R_f 0.96, and heretofore undetected 9α-fluoro-2β-hydroxyhydrocortisone III at R_f 0.49, together with two minor components.

The mother liquor was subjected to preparative paper chromatography using System V, the desired acetonide VI zone eluted with hot acetone, and the eluate evaporated to incipient crystallization. The product was recognized by comparison of infrared spectra (100 μg.) and papergram behavior as being identical with fully characterized 9α-fluoro-2β,16α-dihydroxhydrocortisone 16α,17α-acetonide VI prepared by another method in these Laboratories.

The acetonide VI is characterized by the spectral data: $\lambda_{max}^{H_2SO_4}$ ($E_{1\ cm.}^{1\%}$) 2 hr., 285 mμ (104, inflection), 340 mμ (497), 380 mμ (61, inflection), 550 mμ (11); λ_{max}^{KBr} 2.90 μ, 3.39 μ, 5.80 μ, 5.93 μ, 6.10 μ, 8.15 μ, 9.20 μ, 9.40 μ, 11.20 μ, 11.60 μ, etc.; $\lambda_{max}^{0.066\ N\ NaOH}$ ($E_{1\ cm.}^{1\%}$) at 60°: 1 hr. 230 mμ (354), 250 mμ (160, inflection), 355 mμ (54), 4 hr., 229 mμ (383), 250 mμ (159, plateau), 360 mμ (89).

The acetonide is further characterized by the following data kindly supplied by Dr. N. Rigler of these Laboratories: m.p. 260–261°; $[\alpha]_D$ + 12.9°; $\lambda_{max}^{CH_3OH}$ 239 mμ (ε 13,600).

Anal. Calcd. for $C_{24}H_{33}O_7F$: C, 63.75; H, 7.32; F, 4.22. Found: C, 62.88; H, 7.57; F, 4.53.

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PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE NATURAL PRODUCTS RESEARCH DEPARTMENT OF THE SCHERING CORP.]

17,21-Acetonide Derivatives of 9,11-Disubstituted Cortical Hormones

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A series of 9α,11β-dichloro- and 9α-chloro-11β-formoxycorticosteroids has been converted to the corresponding series of cyclic 17α,21-acetonides. The 17,21-acetonide system, useful as a means of side-chain protection, has also been found to enhance anti-inflammatory activity in the series studied.

The discovery of the ready reaction of the cortical dihydroxyacetone side chain with 2,2-dimethoxypropane, to give a cyclic 17α,21-acetonide,[1] has furnished not only a route to novel hormone analogs, but also a new means of side chain protection.

The variety of readily available 9α,11β-dihalo-[2] and 9α-halo-11β-acyloxycorticosteroids[3] led us to undertake the preparation of the corresponding 17α,21-acetonides, for possible further chemical transformations. The acetonides themselves, however, proved to be biologically interesting and this paper is concerned solely with the preparation, properties, and some reactions of this interesting group of compounds.

The 17α,21-acetonide (IVa) of 9α,11β-dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione (IIIa) was first secured, in 50% yield, by the action of a 2,2-dimethoxypropane-dimethylformamide mixture, containing *p*-toluenesulfonic acid, for three hours under reflux. The course of the reaction was followed by periodically testing samples with triphenyltetrazolium chloride (TPTZ) reagent.

The acetonide (IVa) gave no color with TPTZ reagent, showed $\lambda_{max}^{CH_3OH}$ 236 mμ (16,400) and gave the correct analysis. The infrared spectrum showed that no hydroxyl was present, but absorption maxima were observed at 5.82 μ (20-ketone) and at 6.0, 6.12, and 6.20 μ (1,4-dien-3-one). When IVa was dissolved in 60% aqueous acetic acid and kept at steam bath temperature for ten minutes, cleavage of the acetonide grouping occurred, and 9α,11β-dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione (IIIa), identical in all respects with authentic material, was obtained in excellent yield.

