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Transannular Hydrogen Transfer in the Steroid Series[1]

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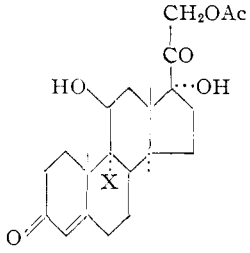
The chemical transformations bearing on the transannular hydrogen transfer–rearrangement of 9β,11β-oxido-Δ⁴-pregnene-17α,21-diol-3,20-dione 21-acetate (II) are described.

The acid-catalyzed scission of the epoxide function in 9β,11β-oxido-Δ⁴-pregnene-17α,21-diol-3,20-dione 21-acetate (II) has been found to be directionally dependent on the nature of the acid catalyst employed. Whereas hydrogen halides and dilute mineral acids evoke normal scission to give the respective halohydrins (I, X = halogen)[2] and glycol (I, X = OH),[1,3] concentrated acids produce predominantly rearrangement of a duodirectional



I, X = halogen, OH

character. In the latter case the course of rearrangement is directed to a minor extent to give the corresponding 11-ketone, whereas the major product appearing results as a consequence of "2,6"-transannular migration of hydrogen.[4] Treatment of 9β,11β-oxido-Δ⁴-pregnene-17α,21-diol-3,20-dione 21-acetate (II) in chloroform solution at 0° with 60% perchloric acid caused the development of a red coloration with the steroid partitioning itself nearly completely in the aqueous phase. Subsequent isolation of the reaction product yielded 10–15% of cortisone acetate[5] together with 65% of an isomeric compound[6] formed as the major product.[7] The homoallylic character of this isomeric substance was suggested by the observation that its 11-mesylate derivative underwent acidolysis to a significant extent with configurational retention to give the corresponding ester derivative in a manner reminiscent of the *i*-steroid phenomenon.[8] This substance, as will be borne out by the chemistry subsequently to be discussed, proved to be 17α-hydroxy-Δ⁸⁽¹⁴⁾-dehydrocorticosterone 21-acetate (III), a structure hardly to have been anticipated on the basis of classical theoretical considerations.

In establishing the structure of III, it was subjected *inter alia* to oxidation with chromic acid in pyridine,[9] to give what subsequently proved to be the Δ⁴,⁸⁽¹⁴⁾-dienedione IV. This substance on treatment with sodium methoxide was readily isomerized to the completely conjugated Δ⁴,⁸⁽⁹⁾-dienedione V. The latter compound was found to be identical with material obtained from 9-bromocortisone acetate (VII) by dehydrobromination of the latter with refluxing pyridine.[10] On the other hand, elimination of the elements of hydrogen bromide from VII with lithium chloride in dimethylformamide[11] afforded the 14β-isomer VI also obtained from the Δ⁴,⁸⁽⁹⁾-dienedione V by isomerization with hydrogen chloride in chloroform. The 14β-isomer VI, unlike its epimer V, afforded a 17-acetate derivative on acetylation with acetic anhydride in pyridine at room temperature for 7 days or 6 hours at 100°. Model inspection suggests a greater degree of steric accessibility of the 17α-OH in the 14β-iso (*cis* C/D) series, a consequence of the orientational change of the 17α-OH from pseudo-axial to pseudo-equatorial.

Since the Δ⁴,⁸⁽⁹⁾-dienedione V exhibited a somewhat unusual ultraviolet absorption for this structure with a low band position at 236.5 mμ as well as

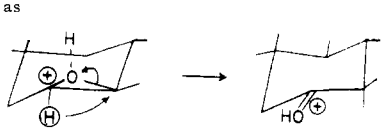
(1) For preliminary accounts of this work see: R. P. Graber, C. S. Snoddy, Jr., and N. L. Wendler, *Chemistry & Industry*, 57 (1956); N. L. Wendler, R. P. Graber and F. W. Bollinger, *ibid.*, 1312 (1956).

(2) (a) J. Fried and E. Sabo, THIS JOURNAL, **75**, 2273 (1953); (b) **76**, 1455 (1954).

(3) R. Littell and S. Bernstein, *ibid.*, **78**, 984 (1956).

(4) Meerwein with extraordinary insight first proposed 2,6-migration of hydrogen in 1924 to account for certain transformations in the camphane series. [See H. Meerwein and R. Wortmann, *Ann.*, **435**, 190 (1924); H. Meerwein and F. Montfort, *ibid.*, **435**, 207 (1924).] Recent corroboration for this transfer theory in the bicyclo[2,2,1]-heptane series has been provided by S. Beckmann and R. Bamberger, *ibid.*, **574**, 65 (1951); **580**, 198 (1953). See also J. D. Roberts and J. A. Yancey, THIS JOURNAL, **75**, 3165 (1953); W. R. Vaughan and R. Perry, Jr., *ibid.*, **75**, 3168 (1953). See also footnotes 29 and 30.

(5) The work of (a) K. Heusler and A. Wettstein (*Helv. Chim. Acta*, **36**, 399 (1953)) and (b) P. Bladon, H. B. Henbest, E. R. H. Jones, B. I. Lowell, G. W. Wood, G. F. Woods, J. Elks, R. M. Evans, D. E. Hathway, J. F. Oughton and G. H. Thomas (*J. Chem. Soc.*, 2921 (1953)) has provided unique and compelling evidence that the mechanism of rearrangement of oxides to ketones is sterospecific and involves a 1,2-Wagner rearrangement of hydrogen with its bonding electrons. The transformation of II to cortisone acetate can, by this interpretation, be represented as



(6) Fried and Sabo, ref. 2a, have described a substance of unknown constitution arising in *ca.* 10% yield from the reaction of hydrogen fluoride on II and possessing characteristics essentially the same as the perchloric acid product herein described. Fried and Sabo, however, established that this substance possessed a new epoxidizable double bond and an easily acylable hydroxyl group. See also ref. 17. In the meantime J. Fried and E. F. Sabo [THIS JOURNAL, **79**, 1130 (1957)] have published details of their findings regarding this substance.

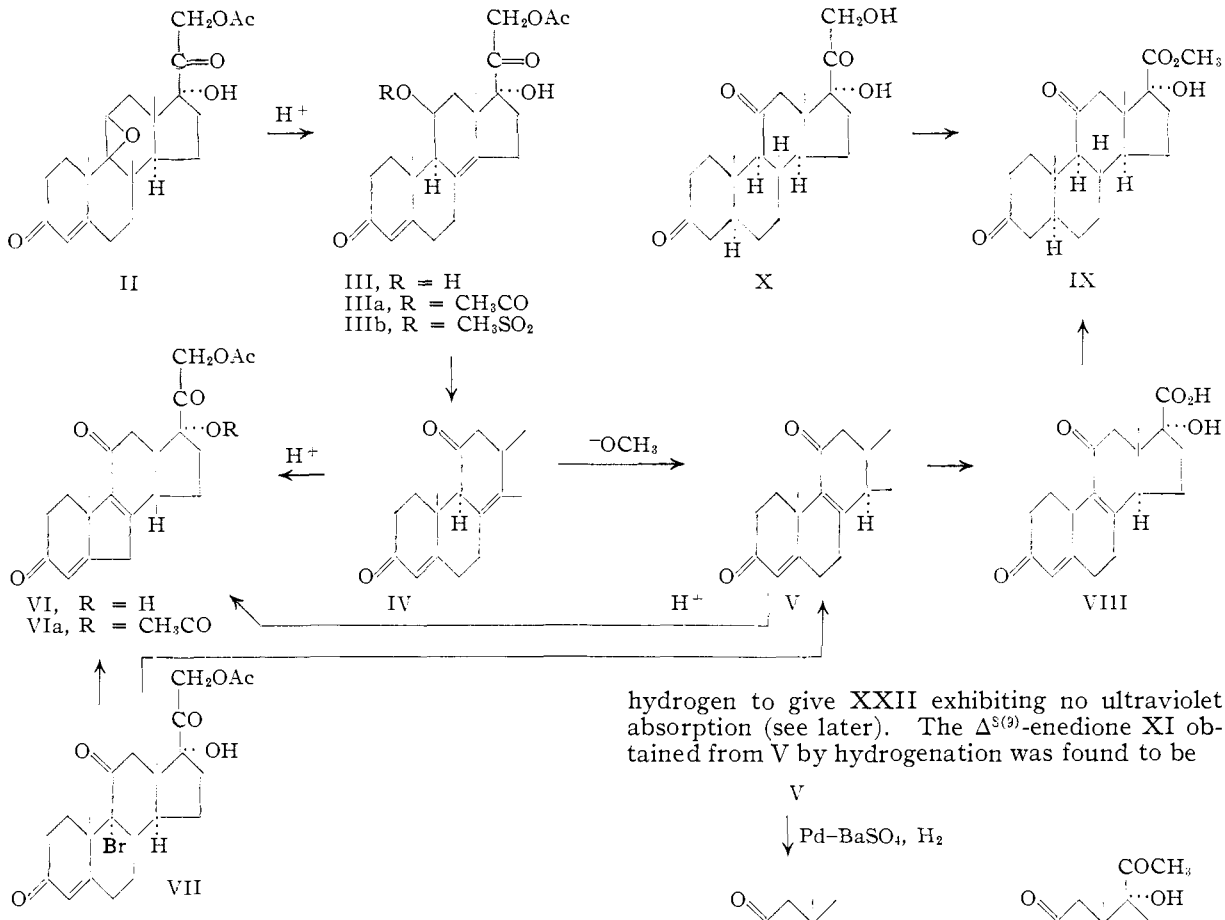
(7) There was also formed *ca.* 10% of I (X = OH) in this reaction.

