ane); λ_{max}^{Nujol} 2.88 μ (OH), 5.74 μ (acetate carbonyl), 5.78 μ (20-carbonyl), 5.85 μ (11-carbonyl), 7.82 and 8.00 μ (C–O–C of acetate).

Anal. Calcd. for $C_{23}H_{33}O_5F$: C, 67.62; H, 8.14. Found: C, 67.74; H, 8.00.

XVF from XIVF.—To a solution of 1.64 g. of XIVF in 50 ml. of acetone and 15 ml. of water was added 1.3 g. of N-bromoacetamide. After 10 minutes agitation at room temperature, the reaction mixture was placed in the refrigerator for 4 hours. Then aqueous sodium sulfite was added, the precipitated solid was removed by filtration, washed with water, dried and crystallized from acetone–hexane affording 1.3 g. of XVF, 17α-fluoropregnan-21-ol-3,11,20-trione acetate, m.p. 208–209°, $[\alpha]^{25}D$ +134° (dioxane); λ_{max}^{Nujol} 5.70 μ (acetate carbonyl), 5.76 μ (20-carbonyl), 5.88 μ (3- and 11-carbonyl), 7.85 and 8.15 μ (C–O–C of acetate).

Anal. Calcd. for $C_{23}H_{31}O_5F$: C, 67.95; H, 7.69. Found: C, 68.17; H, 7.73.

XVIIIF from XVF *via* a Crystalline 4-Bromide.—To a solution of 1.31 g. of XVF in 40 ml. of glacial acetic acid was added a solution of 0.43 g. of bromine in 10 ml. of acetic acid. The bromine color disappeared immediately, and a precipitate formed. The solid was separated by filtration and recrystallized from acetone–methylene chloride–hexane affording thereby 1.49 g. of 4-bromide, m.p. 219–222° dec., $[\alpha]^{25}D$ +135° (dioxane).

Anal. Calcd. for $C_{23}H_{30}O_5FBr$: Br, 16.47. Found: Br, 16.66.

To a solution of 0.5 g. of 4-bromide in 85 ml. of freshly distilled chloroform and 42.5 ml. of *t*-butyl alcohol was added, under a carbon dioxide atmosphere, 0.154 g. of semicarbazide. Agitation was continued for 80 minutes. The reaction mixture was warmed gently after 1 hour of agitation, whereupon the suspended solid dissolved completely leaving a bright yellow solution. The color discharged in 20 minutes and a haze returned. The reaction mixture was then stored at room temperature for 18 hours, concentrated *in vacuo*, and the residue was triturated with water, separated by filtration and dried. There resulted 0.425 g. of crude solid, which gave no Beilstein test and showed λ_{max}^{MeOH} 269 mμ (ϵ 20,100).

To a solution of 0.57 g. of crude semicarbazone in 67 ml. of acetic acid and 13.5 ml. of water was added 1.35 ml. of 99% pyruvic acid. The mixture was heated at reflux with agitation for 15 minutes, cooled, and excess water was added. The product was extracted from the aqueous phase with methylene chloride and the extracts were washed, dried, concentrated and chromatographed over Florisil. A series of fractions, from 50% ether–hexane and 100% ether eluates, melting 224–227° were pooled and recrystallized from acetone–hexane affording XVIIIF, 17α-fluoro-4-pregnen-21-ol-3,11,20-trione acetate (0.170 g.), m.p. 226–226.5°; $[\alpha]^{25}D$ +245° (dioxane), λ_{max}^{MeOH} 238 mμ (ϵ 15,500); λ_{max}^{Nujol} 5.68 μ (acetate carbonyl), 5.72 μ (20-carbonyl), 5.85 μ (11-carbonyl), 5.98 μ (3-carbonyl), 6.18 μ (Δ^4), 8.14 μ (C–O–C of acetate).

Anal. Calcd. for $C_{23}H_{29}O_5F$: C, 68.30; H, 7.23. Found: C, 68.03; H, 7.39.

BLOOMFIELD, N. J.

[CONTRIBUTION FROM LEDERLE LABORATORIES, A DIVISION OF THE AMERICAN CYANAMID CO.]

21-Acetoxy-16α,17α-epoxy-4-pregnene-3,20-dione as a Starting Material for the Synthesis of Triamcinolone

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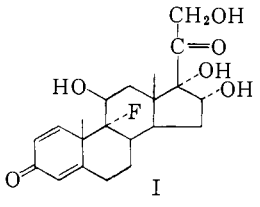
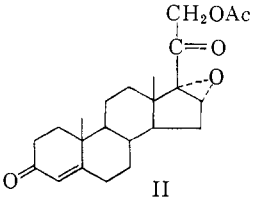
The conversion by several microbiological-chemical pathways of 21-acetoxy-16α,17α-epoxy-4-pregnene-3,20-dione(II) to 21-acetoxy-4,9(11),16-pregnatriene-3,20-dione (XII) and 16α,21-diacetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (XVII) is described. Compounds XII and XVII are intermediates for the synthesis of triamcinolone.

A number of syntheses of the biologically important triamcinolone (I)[2] already have been reported.[3] Our research in this area has continued,



I



II

and we now wish to describe certain *formal* syntheses of triamcinolone (I) which utilize as a starting material 21-acetoxy-16α,17α-epoxy-4-pregnene-3,20-dione (II). This compound is readily available by several stages from diosgenin, and was described first by Julian and co-workers.[4]

In connection with the use of a 16α,17α-epoxy derivative, such as II, for the synthesis of the 16α,17α-diol-containing triamcinolone, it may be noted that previous reports[5] have already demonstrated that the 16α,17α-epoxy group in 16α,17α-epoxy 11α-hydroxyprogesterone may serve two functions. This group may be considered as a protective group for the C-16,17-double bond, the double bond being regenerated by the chromous chloride method of Cole and Julian.[6] The double bond may then be treated with a hydroxylating agent, such as osmium tetroxide, for the introduction of the desired 16α,17α-dihydroxy grouping. Secondly, the 16α,17α-epoxy group by means of the Romo procedure[7] may be converted directly into the 16α-acetoxy-17α-hydroxy moiety.