The 16α-methyl and 16β-methyl analogs (IVb and IVc, respectively) of IVa were next prepared by the following reaction sequences. Addition of chlorine, in carbon tetrachloride-pyridine, to 16α-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate[4] (Ib) and the 16β-methyl analog[5] gave the 9α,11β-dichloro derivatives (IIb and IIc). Although we had previously[2] used acetic acid as the solvent for the preparation of 9α,11β-dichloro compounds, we have since observed that both shorter reaction times and higher yields accompany the use of a carbon tetrachloride-pyridine system. (Thus, for example, 1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate (Ia) gave the 9α,11β-dichloro compund (IIa) in about 75% yield by the carbon tetrachloride procedure, compared

(1) M. Tanabe and B. J. Bigley, *J. Am. Chem. Soc.*, **83**, 756 (1961).

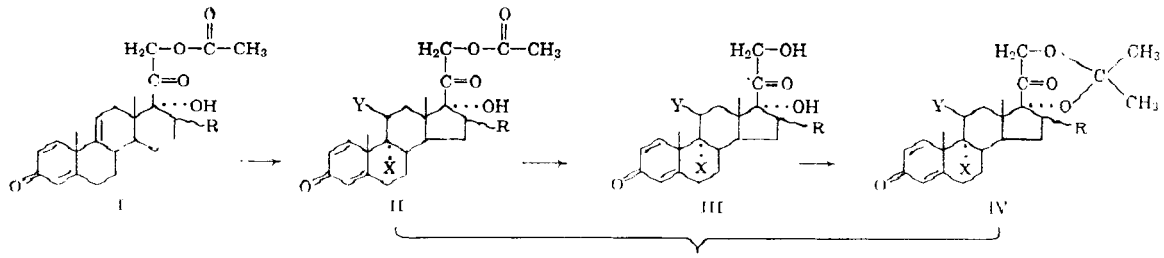
(2) C. H. Robinson, L. E. Finckenor, F. P. Oliveto, and D. H. Gould, *J. Am. Chem. Soc.*, **81**, 2191 (1959).

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

(4) E. P. Oliveto, R. Rausser, L. Weber, A. L. Nussbaum, W. Gebert, C. T. Conigilio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 4431 (1958).

(5) E. P. Oliveto, R. Rausser, H. L. Herzog, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 6687 (1958).

TABLE I



a. R = H
b. R = αCH₃
c. R = βCH₃

a. R = H; X = Cl; Y = Cl
b. R = αCH₃; X = Cl; Y = Cl
c. R = βCH₃; X = Cl; Y = Cl
d. R = H; X = Cl; Y = OCOH
e. R = αCH₃; X = Cl; Y = OCOH
f. R = βCH₃; X = Cl; Y = OCOH

Compound	Procedure and Time, Hr.	M.P., Dec.	$[\alpha]_D$	$[M]_D$	Mμ	$\lambda_{max}^{CH_3OH}$	Calcd. C	Calcd. H	Calcd. Cl	Found C	Found H	Found Cl
IIa[a]	A 1	246–253	+162	+737	237	15,000	60.66	6.20	15.57	60.24	6.14	15.99
IIb	A 1	234–237	+142	+667	238	14,900	61.40	6.44	15.11	61.30	6.43	15.48
IIc	A 1	223–225	+176	+826	237	14,600	61.40	6.44	15.11	61.21	6.68	14.62
IId[b]	B 18	258–262	+162	+753	237	14,500	61.99	6.28	7.64	61.64	6.58	7.36
IIe	B 18	245–252	+136	+651	237	14,900	62.69	6.52	7.40	62.76	6.62	7.66
IIf	B 18	249–251	+178	+853	237	14,900	62.69	6.52	7.40	62.63	6.79	7.46
IIIa[a]	B 18	238–241	+134[c]	+554	237	15,400	61.02	6.34	17.15	61.26	6.30	16.66
IIIb	C 18	224–227	+132[c]	+564	238	16,300	61.83	6.60	16.59	61.98	6.45	16.35
IIIc	C 18	230–234	+167[c]	+714	237	14,900	61.83	6.60	16.59	62.08	7.06	16.11
IIId	C 18	246–249	+145	+613	238	14,900	62.47	6.43	8.39	62.56	6.12	8.57
IIIe	C 18	229–234	+123	+537	237	14,600	63.22	6.69	8.11	63.12	6.63	8.10
IIIf	C 18	234–237	+157	+686	237	14,900	63.22	6.69	8.11	63.37	6.74	8.36
IVa	D 3	212–214	+162	+735	236	16,400	63.57	6.67	15.64	63.82	6.75	15.55
IVb	D 18	230–235	+155	+724	238	16,000	64.24	6.90	15.17	64.30	6.60	15.03
IVc	D 4	207–212	+159	+743	237	15,500	64.24	6.90	15.17	64.29	7.00	14.97
IVd	D 4	224–229	+147	+681	236	15,600	64.85	6.75	7.65	64.97	6.70	7.37
IVe	D 72	228–234	+138	+658	236	15,500	65.47	6.97	7.43	65.64	7.00	7.10
IVf	D 17	225–230	+148	+706	236	15,300	65.47	6.97	7.43	65.25	7.02	7.20