(8) See, for example, *Ann. Repts. Chem. Soc.*, **44**, 172 (1947).

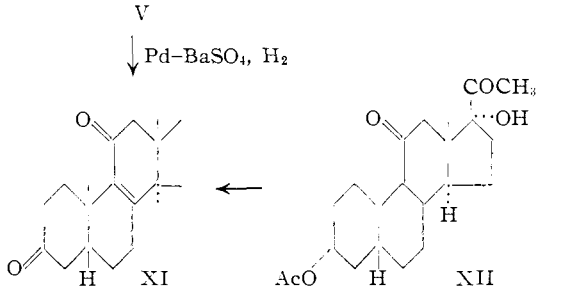
(9) Method of G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(10) Attempted dehydrobromination of VII with collidine resulted in reductive loss of bromine to give cortisone acetate in a manner reminiscent of the behavior of 2-bromocholestanone (see Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, N. Y., 1949, p. 263). On the other hand, the collidine-dehydrobromination of 3β-acetoxy-9α-bromoergostane-11-one yields the corresponding Δ⁸-11-ketone (see ref. 15).

(11) Method of R. P. Holysz, THIS JOURNAL, **75**, 4432 (1953).



low intensity (ε 17,700),[12] it was considered advisable under the circumstances to secure this structure against the possibility that skeletal alteration had supravened. It was also desired to provide unequivocal confirmation for the configuration at C_{14}. Consequently the $\Delta^{4,8(9)}$-dienedione V was hydrolyzed and cleaved with periodic acid to afford the intermediate dienic acid VIII; subsequent reduction of VIII with lithium in liquid ammonia[13] followed by methylation with diazomethane and reoxidation with chromic acid gave the known methyl 17α-hydroxy-3,11-diketoallo-etianate (IX).[14] The latter compound was compared with an authentic sample prepared from allodihydrocortisone (X) by successive periodate cleavage and esterification. Additional corroboration for structure V which also served to resolve the feature of its unique ultraviolet absorption was provided by hydrogenation of the Δ^4-double bond of V to give the $\Delta^{8(9)}$-enedione XI which now exhibited the expected absorption for this system with λ_{max} 256 mμ (8,175). In contrast to V, IV absorbed 1 mole of hydrogen to give XXII exhibiting no ultraviolet absorption (see later). The $\Delta^{8(9)}$-enedione XI obtained from V by hydrogenation was found to be



identical with material isolated as an intermediate by-product from the conversion of pregnane-3α-17α-diol-11,20-dione 3-acetate (XII) to cortisone by a sequence in which bromination–dehydrobromination at C_9 occurred.[15] The identity of XI obtained by these two methods secures additionally the directional course of hydrogenation of V as giving the normal A/B-ring system (5β-H).

At this juncture it has been established that the major rearrangement product III possesses a normal steroid skeleton with unsaturation situated β,γ with respect to the 11-oxygen function. The exact assignment of the β,γ-double bond to the $\Delta^{8(14)}$-position was made possible in the following manner: III was hydrogenated to its 4,5-dihydro derivative XIII and the latter was dehydrated in the form of its 11-mesylate derivative by refluxing pyridine to provide the $\Delta^{9(11),8(14)}$-homoannular diene XIV with λ_{max} 271 mμ (ε, 4,600). Isomerization of XIV with hydrogen chloride in chloroform produced the $\Delta^{8,14}$-heteroannular diene XV, λ_{max} 246 mμ (ε, 21,500). In a similar manner III itself was converted

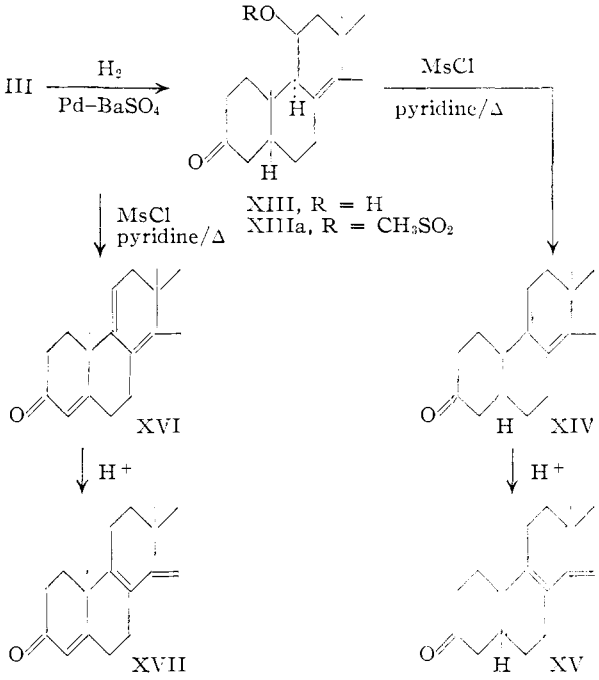
(12) This absorption approximates that for a lone Δ^4-3-ketone. C. Djerassi, A. J. Lemin, G. Rosenkranz and F. Sondheimer [J. *Chem. Soc.*, 2346 (1954)] report for 22a-spirosta-4,8-diene-3,11-dione an ultraviolet absorption spectrum with λ_{max} 236–242 mμ (ε, 20,800).

(13) The reduction of $\Delta^{(8)9}$-11-ketones with lithium in liquid ammonia has been shown in other series to proceed without involvement of C_{14} (E. Schoenewaldt, L. Turnbull, E. M. Chamberlin, D. Reinhold, A. E. Erickson, W. V. Ruyle, J. M. Chemerda and M. Tishler, THIS JOURNAL, **74**, 2696 (1952); F. Sondheimer, R. Yashin, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 2696 (1952)); see also ref. 5.

(14) J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **25**, 988 (1942).

(15) Observations by Dr. G. Hazen and Dr. G. Krsek of these laboratories to be published elsewhere. Also see H. B. Henbest, E. H. R. Jones, A. A. Wagland and T. I. Wrigley, *J. Chem. Soc.*, 2477 (1955).

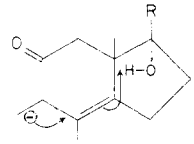
to XVI in which the homoannular diene chromophore manifested itself only as a shoulder at 271 mμ with the main band at 241 mμ (ε 21,600). Isomerization of XVI with hydrogen chloride in chloroform yielded the $\Delta^{4,8,14}$-trieneone XVII with λ_{max} 242 mμ (ε 37,400).[16] Formation of the homoannular dienes XIV as well as XVI establishes the position of β,γ-unsaturation at 8:14. If the double bond had been situated at the alternative 7,8-position, dehydration under the conditions employed should have resulted in formation of the $\Delta^{7,9(11)}$-diene XXV.[17] Additional confirmation for the conclu-



sion that a $\Delta^{8,(14)}$-double bond must be present in the original system in order to give a $\Delta^{9(11),8(14)}$-homoannular diene is provided by the directional course of dehydration of $\Delta^{8(9)}$-11-hydroxy systems (see below and ref. 18).

A discussion of certain points of interest with regard to the more detailed behavior of III and its derivatives is perhaps appropriate at this stage. The double bond at 8:14 appears to decrease the hindrance generally associated with 11β-hydroxyl groups thereby permitting III to be acetylated at room temperature with acetic anhydride in pyridine,[17] conditions which leave an 11β-OH in a saturated normal steroid system unaffected. This fact becomes additionally apparent when it is considered that the introduction of the 8:14 double bond permits the axial 11β-OH of a saturated ring C to assume an equatorial conformation in the resultant cyclohexene. 17α-Hydroxy-$\Delta^{8(9)}$-dehydrocorticosterone 21-acetate (XXIV), which can be isolated as a minor component from the dehydrobromination of I, (X = Br), with N-ethylpiperidine[19] (see later discussion), occupies an intermediate position between III and a normal saturated 11β-hydroxy steroid. Thus, conditions which completely acetylate III and leave 17α-hydroxycorticosterone 21-acetate unaffected (see above) cause acetylation of XXIV to the extent of *ca.* 30%, complete acetylation being achieved within a period of a week. Therefore the relative ease of acetylation of the 11β-OH in these systems may be said to bear the relationship $\Delta^{8(14)}$-11β-OH > $\Delta^{8(9)}$-11β-OH > 11β-OH.