Key intermediates for the synthesis of triamcinolone (I) from the epoxy derivative II appeared to be triene XII and the 16α-acetoxy-17α-hydroxy-

(1) (a) Organic Chemical Research Section, (b) Biochemical Research Section.

(2) The trademark of the Lederle Laboratories, Division of American Cyanamid Co. for triamcinolone is Aristocort.

(3) (a) W. S. Allen and S. Bernstein, THIS JOURNAL, **77**, 1028 (1955); (b) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman and R. H. Blank, *ibid.*, **78**, 5693 (1956); (c) R. W. Thoma, J. Fried, S. Bonanno and P. Grabowich, *ibid.*, **79**, 4818 (1957); (d) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman and R. H. Blank, *ibid.*, **81**, 1689 (1959); (e) S. Bernstein and R. Littell, *J. Org. Chem.*, **24**, 429 (1958); and (f) R. E. Schaub, G. R. Allen, Jr., and M. J. Weiss, THIS JOURNAL, **81**, 4962 (1959).

(4) P. L. Julian, E. W. Meyer, W. L. Karpel and I. Ryden, *ibid.*, **71**, 3574 (1949).

(5) S. Bernstein, J. J. Brown, L. I. Feldman and N. E. Rigler, *ibid.*, **81**, 4956 (1959); and G. R. Allen, Jr., and M. J. Weiss, *ibid.*, **81**, 4968 (1959).

(6) W. Cole and P. L. Julian, *J. Org. Chem.*, **19**, 131 (1954).

(7) J. Romo and A. Romo de Vivar, *ibid.*, **21**, 902 (1956).

pregnadiene XVII, the conversion of which to triamcinolone has already been described.[3a,b,d] The transformation of II to these intermediates is the subject of this paper. It is to be noted that the various syntheses which were elaborated were based on the use of the epoxy blocking group as discussed above.

Microbiological hydroxylation of 21-acetoxy-16α,17α-epoxy-4-pregnene-3,20-dione (II)[8a] with *Rhizopus nigricans*[8b] provided 16α,17α-epoxy-11α,-21-dihydroxy-4-pregnene-3,20-dione (VIII). The assigned structure (VIII) for this product was supported by the following observations. Treatment of VIII in pyridine with an excess of acetic anhydride gave the 11,21-diacetate III, whereas similar treatment with an equivalent of acetic anhydride afforded the 21-monoacetate IX (67% yield). Oxidation of the monoacetate IX with chromium trioxide in pyridine solution produced a crystalline substance whose properties were essentially in agreement with those reported for 21-acetoxy-16α,17α-epoxy-4-pregnene-3,11,20-trione (IV).[9] Additional structural proof was obtained by subsequent transformations to the known triamcinolone intermediates XII and XVII.

Three pathways were then elaborated for the conversion of 21-acetoxy-16α,17α-epoxy-11α-hydroxy-4-pregnene-3,20-dione (IX) into 21-acetoxy-4,9(11),16-pregnatriene-3,20-dione (XII), one of the two triamcinolone intermediates. Treatment of IX with *p*-toluenesulfonyl chloride in pyridine at $-5°$ or at room temperature overnight gave an 84% yield of the 11α-tosylate 21-acetate X. The latter compound on reaction with chromous chloride according to the method of Cole and Julian[6] gave in about 94% yield 21-acetoxy-11α-*p*-toluenesulfonyloxy-4,16-pregnadiene-3,20-dione (VII).[10] Subsequent reaction of VII with sodium acetate in refluxing glacial acetic acid resulted in the elimination of the tosyloxy group to afford 21-acetoxy-4,9(11),16-pregnatriene-3,20-dione (XII) (about 31% over-all yield from VIII).

A procedure wherein the C-9,11-double bond was introduced prior to the introduction of the C-16,17-double bond involved treatment of the 11α-tosyloxy 21-acetate X, with pyridine in hot methanol or ethanol solution[11] to give 21-acetoxy-16α,17α-epoxy-4,9(11)-pregnadiene-3,20-dione (XV).[12] The yield in this step was sensitive to reaction conditions, and it was found that on a 20-40-g. scale, 53–68% yields of the $\Delta^{9(11)}$-16α,-17α-epoxy-21-acetate XV were obtained with the solvent combination methanol–pyridine in the ratio of 3:1. Treatment of XV with chromous chloride then afforded the 4,9(11),16-triene 21-acetate XII in 84% yield.

The third pathway to the desired 4,9(11),16-triene 21-acetate XII involved treatment of 21-acetoxy-16α,17α-epoxy-11α-hydroxy-4-pregnene-3,-20-dione (IX) directly with chromous chloride to give as a non-crystalline product in 94% yield, 21-acetoxy-11α-hydroxy-4,16-pregnadiene-3,20-dione (V). Reaction of the latter with methanesulfonyl chloride in pyridine produced 21-acetoxy-11α-mesyloxy-4,16-pregnadiene-3,20-dione (VI), again as an amorphous solid in 95% yield. Compound VI was then treated with sodium acetate in refluxing acetic acid to give the 4,9(11), 16-triene 21-acetate XII. The over-all yield of XII from II was about 50%.

For the second triamcinolone intermediate, 16α,21-diacetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (XVII), three pathways were elaborated from 21-acetoxy-16α,17α-epoxy-11α-hydroxy-4-pregnene-3,20-dione (IX). The latter compound in the form of its 11α-tosylate X was submitted to the Romo procedure for the introduction of a 16α-hydroxy function. Compound X on treatment with hydrogen bromide in acetic acid gave in quantitative yield the bromohydrin XIV which with acetic anhydride in the presence of *p*-toluenesulfonic acid was converted into 3,17α,-21-triacetoxy-16β-bromo-11α-*p*-toluenesulfonyloxy-3,5-pregnadiene-20-one (XIII) (100% crude yield). Vigorous treatment of the latter product with sodium acetate in acetic acid (19.5 hours reflux) provided in 44–52% yield the desired intermediate, 16α,21-diacetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (XVII). The final step in this reaction sequence is noteworthy in that it involved reactions at three different sites on the steroid molecule: (1) conversion of the 16β-bromo-17α-acetoxy moiety to a 16α-acetoxy-17α-hydroxy moiety; (2) elimination of the 11α-tosyloxy group to yield a C-9,11-double bond; and (3) conversion of the 3-enol acetate to a Δ^4-3-ketone by solvolytic action. This particular route to the 4,9(11)-diene 16α,21-diacetate XVII is attractive in that the operations are simple and the isolations are straightforward. The best over-all yield obtained for the conversion of the 11α-tosyloxy-16α,17α-epoxy 21-acetate X to XVII was 43%.