[a] See ref. 2. [b] See ref. 3. [c] Denotes $[\alpha]_D$ measured in pyridine.

with the yield of about 45–50% furnished by our earlier[2] procedure.)

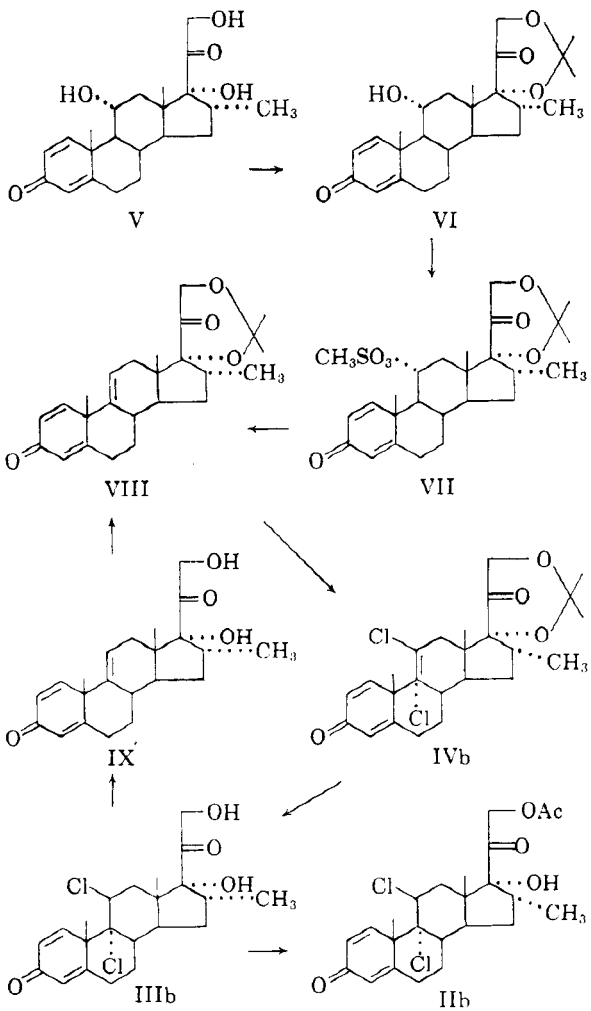
Since IIa, IIb, and IIc were secured using the same experimental conditions, the general procedure is given in the experimental section, and is referred to there and in Table I as Procedure A. In a number of subsequent reactions in which the expermental conditions were essentially the same for several compounds, although with varying reaction times, we have given the general procedure in the experimental section. The reaction times are shown in Table I.

The 16-methyl-9,11-dichloro compounds (IIb and IIc) were hydrolyzed at C-21 with perchloric acid in methanol, to give the corresponding 21-alcohols (IIIb and IIIc) which were then converted to the 17α,21-acetonides (IVb and IVc) by the procedure described above for the formation of IV a (Procedure D; Table I).

The foregoing compounds (IIb, IIc, IIIb, IIIc) all gave satisfactory analyses, which, together with melting points, optical rotations and ultraviolet absorption data, are collected in Table I. In these and in all subsequent examples the infrared spectra were fully in accord with the assigned structures, and detailed infrared data are given only where spectroscopic evidence has special relevance to the discussion.