The isomerization of the $\Delta^{4,8(14)}$-dienedione IV to the $\Delta^{4,8(9)}$-dienedione V together with the epimerization of the latter to its 14β-isomer, has produced several interesting consequences. Thus, whereas IV was isomerized by sodium methoxide exclusively to the less stable epimer V,[20] hydrogen chloride in chloroform failed to evoke this change.[21] Conversely V was irreversibly converted to the more stable isomer VI with hydrogen chloride in chloroform but remained isomerically unaffected with sodium methoxide. In view of the apparent stability at C_{14} of V to the basic conditions employed,[20] the unidirectional isomerization of IV → V appears to be rate determined and subject as well to steric control. The latter is possible if the 17α-OH in virtue of its spatial disposition is considered to participate as an internal proton-donor to the 14α-position in the manner depicted by XVIII. Isomeri-



XVIII

zation with hydrogen chloride in chloroform, on the other hand, by virtue of its ability to effect the conversion of the less stable V to the more stable VI should be a thermodynamically controlled process. The apparent lack of steric control at C_{14} follows from the opportunity afforded to exchange the C_{14}-H externally as well as internally.[22,23]

(16) B. M. Bloom, E. J. Agnello and G. D. Laubach, [*Experientia*, **12**, 27 (1956)] have recently reported the formation of this compound from the treatment of 14α,15α-oxido-Δ^4-pregnene-17α,21-diol-3,20-dione 21-acetate with *p*-toluenesulfonic acid in refluxing benzene. These authors report a molecular extinction of 28,600 at 240 mμ which is considerably lower than that observed by us.

(17) III is readily acylated under room temperature conditions.[6] Since it has been shown (ref. 5b) that $\Delta^{7(8)}$-11β-hydroxysteroids are *not* acetylated under these conditions, this constitutes further evidence excluding the $\Delta^{7(8)}$-position of the double bond in III. It has also been pointed out by Fried and Sabo (ref. 2) that the by-product which they obtained from II with hydrogen fluoride (see ref. 6) could not possess a $\Delta^{(7)}$-double bond for reasons of molecular rotation deviation.

(18) R. F. Hirschmann, C. S. Snoddy, Jr., and N. L. Wendler, THIS JOURNAL, **75**, 3252 (1953).

(19) The conditions employed by Fried and Sabo (ref. 2) for the conversion of I (X = Br) to the 9β,11β-oxide (II), namely, potassium acetate in refluxing ethanol, also give detectable amounts of XXIV as evidenced by paper strip analysis.

(20) Because of the lability of the cortical side chain to alkali [see N. L. Wendler and R. P. Graber, *Chemistry & Industry*, 549 (1956)] the conditions of sodium methoxide isomerization were limited to room temperature treatment for 10 minutes. In view thereof, the conclusions based on the results of these conditions are necessarily limited to them.

(21) IV was isomerized to VI, however, when heated at 100° for 2 hours in dimethylformamide containing hydrogen bromide (see footnote 22).

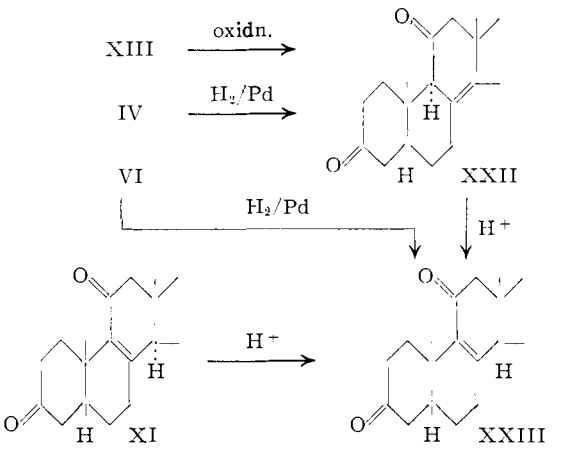
(22) The conversion of V → VI with hydrogen chloride in chloroform at 0° occurred to the extent of about 60% in 1 hour and was essentially complete after 18 hours. Complete isomerization of V → VI was also achieved with dimethylformamide containing one equivalent of hydrogen bromide for 2 hours at 100°.

(23) Certain analogies to this isomerization are afforded by observations concerned with the neopinone–codeinone change; see H. Conroy, THIS JOURNAL, **77**, 5960 (1955).

The isomerization of V → VI induced by lithium chloride in dimethylformamide containing one equivalent of pyridine hydrobromide (compare transformation VII → VI) was found not to occur to any detectable extent either with pyridine hydrobromide in pyridine or with lithium chloride in dimethylformamide alone. The interesting consequence arises that the combination-induced isomerization is concerted in nature[24] requiring both protonation of the C_{11}-C=O as well as assisted removal of the $C_{14\alpha}$-H by dimethylformamide.[25]

Hydrogenation of the Δ^4-double bond in all the systems possessing unsaturation in the functionally substituted C ring (*i.e.*, III, IV, V and VI) was observed to proceed predominantly to give the normal A/B ring system (5β-H).[5,26] The hydrogenation product of V, namely, XI was related as already mentioned (see above) to the natural 5β-H series. XI in turn was acid-isomerized to XXIII, also obtained from VI by hydrogenation. The hydrogenation product of III, namely, XIII on oxidation with chromic acid gave XXII also produced from IV by hydrogenation. The isomerization of XXII to XXIII with hydrogen bromide in dimethylformamide completed the interrelationship of the various 4,5β-dihydro derivatives.

The remaining point of constitution requiring clarification with regard to the immediate structures under consideration concerns the configuration at C_9. It was pointed out earlier that the major rearrangement product III on oxidation with pyridine–chromium trioxide for 18 hours afforded in good yield the $\Delta^{4,8(14)}$-dienedione IV which rapidly isomerized (10 minutes) with sodium methoxide to the $\Delta^{4,8(9)}$-dienedione V; it would appear therefore reasonably assured that III and IV are configurationally the same at C_9. In contrast to the $\Delta^{4,8(14)}$-dienedione IV, however, its 4,5β-dihydro derivative XXII, failed to isomerize: $\Delta^{8(14)} \rightarrow \Delta^{8(9)}$ with sodium methoxide or on an alumina column.[5b] These results appear to be consistent only with a structure possessing a $C_9\alpha$-H which in the case of the 4,5β-dihydro derivative is caged by a *cis* A/B ring system (5β-H) and thus sterically inaccessible to base attack.[27] These considerations therefore permit the assignment of the 9α-orientation of hydrogen to III and its derivatives.

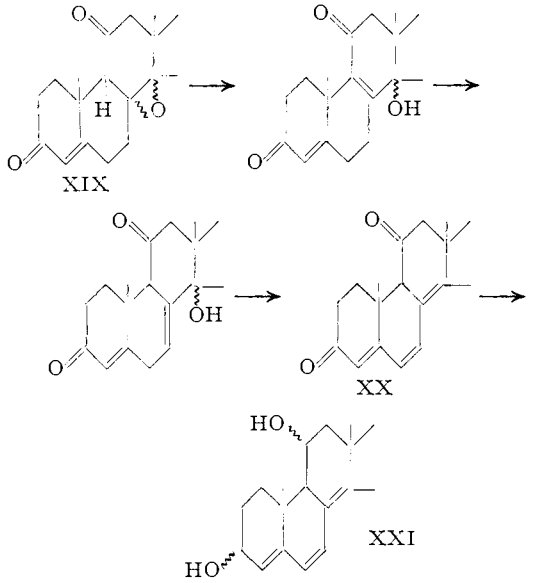


The isolation of 17α-hydroxy-$\Delta^{8(9)}$-dehydrocorticosterone 21-acetate (XXIV) as a by-product from the dehydrobromination of 9α-bromo-17α-hydroxycorticosterone 21-acetate (I, X = Br) with N-ethylpiperidine (see earlier) proved to be of considerable importance in its bearing on the mechanism of the rearrangement of II → III. The constitution of XXIV was established by oxidation with manganese dioxide to give the $\Delta^{4,8(9)}$-dienedione V as well as dehydration with mesyl chloride in pyridine to afford $\Delta^{4,7,9(11)}$-pregnatriene-17α,21-diol-3,20-dione 21-acetate (XXV). Of singular significance was the finding that XXIV on treatment with 60% perchloric acid was converted exclusively to the heteroannular $\Delta^{8,14}$-diene XVII thereby ruling it out as a possible intermediate in the conversion of II → III. In the same connection neither 9α,-17α-dihydroxycorticosterone 21-acetate (I, X = OH)[1,3] nor 9α,11α-oxido-Δ^4-pregnene-17α,21-diol-3,20-dione 21-acetate[2] were appreciably affected by the acidic conditions employed for the conversion of II → III. These systems, it will be noted, are sterically ideal when compared with II for the intervention of a classical 1,2-Wagner shift of the 8β-H, and when extrapolated would lead to the 9β-H-epimer of III.