A second sequence involved treatment of 21-

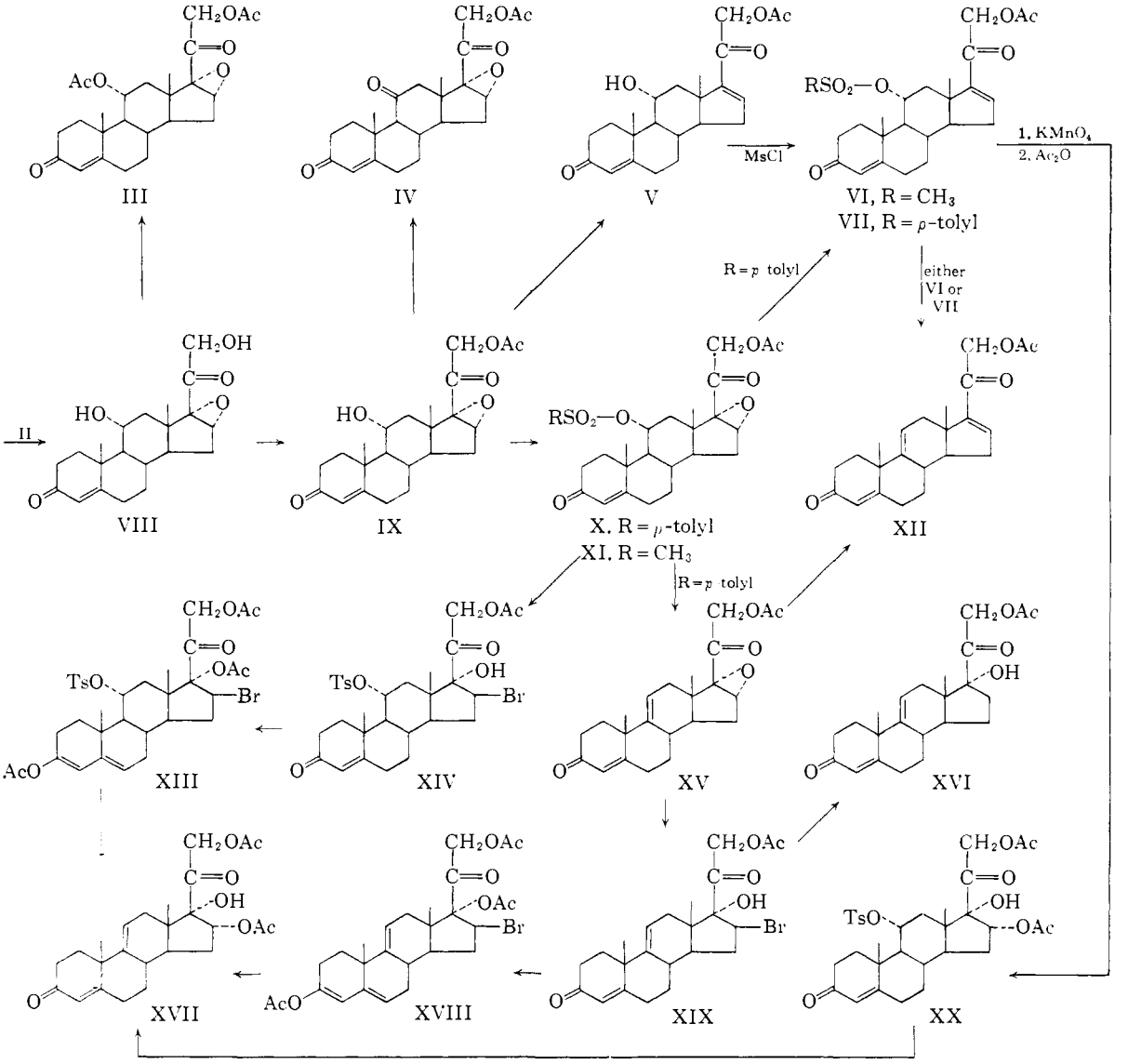
(8) (a) The free steroid 16α,17α-epoxy-21-hydroxy-4-pregnene-3,20 dione was prepared and characterized for use as a paper chromatography reference compound for following the microbiological hydroxylation of the 16α,17α-epoxy-21-acetate II to VIII; its preparation is described in the Experimental Section. (b) A comparable conversion of 16α,17α-epoxyprogesterone to 16α,17α-epoxy-11α-hydroxyprogesterone with *Rhizopus nigricans* has been reported by D. H. Peterson, P. D. Meister, A. Weintraub, L. M. Reineke, S. H. Eppstein, H. C. Murray and H. M. Leigh Osborn, THIS JOURNAL, **77**, 4428 (1955). It is also interesting to note that the Upjohn group [P. D. Meister, *et al.*, *ibid.*, **75**, 55 (1953)] has demonstrated that 11α-hydroxy-4,16-pregnadiene-3,20-dione with *Rhizopus nigricans* provided 11α-hydroxy-17α-progesterone. Thus, in essence, the 16α,17α-epoxy group may be considered a protective grouping for the 16,17-double bond in this fermentation.

(9) W. F. McGuckin and H. L. Mason, *ibid.*, **77**, 1822 (1955).

(10) This compound was first prepared by V. Origoni and S. J. Fox of the Chemical Process Improvement Department of these laboratories.

(11) The more vigorous sodium acetate–acetic acid elimination procedure when tried with the 11α-mesylate 21-acetate XI apparently gave a complex mixture. Possibly this was due to the effect of this reagent mixture on the combined 16α,17α-epoxy- and 20-one-21-acetoxy groups. In this connection see G. R. Allen, Jr., and M. J. Weiss, THIS JOURNAL, **81**, 4968 (1959) (also C. G. Bergstrom, U. S. Patent 2,703,799, March 8, 1955), wherein 16α,17α-epoxy-11α-mesyloxyprogesterone on treatment with anhydrous sodium acetate and glacial acetic acid was converted into 16α,17α-epoxy-4,9(11)-pregnadiene-3,20-dione in practically quantitative yield. Moreover, it is well known that this reaction proceeds with facility in the corticosterone, and hydrocortisone series; see, J. Fried and E. F. Sabo, THIS JOURNAL, **79**, 1130 (1957); and J. Fried, J. E. Herz, E. F. Sabo, A. Borman, F. M. Singer and P. Numerof, *ibid.*, **77**, 1068 (1955).