We have examined a different synthetic route to compounds of the type (IVa–IVc) which merits brief comment. We chose to work in the 16α-methyl series, although there is little doubt that the reactions to be described would be applicable also to the 16β-methyl or nonmethylated analogs.

The readily available 16α-methyl-1,4-pregnadiene-11α,17α,21-triol-3,20-dione[4] (V) was selected as the starting material and was converted to the 17α,21-acetonide (VI) without difficulty. Treatment of VI with methanesulfonyl chloride in pyridine at room temperature gave, in 60% yield, the 11α-mesylate (VII). Conversion of VII to the $\Delta^{9(11)}$-compound (VIII) was effected in modest yield by the action of sodium acetate in acetic acid under anhydrous conditions (acetic anhydride was added to the reaction mixture). Attempts to obtain the $\Delta^{9(11)}$-compound (VIII) from VII using potassium acetate in refluxing ethanol or acetone, or using lithium acetate in dimethylformamide at 95° for five hours resulted in the isolation of unchanged 11α-mesylate in each case.



The 16α-methyl-1,4,9(11)-pregnatriene-17α,21-diol, 3,20-dione 17α,21-acetonide (VIII) prepared by the above sequence was identical in all respects with a specimen prepared directly from 16α-methyl - 1,4,9(11) - pregnatriene - 17α,21 - diol-3,20-dione (IX) by the dimethoxypropane procedure. Addition of chlorine to the 1,4,9(11)-triene (VIII) proceeded smoothly, in chloroform-pyridine solution, to give the desired 9α,11β-dichloroacetonide (IVb; prepared previously by treatment of the 9α,11β-dichloro compound (IIIb) with 2,2-dimethoxypropane-dimethylformamide and *p*-toluenesulfonic acid) in 79% yield. The stability of the 17,21-acetonide under these chlorination conditions, and during the mesylation procedure described earlier, emphasizes the potential synthetic usefulness of this group for synthetic work in the steroid series.

For rigorous proof of our assignments for compounds IVb and VIII, the acetonide (IVb) was cleaved with aqueous acetic acid to the previously described 21-alcohol (IIIb) which was dehalogenated, using chromous chloride in acetone, to give 16α-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione (IX).

The substantial anti-inflammatory activity[6] exhibited by 9α-chloro-11β-formoxy corticoids of the type IId-f and IIId-f, coupled with the enhancement of anti-inflammatory activity accompanying 17,21-acetonide formation in the 9,11-dichloro series IIa-c and IIIa-c, encouraged us to synthesize the 17,21-acetonide derivatives of cortical 9α-chloro-11β-formates.

Two possible routes were considered. One path would require the addition of Cl^+ ^-OCOH to a $\Delta^{9(11)}$-17α,21-acetonide. Alternatively, a 9α-chloro-11β-formate 21-acetate of the type IId-f could be selectively hydrolyzed at C-21, and then subjected to the dimethoxypropane reaction.

The second route seemed more attractive, partly because the resulting 21-alcohols would provide a new series for biological studies. Indeed, when 9α-chloro - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20-dione 11β-formate 21-acetate[3] (IId) was subjected to the action of methanolic perchloric acid, at room temperature for eighteen hours, the product (isolated pure in 40% yield) was the desired 11β-formate 21-alcohol (IIId). That hydrolysis had occurred selectively at C-21 was indicated by the analysis and confirmed by the infrared spectrum [bands at 5.85 μ (20-ketone and formate), 6.02, 6.18, and 6.22 μ (1,4-dien-3-one) and 8.50 μ (formate)]. No acetate absorption was evident in the 8–8.1 μ region.

This 21-alcohol (IIId) was then converted to the 17,21-acetonide (IVd) by the standard procedure (see Table I). The infrared spectrum of IVd exhibited bands at 5.74 and 5.80 μ (formate and 20-ketone), and at 6.00, 6.12, and 6.20 μ (1,4 dien-3-one). No hydroxyl absorption was apparent.