In the light of the foregoing observations, it may be concluded with reasonable certainty that the acid-catalyzed transformation of II → III proceeds from within a protonated species (*e.g.*,

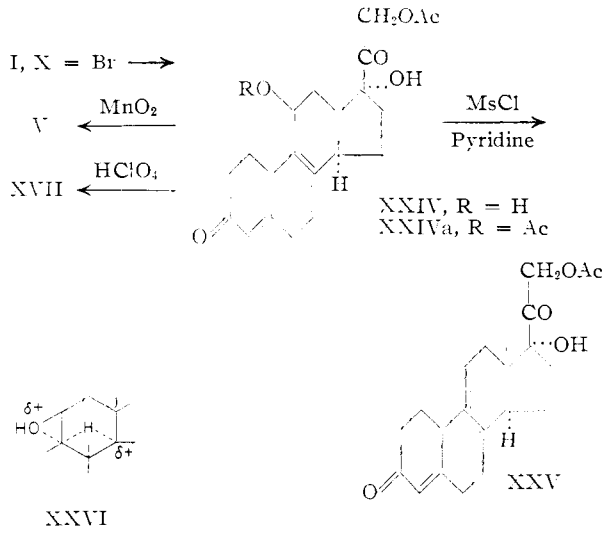
(24) C. G. Swain, *Record of Chem. Prog.*, Kresge–Hooker Science Library, Wayne Univ., **12**, 21 (1951).

(25) A further base-induced transformation which sensibly involves at an intermediate phase an $\alpha\beta \rightarrow \beta\gamma$ change is concerned with the extremely insoluble 8,14-oxido derivative XIX formed from IV on treatment with perbenzoic acid. Treatment of XIX with sodium methoxide caused elimination of the epoxide function with formation of the $\Delta^{4,6,8(14)}$-trienedione XX, λ_{max} 337 mμ (ϵ 25,800). Structure XX was substantiated by lithium aluminum hydride reduction to give a product (XXI) exhibiting characteristic ultraviolet absorption for the $\Delta^{4,8,8(14)}$-triene chromophore at 285 mμ (ϵ 19,150) [*cf.* L. Dorfmann, *Chem. Revs.*, **53**, 47 (1953)]. The sequence involved in the formation of XX may reasonably be represented as



(26) It is noteworthy that in the sapogenin series, A. J. Lemin and C. Djerassi (THIS JOURNAL, **76**, 5672 (1954)) found the $\Delta^{4,8(9)}$-dienone system hydrogenated to give mainly the 4,5α-dihydro derivative.

(27) The steric accessibility of a 9β-H to base attack should not be adversely affected by hydrogenation of the Δ^4-double bond (see ref. 5b).



XXVI)[28] by way of transannular migration of hydrogen with its bonding pair from $C_{14\alpha} \rightarrow C_{9\alpha}$ with attending extrusion of the $C_8\beta$-H. Moreover, since hydrogen transfer of this type should proceed with steric control,[4,29] it follows that the stereochemistry of the product II becomes defined as formulated.[30]

Experimental[31]

Δ^4-Pregnene-9α,11β,17α,21-tetrol-3,20-dione 21-Acetate (I, R = OH).—A suspension of 4.025 g. (10.0 millimoles) of the oxide II in 66.7 ml. of purified dioxane and 33.3 ml. of 2.0 *N* aqueous perchloric acid was stirred at 25°. After a period of 1.5 hours, the solid had dissolved and the solution was light yellow. After a period of 3 days, the bright yellow solution was diluted with 200 ml. of saturated salt solution and extracted with 3 portions of ethyl acetate. The combined extracts were washed with water and 5% aqueous sodium bicarbonate until free of acid and finally with water and saturated salt solution. The washed extracts were dried by filtration through anhydrous magnesium sulfate and the solvents removed *in vacuo* to give 3.95 g. of a partly crystalline yellow residue. Crystallization from acetone–chloroform gave 2.50 g. (65%) of needles, m.p. 224–230° dec. An additional crystallization from acetone afforded 1.575 g. (41.6%) of **Δ^4-pregnene-9α,11β,17α,21-tetrol-3,20-dione**, m.p. 239–246.5° dec. A sample prepared for analysis by recrystallization from the same solvent was obtained as prisms, m.p. 243–249° dec., $[\alpha]^{26}D$ +152° (1.1, acetone), λ_{max} 242 mμ (ϵ 15,600); $\lambda\lambda_{max}^{Nujol}$ 2.9–3.0, 5.84 and 6.1 μ.

Anal. Calcd. for $C_{21}H_{30}O_6$: C, 66.64; H, 7.99. Found: C, 66.61; H, 7.90.

The mother liquor of the 2.50-g. sample above was treated with 8 ml. of pyridine and 8 ml. of acetic anhydride at 25° overnight. A small amount of crystalline solid which had separated was removed by filtration, washed several times with ether and dried, weight 0.109 g., m.p. 219–234°. This material was shown by paper-strip analysis to be a mixture of unidentified materials. The pyridine–acetic anhydride–ether filtrate was concentrated *in vacuo* to an oil. Water (50 ml.) was added to the concentrate and the oil extracted with 3 portions of ethyl acetate. The combined extracts were washed successively with water, 1 *N* hydrochloric acid, sodium bicarbonate solution and finally with water and saturated salt solution. The washed extracts were dried over magnesium sulfate and the solvent removed *in vacuo* to give 1.64 g. of a yellow-brown amorphous residue which was shown by paper-strip analysis to be substantially pure I (R = OH). Crystallization from acetone–ether afforded 0.84 g. (20%) of buff-colored prisms, m.p. 210–216°, undepressed on admixture with a sample prepared from the tetroldione by acetylation as described above. A sample prepared for analysis by recrystallization from acetone–ether was obtained as colorless needles, m.p. 212–214.5°, λ_{max} 242 mμ (ϵ 15,570); $\lambda\lambda_{max}^{Nujol}$ 2.92, 5.79–5.82, 6.1–6.15; $\lambda\lambda_{max}^{CHCl_3}$ 5.75(sh), 5.79, 6.0 and 6.15 μ. It was observed that several samples partly crystallized as prisms during melting, then finally melted at *ca.* 223°.

Anal. Calcd. for $C_{23}H_{32}O_7$: C, 65.69; H, 7.67. Found: C, 65.43; H, 7.51.

Δ^4-Pregnene-9α,17α,21-triol-3,11,20-trione 21-Acetate.—To a solution of 61.3 mg. (0.613 millimole) of chromium trioxide in 2 drops of water and 4.9 ml. of glacial acetic acid was added 386.2 mg. (0.92 millimole) of I (R = OH). The solid dissolved immediately and after 12 minutes the reaction mixture was diluted with 25 ml. of water. Extraction with 3 portions of ethyl acetate followed by the usual washing with water, sodium bicarbonate, etc., gave, after removal of the solvent, 358 mg. (93%) of a crystalline residue, m.p. 228.5–235°. Recrystallization from acetone–ether gave 241 mg. of needles, m.p. 236–242°. An additional recrystallization raised the m.p. to 237–243.5°, λ_{max} 238 mμ (ϵ 15,620); $\lambda\lambda_{max}^{Nujol}$ 2.96, 5.71, 5.75, 5.83, 6.0 and 6.16 μ; $\lambda\lambda_{max}^{CHCl_3}$, 5.7(sh), 5.79, 5.99 and 6.15 μ.

Anal. Calcd. for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 66.14; H, 7.02.

$\Delta^{4,8(14)}$-Pregnadiene-11β,17α,21-triol-3,20-dione 21-Acetate (III). (17α-Hydroxy-$\Delta^{8(14)}$-dehydrocorticosterone 21-Acetate.)—To a stirred, ice-cold solution of 8.05 g. (20.0 millimoles) of 9β,11β-oxido-Δ^4-pregnene-17α,21-diol-3,20-dione 21-acetate (II) in 80 ml. of ethanol-free chloroform was added dropwise 20.0 ml. of ice-cold 60% perchloric acid over a period of 2 minutes. The temperature of the mixture rose to 7° and then dropped again to 0°. After stirring for an additional 15 minutes, the orange-red solution was diluted with 200 ml. of ice-water which discharged the color. The layers were separated and the aqueous layer was extracted twice with 2:1 chloroform–ethyl acetate. The combined solvent layers were washed free of acid with water, and filtered through anhydrous magnesium sulfate. Removal of the solvents *in vacuo* gave 8.70 g. of yellow crystalline solid. To the crude product was added 35 ml. of chloroform and the suspension heated under reflux for 10 minutes; only part of the solid was soluble. The hot suspension was diluted with 175 ml. of benzene, cooled to room temperature for 1 hour and filtered. The colorless crystalline product was washed twice with 1:1 chloroform–benzene followed by three ether washes to remove small amounts of brown gummy material. After drying *in vacuo* there was obtained 3.84 g. (47.6%) of III, m.p. 246.5–257° dec. A sample for analysis was prepared by recrystallization from methanol, m.p. 255–260° dec., $[\alpha]^{25}D$ +293° (1.0, acetic acid), λ_{max} 240 mμ (ϵ 17,200); $\lambda\lambda_{max}^{Nujol}$ 2.93, 3.02, 5.75, 5.81 and 6.1 μ.

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 68.63; H, 7.51; acetyl, 10.69. Found: C, 68.22, 68.53; H, 7.35, 7.13; acetyl, 11.47.