(12) This compound has been reported previously by L. B. Barkley, M. W. Farrar, W. S. Knowles and H. Raffelson, *ibid.*, **76**, 5017 (1954), as an intermediate in their total synthesis of hydrocortisone.



acetoxy - 16α,17α - epoxy - 4,9(11) - pregnadiene-3,20-dione (XV) with hydrogen bromide in acetic acid to give 21-acetoxy-16β-bromo-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (XIX)[12] in 75–99% yield.[13] Subsequent treatment with acetic anhydride containing *p*-toluenesulfonic acid gave 3,17α,21 - triacetoxy - 16β - bromo - 3,5,9(11) pregnatrien-20-one (XVIII) in 90–95% yield. Reaction of XVIII with sodium acetate in acetic acid then afforded XVII. The yield for the final step was disappointingly low. The best yield of crude XVII obtained was 8% and several attempts to improve it were fruitless.

In the third approach, the 16α,17α-diol system was introduced *via* a permanganate hydroxylation. As described above, the chromous chloride reaction with the 16α,17α-epoxy-11α-tosyloxy 21-acetate (X) proceeded in almost quantitative yield to give the corresponding 16-dehydro compound VII. Treatment of this substance (VII) in acetone–acetic acid with excess potassium permanganate for 3 minutes[14] gave 21-acetoxy-16α,-17α-dihydroxy-11α-*p*-toluenesulfonyloxy-4-pregnene-3,20-dione in 66–78% yield. Acetylation in the usual manner afforded (80–100% yield) noncrystalline 16α,21-diacetoxy-17α-hydroxy-11α-*p*-toluenesulfonyloxy - 4 - pregnene - 3,20 - dione (XX). Treatment of the latter compound with sodium acetate in refluxing acetic acid gave the desired XVII, although in low yield.

Acknowledgment.—Analyses were performed by Mr. Louis M. Brancone and associates. Infrared and ultraviolet absorption spectra and optical rotations were carried out by Mr. William Fulmor and associates. We wish to thank Doctors P. Shu, N. Rigler, J. Mowat and co-workers, and Mr. C. Pidacks and associates for supplying generous

(13) Debromination of bromohydrin XIX with Raney nickel to give 21-acetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (XVI) has been reported by the Monsanto group.[12] We have repeated this reaction.

(14) Potassium permanganate oxidation of a 16,17-double bond to give a 16α,17α-diol has been reported by Cooley and co-workers [*J. Chem. Soc.*, 4373 (1955)]. The particular procedure used in our investigation was developed by L. L. Smith and M. Marx of the Chemical Process Improvement Department of these laboratories.

amounts of 16α,17α-epoxy-11α,21-dihydroxy-4-pregnene-3,20-dione (VIII).

Experimental

16α,17α-Epoxy-21-hydroxy-4-pregnene-3,20-dione.—21-Acetoxy-16α,17α-epoxy-4-pregnene-3,20-dione (II) (10 g.) was dissolved in a mixture of chloroform (100 ml.) and methanol (350 ml.); water (34 ml.) was then added and the solution chilled to 10°. Concentrated hydrochloric acid (21 ml.) was added dropwise and the mixture was allowed to stand at room temperature for a period of 40 hours. Additional water was added, and the mixture was extracted with chloroform. The extract was washed to neutrality with saturated sodium bicarbonate solution and then with saturated saline solution, dried over magnesium sulfate and evaporated. This gave a crystalline residue which was crystallized from acetone to give 1.1 g., m.p. 181–184° (fraction 1). Concentration of the mother liquor with the gradual addition of petroleum ether yielded an additional 5.07 g., m.p. 181–184° (fraction 2) (total yield 70%). Recrystallization of fraction 2 from the same solvent pair did not change the melting point, $[\alpha]^{25}D$ +151° (methanol), λ_{max}^{MeOH} 239.5 mμ (ε 17,900); ν_{max}^{KBr} 3470, 1712, 1664, 1620 and 1066 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.44): C, 73.22; H, 8.19. Found: C, 73.19; H, 8.14.

16,17α-Epoxy-11α,21-dihydroxy-4-pregnene-3,20-dione (VIII).—Spores derived from a potato-dextrose agar slant of *Rhizopus nigricans* (ATCC 6227B) were used to inoculate 600 ml. of a corn steep-cerelose medium. After 24 hours incubation on a reciprocating shaker at 28°, the resultant growth was inoculated into 12 l. of the same medium contained in a 20-l. fermentor equipped with an aerator and stirrer. The fermentation was carried out at 28° with stirring at 300 r.p.m. and aeration at the rate of 0.1 liter of air/liter medium/minute. The organism was permitted to grow under these conditions for 24 hours, at which time 3 g. of 21-acetoxy-16α,17α-epoxy-4-pregnene-3,20-dione (II) dissolved in 200 ml. of 70% ethanol was introduced into the fermentation. Incubation was continued under the same conditions for 9 hr. at which time paper chromatographic analysis showed the presence of no starting steroid and a considerable quantity of the desired VIII. The contents of the fermentor were harvested at this time, and the mycelium was removed by filtration. The *p*H of the resultant beer was adjusted to 8.0 with solid sodium bicarbonate, and was extracted with methylene chloride (10 l.). The extract was washed to neutrality with water, dried and evaporated to give 1.78 g. of a hard glass. The beer was then re-extracted with ethyl acetate (10 l.) and the extract was washed to neutrality with water, dried and evaporated. This gave an additional 0.5 g. of a hard glass which was combined with the fraction obtained above from the methylene chloride extract, and submitted to partition chromatography. The combined solid material was dissolved in the stationary phase (20 ml.) from the system ethyl acetate–petroleum ether (90–100°)–methanol–water, 3:2:3:2, and mixed with Celite[15] (40 g.). This mixture was then packed on top of a column consisting of Celite (120 g.) impregnated with the stationary phase (60 ml.) from the same system. Elution with the mobile phase furnished the desired 16α,17α-epoxy-11α,21-diol VIII; m.p. 217–223° after crystallization from ethyl acetate. Recrystallization from acetone–ethyl acetate sharpened the melting point to 218–220°, $[\alpha]^{25}D$ +127° (methanol), λ_{max}^{EtOH} 241 mμ (ε 14,700); ν_{max}^{KBr} 3390, 1712, 1652, 1610 and 1060 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}O_5$ (360.44): C, 69.97; H, 7.83. Found: C, 69.75; H, 7.89.

