glycol system), and a series of crystalline fractions was obtained. These were combined and crystallized from methylene chloride–hexane to give the 17,21-diacetate **18** (110 mg): mp 221–224°; $[\alpha]D$ +38°; λ_{max}^{MeOH} 239 mμ (ϵ 16,900); λ_{max}^{Nujol} 5.71, 5.92, 6.06, 6.15, and 8.0–8.1 μ.

B. From Pregna-4,9(11)-diene-17α,21-diol-3,20-dione 21-Acetate with Acetic Acid–Acetic Anhydride–*p*-Toluenesulfonic Acid.—The 4,9(11)-diene 21-monoacetate (500 mg) was added to glacial acetic acid (8 ml), acetic anhydride (8 ml), and *p*-toluenesulfonic acid (100 mg) and the mixture was stirred at 25° for 26 hr. The reaction mixture was then diluted with water, and filtered; the washed and dried precipitate was subjected to partition chromatography on Chromosorb W (ligroin–propylene glycol system). A series of crystalline fractions were combined to give the 17,21-diacetate **18** (42 mg), mp 218–222°, $[\alpha]D$ +36°, identical in all respects (mixture melting point, infrared comparison, paper chromatographic comparison) with the material obtained from reaction a above.

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