The mother liquor from the 3.84-g. sample above was taken to dryness *in vacuo*, wt. 4.77 g. Paper chromatographic analysis of this material showed it to contain additional amounts of III together with cortisone acetate and a

(28) The dotted lines in this formulation are intended to represent partial bond character with the steric connotations:

$$O\overset{\beta}{\cdots}C_9\overset{\alpha}{\cdots}H\overset{\alpha}{\cdots}C_{14}$$

(29) In recent years the occurrence of transannular hydrogen transfer in medium sized rings has been dramatically demonstrated. In this regard see: A. C. Cope, S. W. Fenton and C. F. Spenser, THIS JOURNAL, **74**, 5884 (1952); V. Prelog and K. Schenker, *Helv. Chim. Acta*, **35**, 2044 (1952); V. Prelog, K. Schenker and W. Küng, *ibid.*, **36**, 471 (1953); V. Prelog, H. J. Urech, A. A. Bothner-By and J. Würsch, *ibid.*, **38**, 1095 (1955); V. Prelog and V. Boarland, *ibid.*, **38**, 1776 (1955); V. Prelog and W. Küng, *ibid.*, **39**, 1394 (1956); A. C. Cope, T. A. Liss and C. W. Wood, *Chemistry & Industry*, 823 (1956).

(30) This instance of transannular-hydrogen transfer in an unbridged 6-membered ring system is unique in several respects: (1) transannular transfer occurs in a system wherein the centers involved are of fixed stereochemistry; (2) proton extrusion takes place as the ultimate step and (3) the product of this transfer reaction is the major one. Recenty A. C. Cope, H. E. Johnson and J. S. Stephenson (THIS JOURNAL, **78**, 5599 (1956)) have demonstrated transannular hydrogen transfer in the cyclohexane series in the performic acid-hydroxylation of cyclohexene.

(31) Unless otherwise indicated, the m.p.'s were taken on a micro-block and are not corrected; the samples were placed on the block at *ca.* 25° below the m.p. The rotations were observed in chloroform and the ultraviolet spectra in methanol.

substantial amount of a more polar material. The amorphous yellow-brown mother liquor material was treated with 30 ml. of pyridine and 15 ml. of acetic anhydride and stirred at 25° overnight. At the end of this time a small amount of crystalline solid was present which was removed by filtration and washed 3 times with ether, wt. 0.394 g., m.p. 223–228°. The ether and excess reagents were removed *in vacuo* to give a partly crystalline residue which was treated with 20 ml. of ether and filtered to give an additional 0.409 g. of crystalline solid, m.p. 229–238°, undepressed on admixture with the sample above and with cortisone acetate.

The filtrate was diluted with 50 ml. of ethyl acetate and 50 ml. of water, the mixture shaken vigorously, separated and the aqueous layer extracted twice more with ethyl acetate. The combined extracts were washed successively with 1 *N* hydrochloric acid, water, 5% aqueous sodium bicarbonate, water and finally with saturated salt solution. The washed extracts were filtered through anhydrous magnesium sulfate and the solvents removed *in vacuo* to give 4.12 g. of amorphous solid. The latter was dissolved in benzene and chromatographed over 206 g. of neutral alumina. After development with benzene and 10% chloroform–benzene, the first fraction eluted (25% chloroform–benzene) weighed 0.155 g. and gave 46.5 mg. of an unidentified material as prisms, m.p. 202.5–207°. The succeeding 7 fractions (50% chloroform–benzene and chloroform) were examined by paper-strip analysis and found to contain diacetate IIIa (see below), in an amount estimated to be 1.57 g., thus raising the total amount of III formed in the perchloric acid reaction to 65.2%. Cortisone acetate was also present in fractions 4–8 and was estimated to amount to 0.316 g. Crystals were obtained from fractions 4–6 by crystallization from acetone–ether, total weight 0.230 g., each sample of which did not depress the m.p. of cortisone acetate. The latter 0.230-g. sample was combined with the two samples isolated above (weights 0.394 and 0.409 g.) and recrystallized from acetone to give 0.708 g. (8.8%) of needles, m.p. 230–233°, undepressed on admixture with cortisone acetate and identified by paper-strip comparison and infrared spectra.

Finally, the column was eluted with acetone and 25% methanol–acetone to yield 3 fractions, total weight 0.920 g. (10.9%), which crystallized on seeding with Δ^4-pregnene-9α,11β,17α,21-tetrol-3,20-dione 21-acetate (I, X = OH). The latter were combined and recrystallized from acetone–ether to give 0.598 g. (7.1%) of prisms, m.p. 215–218.5°, undepressed on admixture with authentic material and further identified by infrared comparison. Thus, the amounts of the three major products formed can be estimated as follows: III together with IIIa, 65.2%; cortisone acetate, 13.9%; (I, X = OH), 10.9%.

Treatment of 9α,11α-oxido-Δ^4-pregnene-17α,21-diol-3,20-dione 21-acetate with 60% perchloric acid as described above for the 9β,11β-oxide resulted in the recovery of unchanged starting material.

A sample of III was treated with 0.5 *N* perchloric acid in aqueous dioxane at 25° for 8 days in an effort to prepare the **21-alcohol**. The product could not be crystallized but on acetylation with acetic anhydride and pyridine at 25° afforded the diacetate IIIa (see below). Hydrolysis of III with sodium methoxide in methanol–tetrahydrofuran by the procedure used in the hydrolysis of the dienedione V (see below) also gave only amorphous material. Again acetylation produced the diacetate IIIa (see below). In both experiments above, paper chromatographic examination of the total re-acetylated material showed it to be substantially pure diacetate.

Osmylation of III resulted in the recovery of starting material as the only recognizable crystalline entity. Likewise selective dehydrogenation of III with selenium dioxide in aqueous ethanol according to the procedure of Callow[32] for the oxidation of $\Delta^{8(14)}$-steroid olefins to $\Delta^{6,8(14)}$-dienes produced no change in the ultraviolet spectrum and the material was recovered unchanged.

$\Delta^{4,8(14)}$-Pregnadiene-11β,17α,21-triol-3,20-dione 11β,21-Diacetate (IIIa).—A solution of 1.61 g. (4.0 millimoles) of III in 10 ml. of pyridine and 10 ml. of acetic anhydride was allowed to stand at 25° for 18 hours. The excess reagents were removed *in vacuo* and the oily residue was dissolved in chloroform. The chloroform solution was washed successively with water, 1.0 *N* hydrochloric acid, water, 5% sodium bicarbonate solution, water and finally with saturated salt solution. The washed chloroform was filtered through anhydrous magnesium sulfate and concentrated *in vacuo* to give 1.98 g. of crude IIIa. The latter was substantially pure by paper chromatographic examination. A sample prepared for analysis by recrystallization from ether–petroleum ether (b.p. 30–60°) was obtained as prisms, m.p. 210–215°, $\lambda\lambda_{max}^{Nujol}$ 3.05, 5.74, 5.81 and 6.16(sh) μ.

Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.57; H, 7.27. Found: C, 67.52; H, 7.32.

8ξ,14ξ-Oxido-Δ^4-pregnene-11β,17α,21-triol-3,20-dione 21-Acetate.—A solution of 402.5 mg. (1.0 millimole) of III in 150 ml. of chloroform was treated with 14.3 ml. of 0.350 *M* perbenzoic acid in benzene (5.0 millimoles). After standing overnight at 0°, the solution was washed with 10% aqueous sodium thiosulfate, water, 5% aqueous sodium bicarbonate and with water. After filtration through magnesium sulfate and removal of the solvents, a residue weighing 480 mg. was obtained. Two recrystallizations from acetone–Skellysolve B gave 192 mg. of the oxide,[2b] m.p. 203–206° dec., λ_{max} 242 mμ (ϵ 14,000); $\lambda\lambda_{max}^{Nujol}$ 2.96, 3.01, 5.75, 5.78 and 6.05–6.1 μ.

Anal. Calcd. for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 65.90; H, 7.24.

$\Delta^{4,8(14)}$-Pregnadiene-11β,17α,21-triol-3,20-dione 11β-Mesylate-21-acetate (IIIb).—To a solution of 1.0 g. of III in 8 ml. of pyridine cooled to 0° was added dropwise with cooling 0.75 ml. of methanesulfonyl chloride. The mixture was allowed to stand at 0–5° for 18 hours. To the mixture was added 10 g. of ice and after 15 minutes the product was extracted with ether. The ether extract was washed successively with dilute aqueous hydrochloric acid, potassium bicarbonate solution and water, dried over anhydrous magnesium sulfate and concentrated to dryness *in vacuo*. After crystallization from ether the product amounted to 1.1 g. (92%), m.p. 145–147° dec. (reported[2b] m.p. 151–152° dec.).