11α,21-Diacetoxy-16α,17α-epoxy-4-pregnene-3,20-dione (III).—A solution of 16α,17α-epoxy-11α,21-diol VIII (125 mg.) in pyridine (10 ml.) was treated with acetic anhydride (3 ml.) and allowed to stand overnight at room temperature. The solution was then evaporated; the residue was dissolved in benzene–petroleum ether (1:1) and chromatographed on silica gel (30 g.). Elution with benzene–ether (1:1) gave the desired III. Crystallization from ethyl acetate–petroleum ether–ether yielded 125 mg., m.p. 161–163°. Recrystallization from ether–petroleum ether raised the melting point to 164–165°, $[\alpha]^{25}D$ +105° (methanol), λ_{max}^{MeOH} 239 mμ (ε 17,200); ν_{max}^{KBr} 1742, 1724, 1678, 1614, 1228 and 1024 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{32}O_7$ (444.51): C, 67.55; H, 7.26; OAc, 19.4. Found: C, 67.32; H, 7.21; OAc, 18.9.

21-Acetoxy-16α,17α-epoxy-11α-hydroxy-4-pregnene-3,20-dione (IX).—A solution of 16α,17α-epoxy-11α,21-dihydroxy-4-pregnene-3,20-dione (VIII) (250 mg.) in pyridine (10 ml.) was treated with acetic anhydride (0.075 ml.), and the mixture was allowed to stand overnight at room temperature. Methanol was added, and the mixture was evaporated. The residue was dissolved in benzene and chromatographed on silica gel (30 g.). Benzene–ether (1:1) eluted the desired compound which was crystallized from acetone–petroleum ether–ether to give 122 mg. of IX, m.p. 173–174°. Recrystallization from the same solvent did not alter the melting point, $[\alpha]^{25}D$ + 133° (methanol), λ_{max}^{MeOH} 241 mμ (ε 16,400); ν_{max}^{KBr} 3448, 1750, 1722, 1668, 1232 and 1054 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}O_6$(402.47): C, 68.63; H, 7.51; OAc, 10.7. Found: C, 68.99; H, 7.26; OAc, 9.8.

In a subsequent preparation using 25 g. of VIII a 67% yield of good quality IX was obtained.

21-Acetoxy-16α,17α-epoxy-4-pregnene-3,11,20-trione (IV).—A solution of 21-acetoxy-16α,17α-epoxy-11α-hydroxy-4-pregnene-3,20-dione (IX) (79 mg.) in pyridine (3 ml.) was treated with a solution of chromium trioxide (97 mg.) in pyridine (5 ml.) at 5°. The resultant mixture was allowed to stand overnight at room temperature. The solution was poured into water and extracted with chloroform. The extract was washed with saturated sodium bicarbonate solution and with saturated saline solution, dried over magnesium sulfate, and evaporated. The residue was crystallized from methanol to give pure IV, m.p. 199–201°, $[\alpha]^{25}D$ +201° (methanol), λ_{max}^{MeOH} 239 mμ (ε 16,100); ν_{max}^{KBr} 1230, 1625, 1670, 1710, 1730 (shoulder), 1740 cm.$^{-1}$; McGuckin and Mason[9] report m.p. 193–194°, $[\alpha]D$ +206° ±4°(1% alcohol), λ_{max}^{MeOH} 238 mμ (ε 16,550).

Anal. Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.10. Found: C, 68.66; H, 7.29.

21-Acetoxy-16α,17α-epoxy-11α-*p*-toluenesulfonyloxy-4-pregnene-3,20-dione (X).—A solution of 21-acetoxy-16α,17α-epoxy-11α-hydroxy-4-pregnene-3,20-dione (IX) (50 g.) in pyridine (250 ml.) was chilled to −5°, *p*-toluenesulfonyl chloride (35 g.) was added, and the mixture was allowed to stand 16 hr. at −5°. The mixture was poured into ice-water and the crystalline product filtered, washed with water, and dried. This gave 58 g. (84%), m.p. 151–154° dec. Recrystallization of a portion from acetone–petroleum ether raised the melting point to 164–166° dec., $[\alpha]^{25}D$ +105° (chloroform), λ_{max}^{MeOH} 228 mμ (ε 25,800); ν_{max}^{KBr} 1756, 1700, 1670, 1622, 1600, 1358, 1228 and 1170 cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{36}O_8S$ (556.65): C, 64.73; H, 6.52; S, 5.76. Found: C, 64.59; H, 6.95; S, 5.58; 5.68.

A similar preparation carried out at room temperature gave similar results.

21-Acetoxy-16α,17α-epoxy-11α-methanesulfonyloxy-4-pregnene-3,20-dione (XI).—A solution of 21-acetoxy-16α,17α-epoxy-11α-hydroxy-4-pregnene-3,20-dione (IX) (1 g.) in pyridine (15 ml.) was chilled to 5°, and methanesulfonyl chloride (1.5 ml.) was added. The mixture was allowed to stand overnight at 5°, water and methylene chloride were added. The layers were separated and the water layer further extracted with methylene chloride. The combined methylene chloride extract was washed once with 5% hydrochloric acid, once with sodium bicarbonate solution, and five times with water. The extract was dried over magnesium sulfate, and evaporated to give the mesylate XI as a hard glass (1.1 g.) which resisted crystallization; ν_{max}^{KBr} 1754, 1726, 1674, 1620, 1342, 1230 and 1170 cm.$^{-1}$.