The 16α- and 16β-methyl analogs (IIIe, IIIf, IVe, and IVf) of the two compounds just described were prepared by essentially the same procedures, starting from the 9α-chloro-11β-formoxy-21-acetoxy compounds (IIe and IIf.) [See Table I, and Experimental Section, procedures B, C, and D.]

The anti-inflammatory activities (measured by the granuloma pouch assay) of the acetonides described above are compared with the activities of the precursors bearing the free cortical side chain (Table II).[6] The interesting point emerges that enhancement of activity occurs on acetonide formation, both in the 9α,11β-dichloro and 9α-chloro-11β-formoxy series, particularly when a 16α-methyl group is present.

It is worth while at this stage to compare and contrast these observations with the activities reported for other corticoid cyclic ketals and acetals.

In the prednisone acetate series, a 6α,7α-acetonide has been reported,[7] and very recently the 11β,-

(6) S. Tolksdorf, F. Warren, and P. L. Perlman, *Fed. Proc.*, 19, 158 (1960).

(7) J. A. Zderic, H. Carpio, and C. Djerassi, *J. Org. Chem.*, 24, 909 (1959).

TABLE II

ANTI-INFLAMMATORY ACTIVITY OF SOME 9,11-DISUBSTITUTED CORTICAL 17α,21-ACETONIDES AND OF THE PARENT 17α,21-DIOLS

Compound	Activity[a]
9α,11β-Dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione 17α-21-acetonide (IVa)	11.1(10.2–12.1)[b]
9α,11β-Dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione (IIIa)	8.5(7.8–9.3)
9α,11β-Dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17α,21-acetonide (IVb)	13.8(11.1–17.3)
9α,11β-Dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione (IIIb)	5 (0.4–8.0)
9α,11β-Dichloro-16β-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17α,21-acetonide (IVc)	14 (11.3–17.1)
9α,11β-Dichloro-16β-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione (IIIc)	13 (8.2–20.6)
9α-Chloro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 11β-formate 17α,21-acetonide (IVe)	11.6
9α-Chloro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 11β-formate (IIIe)	1.3
9α-Chloro-16β-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 11β-formate 17α,21-acetonide (IVf)	~7
9α-Chloro-16β-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 11β-formate (IIIf)	0.5

[a] Activity measured by the granuloma pouch assay (Prednisolone 21-acetate = 1). We thank Dr. S. Tolksdorf (Biochemistry Department, Schering Corp.) for permission to cite some of these figures prior to publication. [b] 95% confidence limits in parentheses.

12β-acetonide of 12β-hydroxyprednisolone 21-acetate has been described by the same workers.[8] These compounds were stated[7,8] to show little or no anti-inflammatory activity. However, no data were provided for the parent 11,12-glycol, which may well also be essentially inactive, while the 6,7-glycol was reported to show low activity.

A closer analogy (namely potentiation of activity in an already active compound by acetonide formation) is provided by the interesting observations made by Fried *et al.*[9] concerning 16α,17α-cyclic ketals and acetals. The Squibb group found that the anti-inflammatory activity (measured by the liver glycogen assay) of a number of 16α,17α-ketals and acetals of 9α-fluoro-16α-hydroxyprednisolone acetate and 9α-fluoro-16α-hydroxyhydrocortisone acetate exceeded the activity of the parent 16α,17α-glycols.

A similar finding was later reported[10] for the case of 6α-chloro-α-fluoro-16α-hydroxyprednisolone acetate 16α,17α-acetonide.

The 16α,17α-acetonides cited above[9,10] were derived from 9α-halogeno-corticoids, but recently the acetonides of 16α-hydroxyhydrocortisone acetate and 16α-hydroxyprednisolone acetate, and their 6α-methyl analogs have been described.[11] Potentiation of activity (as measured by liver glycogen and thymus involution assays), similar to that observed earlier for 9α-halogeno-corticoids, was reported.

One interesting difference between the 16α,17α-acetonides and the 17α,21-acetonides is seen in the behavior of the two series towards acid hydrolysis. The 17α,21-acetonides can be cleaved, in general, without much difficulty upon aqueous acid treatment, whereas the 16α,17α-cyclic acetals and ketals were stated[9] to be strongly resistant to acid cleavage. It was, in fact, partly on this basis that the Squibb workers speculated that the increased activities might be due to the acetonide grouping itself.