Acidolysis of IIIb.—A solution of 750 mg. of IIIb in 5 ml. of propionic acid was treated with 750 mg. of potassium bicarbonate and heated in a nitrogen atmosphere at 100° for 1 hour. The reaction mixture was evaporated *in vacuo* and water added to precipitate the product. The latter was isolated by ether extraction and the ether extract washed free of acid, dried and concentrated. The residue obtained after concentration was chromatographed on neutral alumina to yield a small amount of $\Delta^{4,8(14)}$-pregnadiene-11β,17α,21-triol-3,20-dione 11-propionate-21-acetate, m.p. 250–255°; the latter was identical by mixed m.p. and infrared comparison with an authentic sample prepared by propionylation of II with propionic anhydride in pyridine.[2b]

Similar treatment of IIIb with sodium acetate in acetic acid afforded a product containing IIIa by paper chromatography. A considerable amount of XVI and/or XVII appears to accompany the acidolysis reactions.

$\Delta^{4,8(14)}$-Pregnadiene-17α,21-diol-3,11,20-trione 21-Acetate (IV). ($\Delta^{8(14)}$-Dehydrocortisone Acetate).—To a solution of 402.5 mg. (1.0 millimole) of $\Delta^{4,8(14)}$-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate (III) in 4 ml. of pyridine was added a solution of 333 mg. (3.33 millimoles) of chromium trioxide in 0.33 ml. of water and 1.0 ml. of pyridine. The mixture was allowed to stand at 25° overnight and then diluted with 30 ml. of water and 20 ml. of ethyl acetate. A brown insoluble solid was removed by filtration through Celite and the residue washed thoroughly with water and ethyl acetate. The layers of the filtrate were separated and the aqueous layer extracted twice with ethyl acetate. The combined ethyl acetate layers were washed successively with dilute hydrochloric acid, water and saturated salt solution, and filtered through anhydrous magnesium sulfate. After removal of the solvent, 365 mg. (91.1%) of nearly colorless crystalline solid was obtained. Two recrystallizations from acetone–Skellysolve B afforded 172 mg. (42.9%) of prismatic needles, m.p. 225–229° dec., $[\alpha]^{25}D$ +449° (0.95), λ_{max} 239 mμ (ϵ 15,650); $\lambda\lambda_{max}^{Nujol}$ 3.1, 5.75, 5.80, 5.89, 6.02 and 6.15 μ; $\lambda\lambda_{max}^{CHCl_3}$ 3.00–3.05, 5.75 (sh), 5.80, 5.90, 6.02 and 6.15 μ.

Anal. Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.21; H, 7.22.

In another run, 8.05 g. (20.0 millimoles) of III was

(32) R. K. Callow, *J. Chem. Soc.*, 462 (1936).

oxidized exactly as described above to give 7.57 g. (94.6%) of crude IV; one recrystallization from ethyl acetate gave 5.79 g. (72.4%) of pure IV, m.p. 227–231°, λ_{max} 238 mμ (ε 16,350).

An attempt to hydrolyze the dienedione IV to its **21-alcohol** by treatment with 0.50 *N* perchloric acid in aqueous dioxane at 25° for 8 days gave only amorphous material which, however, on reacetylation with pyridine and acetic anhydride afforded the original 21-acetate.

Treatment of IV with selenium dioxide[32] produced no change in the ultraviolet spectrum and the material was recovered unchanged.

The epimerization of Δ^7-11-ketones with a 9β-hydrogen to the natural 9α-configuration has been reported by Bladon, *et al.*[5b]; the procedure involves treatment with a specially prepared alumina. A sample of IV was adsorbed on this alumina, allowed to stand at 25° for 18 hours, and then eluted. The material was recovered unchanged.

Attempts to isomerize the $\Delta^{4,8(14)}$-dienedione IV to a $\Delta^{4,8(9)}$-dienedione (V or VI) with either (a) lithium chloride in dimethylformamide at 100° for two hours, or (b) hydrogen chloride in ethanol-free chloroform at 0° for one hour failed. In the latter case, the product was contaminated by a chlorine-containing impurity, which, however, was converted to the original dienedione IV by short treatment with refluxing pyridine.

$\Delta^{4,8(14)}$-Pregnadiene-17α,21-diol-3,11,20-trione 17α,21-Diacetate.—A 235-mg. (0.587 millimole) sample of IV in 8.0 ml. of glacial acetic acid and 3.0 ml. of acetic anhydride was treated with 235 mg. of *p*-toluenesulfonic acid monohydrate and the resulting yellow solution stored at 25° overnight. Addition of 50 g. of ice caused the separation of a yellow-brown oil which was extracted with four portions of chloroform. The combined extracts were washed four times with water, once with 5% aqueous sodium bicarbonate, again with water and finally with saturated salt solution. After filtration through anhydrous magnesium sulfate and removal of the solvent an amorphous residue was obtained. One crystallization from acetone–ether gave 169 mg. (65%) of needles, m.p. 212–214°, λ_{max} 238 mμ (ε 15,100); $\lambda\lambda_{max}$ 5.70, 5.75, 5.86, 5.97 and 6.10 μ (no hydroxyl bands in the 3.0 μ region were observed).

Anal. Calcd. for $C_{25}H_{30}O_7$: C, 67.86; H, 6.83; acetyl, 19.45. Found: C, 67.67; H, 6.82; acetyl, 20.8.

A solution of 114.6 mg. (0.25 millimole) of the diacetate above in 3.0 ml. of chloroform was treated with 1.96 ml. of 0.383 *M* perbenzoic acid in benzene (0.75 millimole) and the mixture stored at 0° overnight. The mixture was then extracted twice with 10% sodium thiosulfate solution, washed twice with water, once with 5% sodium bicarbonate solution, again with water and finally with saturated salt solution. Filtration through anhydrous magnesium sulfate and removal of the solvents *in vacuo* gave a colorless crystalline residue, weight 125 mg. One recrystallization from acetone–ether afforded 92.9 mg. (81%) of **8ξ,14ξ-oxido-Δ^4-pregnene-17α,21-diol-3,11,20-trione 17α,21-diacetate** as needles, m.p. 209–211°, depressed on admixture with the starting diacetate, λ_{max} 238 mμ (ε 16,600); $\lambda\lambda_{max}^{Nujol}$ 5.7, 5.75, 5.85, 5.99 and 6.15 μ (no hydroxyl bands in the 3.0 μ region were observed).

Anal. Calcd. for $C_{25}H_{30}O_8$: C, 65.49; H, 6.60. Found: C, 65.59, 65.46; H, 6.43, 6.51.

$\Delta^{4,8(9)}$-Pregnadiene-17α,21-diol-3,11,20-trione 21-Acetate (V). ($\Delta^{8(9)}$-Dehydrocortisone Acetate). (A). By Pyridine Dehydrobromination of 9α-Bromo-Δ^4-pregnene-17α,21-diol-3,11,20-trione 21-Acetate (VII).—The pyridine dehydrobromination of 9α-bromocortisone acetate (VII)[2] was carried out as follows. A solution of 2.41 g. (5.0 millimoles) of VII in 36 ml. of dry purified pyridine was heated under reflux for one hour in an atmosphere of nitrogen. The yellow solution was then concentrated *in vacuo* to give a yellow crystalline residue which was dissolved in 50 ml. of ethyl acetate and 50 ml. of water. The layers were separated and the water layer extracted with two 50-ml. portions of ethyl acetate. The yellow extracts were combined and washed twice with 1.25 *N* hydrochloric acid, with water, with 5% aqueous sodium bicarbonate, again with water and finally with saturated salt solution. The solution was filtered through anhydrous magnesium sulfate and concentrated to dryness *in vacuo* to give 2.01 g. (100%) of yellow crystals, m.p. 233–241° dec. Paper chromatographic analysis of this crude material showed only one spot. Recrystallization from acetone afforded 1.395 g. (69.7%) of yellow prisms, m.p. 241–248° dec. One additional recrystallization did not raise the m.p.; the m.p. (cap.) was 249–250° dec., $[\alpha]^{25}D$ +422° (1.05), λ_{max} 236.5 mμ (ε 17,700); $\lambda\lambda_{max}^{Nujol}$ 2.99, 5.72, 5.80, 6.04 and 6.24 μ.

Anal. Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.04; H, 6.75.

The corresponding **21-alcohol** derived from V was prepared by two methods as follows: **(a) By Sodium Methoxide Hydrolysis.**—A 200.5-mg. (0.5 millimole) sample of V in 20 ml. of tetrahydrofuran and 8 ml. of methanol was placed under nitrogen and 0.54 ml. of 0.97 *N* sodium methoxide in methanol (0.525 millimole) added. The mixture was stirred for 10 minutes at 25° and neutralized with a slight excess of glacial acetic acid. The solvents were removed *in vacuo* and the residue dissolved in 25 ml. of water and 25 ml. of ethyl acetate. The layers were separated and the aqueous layer re-extracted with two portions of ethyl acetate. The combined extracts were washed with water, 5% aqueous sodium bicarbonate solution, water and with saturated salt solution, filtered through magnesium sulfate and taken to dryness *in vacuo* to give 170 mg. (95%) of a partly crystalline yellow residue. One crystallization from acetone–ether gave 63 mg. of bright yellow prisms, m.p. 239–243° dec. A sample recrystallized for analysis melted (cap.) at 249–252° dec., λ_{max} 237 mμ (ε 17,900); $\lambda\lambda_{max}^{Nujol}$ 3.0, 5.87, 6.01–6.08 and 6.25 μ.