21-Acetoxy-11α-*p*-toluenesulfonyloxy-4,16-pregnadiene-3,20-dione (VII).[10]—By the procedure as given below for V, 21-acetoxy-16α,17α-epoxy-11α-*p*-toluenesulfonyloxy-4-pregnene-3,20-dione (X) (10 g.) was converted into VII in 94% crude yield, m.p. 150–152°. Recrystal-

(15) The adsorbent was specially treated Celite "545" which had been washed with 6 *N* hydrochloric acid, water, and finally with 3A alcohol and then dried at 100°. Celite is the trademark of Johns-Manville Co. for diatomaceous silica products. For a complete description of this technique see R. Littlell and S. Bernstein, THIS JOURNAL, **78**, 984 (1956).

lization from acetone–petroleum ether raised the m.p. to 158–159°, $[\alpha]^{25}D$ +69° (chloroform), λ_{max}^{MeOH} 231 mμ (ε 31,400); ν_{max}^{KBr} 1748, 1676, 1612, 1584, 1500, 1334, 1218, 1172, 904 and 692 cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{38}O_7S$ (540.65): C, 66.64; H, 6.71; S, 5.93. Found: C, 66.75; H, 6.89; S, 6.18.

Conversion of 21-Acetoxy-11α-*p*-toluenesulfonyloxy-4,16-pregnatriene-3,20-dione (VII) to 21-Acetoxy-4,9(11),16-pregnatrien-3,20-dione (XII).—A solution of VII (1 g.) in glacial acetic acid (25 ml.) containing sodium acetate (1.g.) was refluxed for 3 hr. The acetic acid was evaporated, and the residue taken up in methylene chloride and water. The layers were separated, and the water layer was extracted with methylene chloride. The combined extracts were washed with saturated sodium bicarbonate solution and with saline solution, and dried over magnesium sulfate. The extract was evaporated and the residue was crystallized from acetone–petroleum ether; this gave 400 mg. (59%) of XII, m.p. 124–125°, λ_{max}^{MeOH} 238 mμ (ε 25,500). The infrared spectrum was identical to that of an authentic sample.[3a]

21-Acetoxy-16α,17α-epoxy-4,9(11)-pregnadiene-3,20-dione (XV).—A solution of 21-acetoxy-16α,17α-epoxy-11α-*p*-toluenesulfonyloxy-4-pregnene-3,20-dione (X) (1.11g.) in a mixture of absolute ethanol (50 ml.) and pyridine (1 ml.) was refluxed for 40 hr. The solvents were evaporated and the residue was dissolved in methylene chloride. The methylene chloride solution was washed with water, dried over magnesium sulfate and evaporated. This gave 0.92 g. of a hard glass which was dissolved in benzene and chromatographed on silica gel (75 g.). Elution with ether gave the desired product XV which was crystallized from acetone–petroleum ether, m.p. 153–155°. Recrystallization from the same solvent pair raised the m.p. to 155–157°, λ_{max}^{MeOH} 238 mμ (ε 17,700); ν_{max}^{KBr} 1758, 1726, 1670, 1648(shoulder), 1612, 1222 and 1054 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{28}O_5$ (384.45): C, 71.85; H, 7.34. Found: C, 71.62; H, 7.66.

The 11α-tosyloxy 21-acetate X was heated with various combinations of methanol or ethanol–pyridine and collidine–pyridine. The best yields (53–68%) of VI were obtained on a 20- and 40-g. scale with the solvent combination methanol–pyridine (3:1).

Compound XV has been reported,[12] without characterization, as a non-crystalline solid.

Conversion of 21-Acetoxy-16α,17α-epoxy-4,9(11)-pregnadiene-3,20-dione (XV) to 21-Acetoxy-4,9(11),16-pregnatriene-3,20-dione (XII).—Treatment of XV (3 g.) by the chromous chloride procedure, as given below for V, afforded an 84% yield of XII, m.p. 121–123°. The infrared spectrum of the product was identical to that of an authentic sample.[3a]

21-Acetoxy-11α-hydroxy-4,16-pregnadiene-3,20-dione (V).—A solution of 21-acetoxy-16α,17α-epoxy-11α-hydroxy-4-pregnene-3,20-dione (IX) (60.8 g.) in acetic acid (250 ml.) was treated with chromous chloride (0.5 *N*, 800 ml.) under an atmosphere of carbon dioxide.[6] The reaction was allowed to proceed for 5 minutes after which water and methylene chloride were added. The layers were separated and the water layer extracted with methylene chloride. The extracts were combined and washed with saturated sodium bicarbonate solution and with water. The combined extracts were dried over magnesium sulfate and evaporated. The residue was dissolved in acetone (500 ml.); concentrated hydrochloride acid (2 ml.) was added, and the mixture was refluxed for one hour. The acetone was distilled off under reduced pressure and the solid residue dissolved in methylene chloride. The washed extract was dried over magnesium sulfate and evaporated. This gave a hard glass (55 g., 94%) which could not be crystallized; $[\alpha]^{25}D$ +103° (methanol), λ_{max}^{MeOH} 240 mμ (ε 23,200); ν_{max}^{KBr} 3422, 1758, 1680, 1622, 1596 and 1238 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}O_5$ (386.47): C, 71.48; H, 7.82. Found: C, 70.98; H, 7.87.

21-Acetoxy-11α-methanesulfonyloxy-4,16-pregnadiene-3,20-dione (VI).—A solution of 21-acetoxy-11α-hydroxy-4,16-pregnadiene-3,20-dione (V) (54.5 g.) in pyridine (600 ml.) was chilled to 5° and methanesulfonyl chloride (50 ml.) was added. The mixture was allowed to stand overnight at room temperature; water and methylene chloride were added. The layers were separated, and the water layer was further extracted with methylene chloride. The extracts were combined, washed with water, dried over magnesium sulfate and evaporated. This gave a hard glass (62 g.) (95%) which resisted crystallization; $[\alpha]^{25}D$ +89° (methanol), λ_{max}^{MeOH} 238 mμ (ε 24,100); ν_{max}^{KBr} 1754, 1700, 1622, 1596, 1342, 1220, 1168 and 922 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{32}O_7S$ (464.57): C, 62.04; H, 6.94; S, 6.90. Found: C, 62.43, 62.20; H, 7.30, 7.21; S, 7.03.