EXPERIMENTAL[13]

Procedure A. Preparation of the 9α,11β-dichloro derivatives (IIa, IIb, and IIc) *from the 1,4,9(11)-pregnatrienes* (Ia, Ib and Ic). To a stirred suspension of the appropriate 1,4,9-(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate Ia, (Ib, or Ic, 1.0 g.) in carbon tetrachloride (40 ml.) was added pyridine (3.3 moles per mole of steroid) and a solution of chlorine (1.1 moles per mole of steroid) in tetrahydrofuran (*ca.* 3 ml.). The reaction mixture was stirred at room temperature for 1 hr., diluted with methylene chloride (100 ml.), and was then washed successively with 10% aqueous sodium thiosulfate solution, 10% aqueous sulfuric acid, 10% aqueous sodium carbonate, and water. The methylene chloride–carbon tetrachloride solution was then dried (magnesium sulfate) and evaporated *in vacuo* to give the crude product, which was crystallized from acetone-hexane to furnish the pure 9α,11β-dichloro derivative (IIa, IIb, and IIc).

Procedure B. Preparation of 9α-chloro-11β-formoxy derivatives (IId, IIe, and IIf) *from the 1,4,9(11)-pregnatrienes* (Ia, Ib, and Ic). To a stirred solution of the 1,4,9(11)-pregnatriene (Ia, Ib, or Ic, 1.0 g.) in formic acid (40 ml.; 98%) containing sodium formate (4.0 g.), was added *N*-chlorosuccinimide (1.1 moles per mole of steroid) and a solution of hydrogen chloride (1.1 moles per mole of steroid) in tetrahydrofuran (*ca.* 3 ml.). The reaction mixture was stirred at room temperature for 18 hr., poured into water (400 ml.), and filtered. The residue was washed with water, dried, and crystallized from acetone-hexane to give the pure 9α-chloro-11β-formoxy derivative (IId, IIe, or IIf).

Procedure C. Hydrolysis of 9,11-disubstituted 21-acetates (IIa–IIf) *to the corresponding 21-alcohols* (IIIa–IIIf). A solution (or suspension) of the 9,11-disubstituted 21-acetate (IIa–IIf, 1.0 g.) in 0.27*N*-methanolic perchloric acid (70 ml.) was allowed to stand (or was stirred) at room tempera-

(8) J. A. Zderic, H. Carpio, and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 446 (1960).

(9) J. Fried, A. Borman, W. B. Kessler, P. Grabowich, and E. F. Sabo, *J. Am. Chem. Soc.*, **80**, 2338 (1958).

(10) H. J. Ringold, O. Mancera, C. Djerassi, A. Bowers, E. Batres, H. Martinez, E. Necoechea, J. Edwards, M. Velasco, C. Casas Campillo, and R. I. Dorfman, *J. Am. Chem. Soc.*, **80**, 6464 (1958).

(11) S. Bernstein, R. Littell, J. J. Brown, and I. Ringler, *J. Am. Chem. Soc.*, **81**, 4573 (1959).

(12) Melting points were obtained on the Kofler block. Rotations were measured at 25° in dioxane solution, unless otherwise stated, at about 1% concentration. We are indebted to the Physical Chemistry Department, Schering Corp., for measurement of ultraviolet and infrared spectra, and rotations. Microanalyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, Long Island, by Galbraith Laboratories, Knoxville, Tenn., and by Mr. Conner (Microanalytical Laboratory, Schering Corp.).

ture for 18 hr. The reaction mixture was then poured into water (700 ml.) and filtered. The residue was washed with water, dried, and crystallized from acetone-hexane to yield the pure 21-alcohol (IIIa–IIIf).