Anal. Calcd. for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.16; H, 7.18.

A small sample of the material, m.p. 239–243°, was acetylated with acetic anhydride and pyridine and the product shown by paper strip, mixed m.p., and infrared comparison to be authentic V.

(b) By Potassium Bicarbonate Hydrolysis.—A suspension of 1.20 g. (3.0 millimoles) of V in 36 ml. of methanol was heated to reflux in an atmosphere of nitrogen; 9 ml. of 1.0 *M* aqueous potassium bicarbonate (9.0 millimoles) was then added. The solid dissolved in one minute and the light reddish-brown solution was refluxed for 5 minutes. The reaction mixture was neutralized with 0.9 ml. of glacial acetic acid and the methanol removed *in vacuo*. The solid which separated was extracted with 1:1 ethyl acetate–chloroform and the extracts washed with water, 5% aqueous sodium bicarbonate, water and saturated salt solution. After drying by filtration through magnesium sulfate, the solvents were removed *in vacuo* to give 1.04 g. (96.7%) of yellow crystals. Two recrystallizations from acetone afforded material, m.p. 240.5–252° dec., identical by infrared comparison with material prepared by sodium methoxide hydrolysis.

(B) By Alkaline Isomerization of the $\Delta^{4,8(14)}$-Dienedione IV.—A solution of 2.00 g. (5.0 millimoles) of the dienedione IV in 300 ml. of tetrahydrofuran and 50 ml. of methanol was placed under a nitrogen atmosphere and 16.62 ml. of 0.376 *N* sodium methoxide in methanol (6.25 millimoles) was added with stirring at 23°. After 10 minutes, 0.50 ml. of glacial acetic acid was added to neutralize the solution and the reaction mixture was concentrated *in vacuo* to a yellow gum. The residue was dissolved in 100 ml. of water and 250 ml. of ethyl acetate, the mixture shaken and separated, and the aqueous layer extracted twice with ethyl acetate. The combined extracts were washed with water, 5% aqueous sodium bicarbonate, water and saturated salt solution, filtered through anhydrous magnesium sulfate and the solvents removed *in vacuo* to give a pale yellow foam, weight 1.835 g. A 10-mg. sample of the product was reacetylated with pyridine and acetic anhydride for one-half hour at 65°. Paper-strip analysis of this material showed it to consist mainly of two components, one with an R_f value the same as the starting dienedione IV and the other with an R_f value the same as the isomeric dienedione V. The remainder of the product was crystallized from acetone to give 293 mg. (16.5%) of yellow prisms, m.p. 235–245° dec., undepressed on admixture with the 21-alcohol of V prepared above. The infrared spectra of the two samples were identical. In another run, a product, m.p. 225–230° dec., was obtained in the same manner. A sample of this material on acetylation with pyridine and acetic anhydride gave, after one recrystallization, material of m.p. 227.5–236° dec., undepressed on admixture with V and identical in the

infrared; this acetylated material depressed the m.p. of the starting dienedione acetate IV.

The mother liquor of the 293-mg. sample above was acetylated in the usual manner and 250 mg. of this material separated by chromatography on Whatman No. 4 paper. Additional V was isolated from the more polar spot and IV was obtained from the less polar spot, m.p. 218.5–227°, identical by mixed m.p. and infrared with the starting material IV.

(C) By Oxidation of XXIV.—To a solution of 100 mg. (0.248 millimole) of $\Delta^{4,8(9)}$-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate (XXIV) in 10 ml. of chloroform was added 1.0 g. (11.5 millimoles) of manganese dioxide.[33] The mixture was stirred for 22 hours at room temperature (22°), filtered, the residue washed with chloroform and the filtrate concentrated to yield 79.7 mg. of crude material. This mixture was chromatographed on Whatman No. 4 paper to yield 16 mg. (16%) of unoxidized starting material and 23 mg. (27%, based on starting material consumed) of crude $\Delta^{4,8(9)}$-pregnadiene-17α,21-diol-3,11,20-trione 21-acetate (V). The crude material was crystallized twice from acetone–hexane to yield 10.9 mg. (13%, based on starting material consumed) of product, m.p. 232–239° dec., identical with previously obtained material by mixed m.p., infrared spectral comparison and paper strip comparison.

Several experiments carried out on the dienedione V are worthy of mention. In an early attempt to ascertain the disposition of double bonds in V, a sample was reduced with lithium aluminum hydride to give an oily mixture of products which had only end absorption in the ultraviolet. Treatment of a sample of V with selenium dioxide in aqueous alcohol gave only unchanged starting material.[32] Two unsuccessful attempts to isomerize V to the epimeric dienedione VI were carried out (compare below). A solution of V in 60% aqueous perchloric acid was held at 25° and sampled at intervals. Even after 23 hours, no VI could be detected by paper-strip analysis although considerable hydrolysis of the 21-acetate function had occurred and a small amount of an unknown by-product formed. Finally, treatment of V with lithium chloride in dimethylformamide at 100° under nitrogen for 23 hours gave only unchanged starting material by m.p., infrared, and paper-strip analysis.

$\Delta^{4,8(9)}$-17α-Hydroxy-3,11-diketoetiadienic Acid (VIII).—A mixture of 358.5 mg. (1.0 millimole) of the 21-alcohol of V and 250.8 mg. (1.1 millimoles) of periodic acid dihydrate in 50 ml. of tetrahydrofuran and 12 ml. of water was allowed to stand at 25° overnight. Removal of the tetrahydrofuran *in vacuo* caused the separation of a yellow oil which was extracted with three portions of ethyl acetate. The combined extracts were washed twice with water and once with saturated salt solution, filtered through anhydrous magnesium sulfate and concentrated *in vacuo* to give a yellow crystalline residue, weight 365 mg. Recrystallization from acetone gave 216 mg. of the etio-acid VIII, m.p. 228–232° dec. A sample prepared for analysis by recrystallization from acetone–ether had the m.p. (cap.) 238.5–240.5° dec., λ_{max} 235 mμ (ϵ 18,300); $\lambda\lambda_{max}^{Nujol}$ 2.92–3.05, 5.75, 6.0–6.12 and 6.27 μ.

Anal. Calcd. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.41; H, 7.23.

Methyl 17α-Hydroxy-3,11-diketoalloetianate (IX).—To the deep blue solution obtained from 113 mg. (16.3 millimoles) of lithium dissolved in 50–60 ml. of liquid ammonia was added with stirring a solution of 172.6 mg. (0.5 millimole) of the etio-acid VIII in 18 ml. of dry tetrahydrofuran. After 10–15 minutes, the solution was no longer blue. Therefore, an additional 104 mg. (15.0 millimoles) of lithium was added. Again, after 1 hour, a third portion of lithium was introduced, 115 mg. (16.6 millimoles). After a total time of 5 hours, the deep blue solution was treated with portions of solid ammonium chloride and the resulting nearly colorless solution allowed to evaporate until the ammonia had disappeared. Water was added to the remaining solution and the tetrahydrofuran removed *in vacuo*. The aqueous solution was acidified with 6 *N* hydrochloric acid and the organic material extracted with five portions of ethyl acetate. After washing the combined extracts with water, they were extracted with five portions of 5% aqueous sodium bicarbonate. Acidification of the combined bicarbonate extracts and extraction with ethyl acetate gave 160 mg. of light brown amorphous solid which showed no maxima in the ultraviolet.

The crude reduced acid was dissolved in 5 ml. of methanol and 20 ml. of ether and treated with an excess of ethereal diazomethane. Removal of the solvents gave 170 mg. of crude methyl ester which was dissolved in 5 ml. of glacial acetic acid and treated with 93 mg. (0.93 millimole) of chromium trioxide in 5 drops of water and 6.0 ml. of acetic acid. After standing at 25° for three hours, the acetic acid was removed *in vacuo*. To the residue was added 75 ml. of water and the reoxidized ester extracted with 3 portions of ethyl acetate. The combined extracts were washed with water, 5% aqueous sodium bicarbonate, water and with saturated salt solution, then dried by filtration through anhydrous magnesium sulfate and the solvent removed *in vacuo* to give 110 mg. of a colorless oil. One recrystallization from acetone gave 33 mg. of plates, m.p. 199–215°, undepressed on admixture with a sample of authentic IX, m.p. 198–208°. An additional recrystallization gave 13 mg., m.p. 212.5–226.5°, which by paper-strip comparison consisted of IX together with a small amount of a second more polar material. Therefore, the combined mother liquors were concentrated to dryness and chromatographed over 4.75 g. of neutral alumina. The fractions eluted with benzene and 10% chloroform–benzene were combined, wt. 45.2 mg., and recrystallized to give 23 mg., m.p. 199–211°.

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.65; H, 8.73.

This material was identical by mixed m.p., infrared and paper-strip comparison with authentic IX prepared from allopregnane-17α,21-diol-3,11,20-trione[34] by successive periodic acid cleavage followed by esterification with diazomethane.