Conversion of 21-Acetoxy-11α-methanesulfonyloxy-4,16-pregnadiene-3,20-dione (VI) to 21-Acetoxy-4,9(11),16-pregnatriene-3,20-dione (XII).—A solution of VI (2.2 g.) in glacial acetic acid (60 ml.) containing sodium acetate (1.9 g.) was refluxed for 2 hr. The acetic acid was removed by distillation under reduced pressure, and the residue was taken up in methylene chloride and water. The layers were separated, and the water layer was extracted twice with methylene chloride. The combined extracts were washed with saturated sodium bicarbonate solution and twice with saturated saline solution. The extract was dried over magnesium sulfate and evaporated. The residue was dissolved in benzene and chromatographed on silica gel (75 g.). Benzene–ether (1:1) eluted the desired compound, which when crystallized from acetone–petroleum ether gave pure XII (925 mg., 34%), m.p. 123–124°. The infrared spectrum was identical to that of an authentic sample.[3a]

In another preparation with 62 g. of VI, there was obtained 26.5 g. (49%) of good quality XII.

21-Acetoxy-16β-bromo-17α-hydroxy-11α-*p*-toluenesulfonyloxy-4-pregnene-3,20-dione (XIV).—A solution of 21-acetoxy-16α,17α-epoxy-11α-*p*-toluenesulfonyloxy-4-pregnene-3,20-dione (X) (25 g.) in glacial acetic acid (200 ml.) was chilled to 15° and treated with 25 ml. of (30–32%) hydrobromic acid in acetic acid. The mixture was allowed to stand for 0.5 hour, when water was slowly added. This gave a crystalline solid which was collected by filtration and washed well with water. The residue was dried carefully *in vacuo*. This gave 28 g., m.p. 120–122° dec. (98%). This compound proved to be quite sensitive to light and heat. Crystallization from acetone–water (no heat) sharpened the melting point to to 121–122° dec.; ν_{max}^{KBr} 3460, 1742, 1672, 1618, 1602, 1496, 1352 and 1173 cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{37}BrO_8S$ (637.58): C, 56.51; H, 5.85; S, 5.03; Br, 12.53. Found: C, 56.27; H, 6.08; S, 4.79; Br, 12.93.

3,17α,21-Triacetoxy-16β-bromo-11α-*p*-toluenesulfonyloxy-3,5-pregnadien-20-one (XIII).—A solution of 21-acetoxy-16β-bromo-17α-hydroxy-11α-*p*-toluenesulfonyloxy-4-pregnene-3,20-dione (XIV) (4 g.) in acetic anhydride (35 ml.) was treated with *p*-toluenesulfonic acid (1.34 g.), and the mixture was allowed to stand at room temperature for 16 hr. The solution was then chilled to 5°, water (35 ml.) was added and the mixture stirred for 1 hr. Additional water (50 ml.) was added and the crystalline material was collected by filtration and washed well with water. This gave 4.50 g. of XIII, m.p. 134° dec. (100%). A portion was crystallized several times from acetone–water (no heating was employed); m.p. 152° dec., $[\alpha]^{25}D$ −62° (chloroform); λ_{max}^{MeOH} 227 mμ (ε 30,800); ν_{max}^{KBr} 1748, 1678, 1642, 1598, 1494, 1368 and 1226 cm.$^{-1}$.

Anal. Calcd. for $C_{34}H_{41}BrO_{10}S$ (721.64): C, 56.59; H, 5.73; S, 4.44; Br, 11.07. Found: C, 55.98; H, 6.03; S, 4.47; Br, 10.76.

A preparation starting with 20 g. of XIV gave XIII, m.p. 133–135° dec., in 99% yield.

Conversion of 3,17α,21-Triacetoxy-16β-bromo-11α-*p*-toluenesulfonyloxy-3,5-pregnadien-20-one (XIII) to 16α,21-Diacetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (XVII).—A solution of XIII (1 g.) in glacial acetic acid (18 ml.) containing sodium acetate (2 g.) was refluxed for 19.5 hr. Water was added and the mixture was extracted with methylene chloride. The extract was washed with water, once with saturated sodium bicarbonate solution, and finally with water. The extract was dried over magnesium sulfate, treated with charcoal, filtered and evaporated. The residue was dissolved in benzene and chromatographed on silica gel (30 g.). Elution with benzene–ether (1:1) gave solid material which was crystallized from acetone–petroleum ether to yield 190 mg. of XVII, m.p. 120–122° with gas evolution, resolidification and remelting at 184–

186°; λ_{max}^{MeOH} 239 mμ (ε 14,200). Its infrared spectrum was identical to that of an authentic sample of XVII.[3b,d]

In a like manner with 2 g. of XIII there was obtained a 44% yield of XVII, m.p. 119–120°, 188–189°; λ_{max}^{MeOH} 238 mμ (ε 17,800). In this preparation methanol was used as the solvent for crystallization. No chromatography was required.

A preparation starting with 5 g. of XIII (134° material) and carried out as above without chromatography gave 49% XVII, m.p. 120–122° (gas) and 188–189°. Methanol was used as the recrystallization solvent. An additional 3%, m.p. 122–124° (gas) and 186–188°, was obtained by chromatography of the mother liquor.

21-Acetoxy-16β-bromo-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (XIX).—A solution of 21-acetoxy-16α,17α-epoxy-4,9(11)-pregnadiene-3,20-dione (XV) (3.35 g.) in acetic acid (25 ml.) was treated with hydrobromic acid (30–32%, 3 ml.) in a similar manner to that described above for the preparation of XIV. The crystalline residue was carefully dried *in vacuo* to give material melting at 138° dec. Crystallization from acetone–petroleum ether yielded 2.67 g. of XIX, m.p. 148° dec. (fraction 1), and the mother liquor provided an additional 0.37 g., m.p. 152° dec. (total yield 75%). Fraction 1 was used for characterization purposes; $[\alpha]^{25}D$ +71° (chloroform), λ_{max}^{MeOH} 238 mμ (ε 17,000); ν_{max}^{KBr} 3416, 1742, 1722, 1672, 1618, 1254 and 1070 cm.$^{-1}$. Compound XIX has been reported[12] to have m.p. 146–147° dec.