Procedure D. Formation of 17α,21-acetonides (IVa–IVf) *from the 9,11-disubstituted 21-alcohols* (IIIa–IIIf). To a suspension of the 9,11-disubstituted 21-alcohol (IIIa–IIIf; 1.0 g.) in 2,2-dimethoxypropane (15 ml.) and dimethylformamide (5 ml.) was added *p*-toluenesulfonic acid monohydrate (20 mg.), and the reaction mixture was refluxed (3–72 hr.) until a negative T.P.T.Z. reaction was observed. The reaction mixture was then cooled, poured onto solid sodium bicarbonate (100 mg.), and evaporated at 60° in a draft of air. The resulting crude product was dissolved in methylene chloride–ether (1:9) and filtered through a column of Florisil. Evaporation of the eluate gave solid, which was crystallized to give the pure 17α,21-acetonide derivative (IVa–IVf).

16α-Methyl-1,4-pregnadiene-11α,17α,21-triol-3,20-dione 17α,21-acetonide (VI). To a solution of 16α-methyl-1,4-pregnadiene-11α,17α,21-triol-3,20-dione (V, 1.0 g.) in dimethylformamide (5 ml.) and 2,2-dimethoxypropane (15 ml.) was added *p*-toluenesulfonic acid monohydrate (20 mg.), and the mixture was refluxed for 4 hr. The reaction mixture was then poured into 0.5% aqueous sodium bicarbonate (200 ml.), extracted with methylene chloride, and the methylene chloride extract was evaporated to dryness. The residue was dissolved in methylene chloride–ether (1:9) and the solution was filtered through a Florisil column. Evaporation of the filtrate and crystallization of the resulting solid from acetone-hexane yielded VI (500 mg.), m.p. 195–200° (after melting at 130–140° and resolidifying), $[\alpha]_D$ +46°, $\lambda_{max}^{CH_3OH}$ 247 mμ (15,700), λ_{max}^{Nujol} 2.96, 5.78, 6.02, 6.18, 6.24.

Anal. Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.53; H, 8.69 μ.

In one experiment, VI was isolated in a different crystal form, m.p. 203–206°, $[\alpha]_D$ +49°, $\lambda_{max}^{CH_3OH}$ 247 mμ (15,600) λ_{max}^{Nujol} 2.88, 5.80, 6.02, 6.15, 6.24 μ.

Anal. Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.89; H, 8.53.

These two crystalline modifications were found to show identical migration rates on paper chromatography, and the material showing double m.p. 130–140° and 195–200° could be converted to the material of m.p. 203–206° by seeding a hot turbid solution (acetone-hexane) of the former with the latter.

16α-Methyl-1,4-pregnadiene-11α,17α,21-triol-3,20-dione 11α-methane sulfonate 17α,21-acetone (VII). To a solution of 16α - methyl - 1,4 - pregnadiene - 11α,17α,21 - triol - 3,20-dione 17α,21-acetonide (VI, 1.0 g.) in pyridine (10 ml.), chilled in an ice bath, was added methanesulfonyl chloride (0.6 ml.). The ice bath was removed and the reaction mixture was stirred at room temperature for 3 hr. The reaction mixture was diluted with methylene chloride (100 ml.), washed successively with water, 10% aqueous sulfuric acid and water, dried (magnesium sulfate) and evaporated to dryness. Crystallization from acetone-hexane gave VII in two crops (total weight 0.6 g.). A second crystallization gave the analytical sample: m.p. 163–168° dec., $[\alpha]_D$ +63°, $\lambda_{max}^{CH_3OH}$ 242 mμ (18,000), λ_{max}^{Nujol} 5.78, 6.05, 6.16, 6.24 μ.

Anal. Calcd. for $C_{26}H_{36}O_7S$: C, 63.39; H, 7.37; S, 6.51. Found: C, 63.77; H, 7.45; S, 6.41.

16-αMethyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione-17α,21-acetonide (VIII). (1) *From 16α-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione* (IX). To a refluxing solution of IX (1.0 g.) in 2,2-dimethoxypropane (15 ml.) and dimethylformamide (5 ml.) was added *p*-toluenesulfonic acid (20 mg.). The reaction mixture was refluxed for 4 hr., and was then cooled, poured onto solid sodium bicarbonate (100 mg.), and evaporated in a stream of air (at 60°) to an oily residue. This material was chromatographed on Florisil (40 g.) and the solids eluted with ether-hexane (2:3) were crystallized from aqueous methanol to furnish VIII (400 mg.), m.p. 180–184°, $[\alpha]_D$ +18,°$\lambda_{max}^{CH_3OH}$ 238 mμ (16,500), λ_{max}^{Nujol} 5.82, 6.00, 6.14, 6.22 μ.