Anal. Calcd. for $C_{23}H_{29}O_5Br$ (465.38): C, 59.36; H, 6.28; Br, 17.17. Found: C, 59.32; H, 6.62; Br, 16.52, 16.68.

In another preparation with 5 g. of XV there was obtained 5.97 g. (99%) of XIX, m.p. 150–152° dec.

3,17α,21-Triacetoxy-16β-bromo-3,5,9(11)-pregnatrien-20-one (XVIII).—A solution of 21-acetoxy-16β-bromo-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (XIX) (2.67 g.) in acetic anhydride (130 ml.) was treated with *p*-toluenesulfonic acid (0.89 g.) in a manner similar to that described above for the preparation of XIII. After the usual workup, the crystalline residue was carefully dried *in vacuo;* this gave 1.51 g. (49%) of XVIII, m.p. 94° dec. This compound was quite unstable and attempts to recrystallize it were unsuccessful; λ_{max}^{MeOH} 236 mμ (ε 16,800); ν_{max}^{KBr} 3450, 1752, 1668, 1230 and 1126 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{33}BrO_7$ (533.45): C, 60.8; H, 6.25; Br, 15.1. Found: C, 58.79; H, 6.42; Br, 15.28.

Subsequent preparations gave yields of 95% (1-g. scale) and 90% (5-g. scale).

Conversion of 3,17α,21-Triacetoxy-16β-bromo-3,5,9(11)-pregnatrien-20-one (XVIII) to 16α,21-Diacetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (XVII).—A solution of XVIII (1 g.) in acetic acid (30 ml.) containing sodium acetate (2 g.) was refluxed for 3 hr. (the solution turned black after 1 hr.). Most of the acetic acid was then removed by distillation under reduced pressure, and water (100 ml.) was added. This gave a dark brown precipitate which was collected by filtration and discarded. Additional water was then added to the filtrate and the mixture was extracted with methylene chloride. The extract was washed with saturated sodium bicarbonate solution and water. The extract was then dried over magnesium sulfate and evaporated. The residue was crystallized from acetone–petroleum ether to give 63 mg. (8%), m.p. 182–184°. Recrystallization from the same solvent pair raised the m.p. to 184–187°, λ_{max}^{MeOH} 238 mμ (ε 16,500). Its infrared spectrum was identical to that of an authentic sample.[3b,d]

21-Acetoxy-16α,17α-dihydroxy-11α-*p*-toluenesulfonyloxy-4-pregnene-3,20-dione.—A solution of 21-acetoxy-11α-*p*-toluenesulfonyloxy-4,16-pregnadiene-3,20-dione (VII) (5 g.) in acetone (100 ml.) was treated with a solution of potassium permanganate (1.75 g.) in 85% aqueous acetone (100 ml.) at 0° for 3 minutes.[14] Sodium bisulfite solution (10%, 20 ml.) was added, and the insoluble, inorganic salts were removed by filtration. The filtrate was concentrated to near dryness, and water was added. This produced crystals, which were collected by filtration and air-dried; 4.12 g. (78%), m.p. 148–150° dec., $[\alpha]^{25}D$ +29° (pyridine), λ_{max}^{MeOH} 229 mμ (ε 24,600); ν_{max}^{KBr} 3450, 1750, 1730, 1668, 1618, 1600, 1352, 1232, 1173 and 1092 cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{38}O_9S$ (574.66): C, 62.70; H, 6.67; S, 5.58. Found: C, 62.53; H, 6.86; S, 5.45.

Attempts to recrystallize this product from chloroform–petroleum ether raised the melting point but apparently led to some decomposition of the compound according to the elemental analyses.

A preparation on twice the above scale gave a 66% yield of product, m.p. 136–138° dec.

16α,21-Diacetoxy-17α-hydroxy-11α-*p*-toluenesulfonyloxy-4-pregnene-3,20-dione (XX).—21-Acetoxy-16α,17α-dihydroxy-11α-*p*-toluenesulfonyloxy-3,20-dione (1.7 g.) was dissolved in pyridine (15 ml.) and acetic anhydride (5 ml.) was added. The solution was allowed to stand overnight at room temperature. Water was added, and the mixture was extracted with methylene chloride. The extract was washed with saline solution, dried over magnesium sulfate, and evaporated to give 1.45 g. (80%) of an amorphous powder, m.p. 85° (gas evolution), decomposition at 119°. This material resisted crystallization. A portion was dried over benzene *in vacuo* for 3 hr., m.p. 115° dec., $[\alpha]^{25}D$ +37° (methanol), λ_{max}^{MeOH} 229 mμ (ε 24,000); ν_{max}^{KBr} 3494, 1752, 1678, 1624, 1604, 1500, 1376, 1232, 1176 and 1098 cm.$^{-1}$.

Anal. Calcd. for $C_{32}H_{40}O_{10}S$ (616.70): C, 62.32; H, 6.54; S, 5.20. Found: C, 62.25; H, 6.53; S, 5.25, 5.34.

In another preparation with 3 g. of diol, a quantitative yield (3.22 g.) of a hard glass was obtained identical to that of the analytical sample described above.

Conversion of 16α,21-Diacetoxy-17α-hydroxy-11α-*p*-toluenesulfonyloxy-4-pregnene-3,20-dione (XX) to 16α,21-Diacetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (XVII).—A solution of XX (0.5 g.) and sodium acetate (0.5 g.) in acetic acid (20 ml.) was refluxed for 3 hr. The acetic acid was evaporated, and the residue was dissolved in methylene chloride–water. The organic layer was separated, washed with saturated saline solution, saturated sodium bicarbonate solution, and finally with saturated saline solution. The extract was dried over magnesium sulfate, evaporated, and the residue was crystallized from methanol to give 43 mg. of XX, m.p. 120–122° (gas evolution), resolidification and remelting at 184–186° (fraction 1). An additional 30 mg., m.p. 120–122°, 184–186° (fraction 2) was obtained from the mother liquor by chromatography (20% total yield). Fraction 1 had λ_{max}^{MeOH} 237 mμ (ε 15,500); fraction 2 had λ_{max}^{MeOH} 238 mμ (ε 16,700). Both fractions possessed identical infrared spectra comparable to that of an authentic sample.[3b,d]

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