Anal. Calcd. for $C_{25}H_{32}O_4$: C, 75.72; H, 8.14. Found: C, 75.85; H, 8.22.

(2) *From 16α-methyl-1,4-pregnadiene-11α,17α,21-triol-3,-20-dione 11α-methanesulfonate 17α,21-acetonide* (VII). To a refluxing mixture of anhydrous sodium acetate (1.0 g.) in glacial acetic acid (10 ml.) and acetic anhydride (1 ml.) was added the 11α-mesylate (VII, 1.0 g.) and reflux was continued for 1 hr. The reaction mixture was then cooled, and added cautiously to 20% aqueous sodium carbonate solution (100 ml.). The aqueous mixture was extracted with methylene chloride, and the extract was washed with water, dried (magnesium sulfate) and evaporated to dryness. The residue was chromatographed on Florisil (40 g.), and the solids eluted with ether-hexane (2:3) were crystallized from aqueous methanol to give VIII (100 mg.), m.p. 180–184°, identical in all respects (mixed melting point, infrared spectrum, paper chromatography) with VIII prepared as in (1) above.

9α,11β-Dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17α,21-acetonide (IVb) *from 16α-methyl-1,4,9-(11)-pregnatriene-17α,21-diol-3,20-dione 17α,21-acetonide* (VIII). Chlorine gas was bubbled at a slow rate for 30 seconds into a solution of VIII (1.0 g.) in chloroform (40 ml.) and pyridine (5 ml.), and the mixture was then stirred at room temperature for 30 min. Methylene chloride (100 ml.) was then added, and the solution was washed successively with *N*-aqueous sodium thiosulfate solution, 5% aqueous hydrochloric acid, and water. The washed organic solution was dried (magnesium sulfate) and evaporated to dryness. The residue was crystallized from acetone-hexane to give IVb (790 mg.), m.p. 230–235° dec., identical in all respects with authentic IVb (prepared from 9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione, IIIb, by Procedure D).

9α,11β-Dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione (IIIb) *from 9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17α,21-acetonide* (IVb). To a solution of IVb (1.0 g.) in glacial acetic acid (15 ml.) at 80° was added water (10 ml.) over a 10-min. period during which the temperature was raised to 95°. The reaction mixture was cooled and filtered to yield a crystalline solid (800 mg.), m.p. 218–226° dec. (Paper chromatography demonstrated that this material was substantially pure IIIb, with <10% of unchanged IVb present.) Crystallization from acetone furnished pure IIIb, m.p. 225–228° dec., identical with authentic IIIb as evidenced by mixed melting point comparison, identity of infrared spectra, and paper chromatography.

16α-Methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione (IX) *from 16α-methyl-9α,11β-dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione* (IIIb). A solution of IIIb (500 mg., obtained by acetonide cleavage of IVb) in hot acetone (125 ml.) was cooled to room temperature and the system flushed with nitrogen gas. Chromous chloride solution (25 ml.) was added and the mixture allowed to stand at room temperature for 0.5 hr. The reaction mixture was poured into water (700 ml.), extracted with methylene chloride, washed with water, dried (magnesium sulfate), and evaporated to dryness. Crystallization from acetone-hexane afforded IX (225 mg.), m.p. 225–230°, identical with authentic IX as shown by mixed melting point, infrared and paper chromatographic comparisons.

9α,11β-Dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 21-acetate (IIb) *from 9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione* (IIIb). Acetylation of IIIb (200 mg., obtained by acetonide cleavage) with pyridine (4 ml.) and acetic anhydride (0.4 ml.), at room temperature for 18 hr., yielded, after crystallization of the product from acetone-hexane, pure IIb (90 mg.), m.p. 235–239° dec., identical in all respects with authentic IIb.

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