It was ascertained independently that Δ^4-17α-hydroxy-3,11-diketoetienic acid, the acid obtained from cortisone on periodic acid cleavage, on reduction with lithium and ammonia as described above, followed by esterification with diazomethane and reoxidation with chromium trioxide lead mainly to the same alloester IX.

$\Delta^{4,8(9)}$-14-Isopregnadiene-17α,21-diol-3,11,20-trione 21-Acetate (VI). (A) By Lithium Chloride–Dimethylformamide Dehydrobromination of 9α-Bromo-Δ^4-pregnene-17α,-21-diol-3,11,20-trione 21-Acetate (VII).—A mixture containing 7.23 g. (15.0 millimoles) of the bromoketone VII and 7.5 g. (0.177 mole) of lithium chloride in 75 ml. of dimethylformamide was heated for 2 hours at 100° in an atmosphere of nitrogen. The solution was then cooled to 60° and 225 ml. of water added in portions. After cooling at 0° for two hours, the suspension was filtered, the crystalline residue washed thoroughly with water and dried *in vacuo*, weight 5.47 g. (91%), m.p. 186–193°. This material was shown to be essentially pure VI by paper strip analysis. One recrystallization from ethyl acetate gave 4.65 g. (77%), m.p. 193–196°, identical in all respects to material prepared by acid isomerization of V (see below). A sample prepared for analysis had the m.p. 195–198°, $[\alpha]^{25}D$ +348° (0.87), λ_{max} 237.5 mμ (ϵ 19,700); $\lambda\lambda_{max}^{CHCl_3}$ 2.92–2.98, 5.71, 5.79, 5.99 and 6.17 μ.

Anal. Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.20; H, 7.25.

(B) By Isomerization of the Dienedione V. (a) *Via* Hydrogen Chloride in Chloroform.—Dry hydrogen chloride was passed into an ice-cold solution of 2.00 g. (5.0 millimoles) of V in 150 ml. of ethanol-free chloroform. Within 5 minutes, the solution was orange-red in color and a red oil had separated. The introduction of hydrogen chloride was continued for 1 hour. Addition of 100 ml. of water discharged the red color and the oil redissolved to give a yellow chloroform layer which was separated and washed free of acid with three portions of water. Filtration through anhydrous magnesium sulfate and removal of the solvent gave a partly crystalline pale yellow residue, wt. 2.10 g.; paper-strip analysis indicated this to be a mixture of V and VI in the ratio of *ca.* 40:60. This material was chromatographed over 210 g. of neutral alumina. The fractions eluted with 25% chloroform–benzene and 35% chloroform–

(33) Manganese dioxide prepared according to the procedure of M. Harfenist, A. Bavley and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).

(34) J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **25**, 988 (1942)

benzene and which were mainly VI by paper-strip analysis were combined, wt. 515 mg., and recrystallized. After removal of a small first crop, wt. 87 mg., which was mainly V, the mother liquor on concentration afforded 286 mg. (14.3%) of VI, m.p. 186–194°, undepressed on admixture with material prepared in (A) above, and identical by paper-strip comparison and infrared.

The experiment above was repeated using 40.0 mg. (0.10 millimole) of V in 4.0 ml. of ethanol-free chloroform. After passing in hydrogen chloride for 1 hour, the solution and oil were stored at 0° for 18 hours and then worked up as described above. The crude product was shown to be essentially pure VI by paper strip analysis and on recrystallization afforded 25.1 mg. (62.8%) of crystals, m.p. 188.5–193°, identical to that prepared in (A) above by mixed m.p., paper-strip and infrared comparison.

(b) *Via* **Lithium Chloride–Dimethylformamide–Hydrogen Bromide.**—A mixture of 50.0 mg. (0.125 millimole) of V and 53.0 mg. (1.25 millimoles) of lithium chloride in 0.625 ml. of 0.20 *N* hydrogen bromide (0.125 millimole) in dimethylformamide was heated for 2 hours in an atmosphere of nitrogen. Addition of 6.0 ml. of water and saturation with sodium chloride caused the separation of crystals which were removed by filtration, washed thoroughly with water and dried *in vacuo* to give 45.3 mg. (90.6%) of needles, m.p. 180–191°, undepressed on admixture with material prepared by hydrogen chloride isomerization of V. The identity was confirmed by paper-strip and infrared comparison.

(c) *Via* **Lithium Chloride–Dimethylformamide–Pyridine Hydrobromide.**—A solution of 200 mg. (0.50 millimole) of V, 64 mg. (1.50 millimoles) of lithium chloride and 80 mg. (0.5 millimole) of pyridine hydrobromide in 5.0 ml. of dimethylformamide was heated for 2 hours at 100° under nitrogen. The mixture was cooled to 25° and 5.0 ml. of water added. The crystalline solid which separated was removed by filtration, washed three times with water and dried *in vacuo* to give 80 mg. of crude V, m.p., 225–235°, identified by paper-strip comparison. Recrystallization gave 32 mg., m.p. 229–235° dec. Addition of 50 ml. of saturated salt solution to the aqueous dimethylformamide filtrate above caused the separation of an additional 105 mg. of crystals, m.p. 177–193°, identified as substantially pure VI by paper-strip comparison. Recrystallization afforded 67.5 mg. of pure VI, m.p. 193–197°, undepressed on admixture with material prepared *via* hydrogen chloride isomerization and identified by paper-strip comparison.

(C) **By Isomerization of the Dienedione IV with Lithium Chloride–Dimethylformamide–Hydrogen Bromide.**—A solution of 100 mg. (0.25 millimole) of the dienedione IV in 0.51 ml. of dimethylformamide containing 100 mg. of lithium chloride (0.236 millimole) was treated with 1.0 ml. of 0.337 *N* hydrogen bromide (0.337 millimole) in dimethylformamide and heated on a steam-bath for 1 hour. The reaction mixture was diluted with water to afford 70–75 mg. of crystalline $\Delta^{4,8}$-dienedione VI which after recrystallization (Norite) from acetone–ether melted at 191–192.5° and was not depressed on admixture with authentic material. The infrared spectra of the two samples were essentially the same.

$\Delta^{4,8(9)}$-14-Isopregnadiene-17α,21-diol-3,11,20-trione 17α,21-Diacetate (VIa).—The 17α,21-diacetate VIa was prepared by treatment of 100 mg. of VI with 3 ml. each of pyridine and acetic anhydride for 7 days at 25°. The excess reagents were then removed *in vacuo* at 25° and the residue dissolved in ethyl acetate. The ethyl acetate solution was washed with water, 1.25 *N* hydrochloric acid, water, 5% aqueous sodium bicarbonate, water and saturated salt solution and dried by filtration through anhydrous magnesium sulfate. Removal of the solvent *in vacuo* gave an amorphous residue, weight 115 mg., which was estimated to contain *ca.* 95% of the 17α,21-diacetate by paper-strip analysis. Separation of the diacetate from unchanged VI was carried out by chromatography on Whatman No. 4 paper. Elution of the diacetate band gave 106 mg. of oily residue which on crystallization from acetone–ether afforded 72.5 mg. of VIa as needles, m.p. 183–185°, $[\alpha]^{25}D$ +275° (0.965), λ_{max} 237.5 mμ (ϵ 19,900); $\lambda\lambda_{max}^{Nujol}$ 5.74, 5.80, 6.04 and 6.30 μ (no hydroxyl bands observed).

Anal. Calcd. for $C_{25}H_{30}O_7$: C, 67.86; H, 6.83. Found: C, 67.87; H, 6.47.

The 21-alcohol derived from VI was prepared by treatment of VI with (a) sodium methoxide in methanolic tetrahydrofuran or (b) potassium bicarbonate in aqueous methanol as described above for the 21-alcohol of the dienedione V. The material could not be crystallized, but reacetylation of small samples followed by paper-strip analysis indicated that no other structural change had occurred. The corresponding etio-acid **$\Delta^{4,8(9)}$-17α-hydroxy-3,11-diketo-14-isoetiadienic acid** was prepared by periodic acid oxidation of the amorphous 21-alcohol as described above. The m.p. after recrystallization from acetone–ether was 235.5–239° dec., λ_{max} 241 mμ (ϵ 19,350); $\lambda\lambda_{max}^{Nujol}$ 2.82–3.0, 5.79 and 6.0–6.2 μ. The m.p. was depressed on admixture with the epimeric acid VIII.

Anal. Calcd. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.68; H, 6.99.

Several attempts to back-isomerize VI at C_{14} were unsuccessful, thus: (1) Treatment of VI with anhydrous hydrogen chloride in ethanol-free chloroform at 0° for 1 hour gave back unchanged starting material, identified by mixed m.p. and by paper-strip comparison with authentic material, and (2) heating VI at 100° for 1 hour in pyridine in the presence of pyridine hydrobromide gave only unchanged VI identified as above.

$\Delta^{8(9)}$-Pregnene-17α,21-diol-3,11,20-trione 21-Acetate (XI).—A solution of 200 mg. (0.5 millimole) of the yellow dienedione V in 15 ml. of methanol was stirred in an atmosphere of hydrogen in the presence of 50 mg. of 5% palladium-on-barium sulfate. In about 0.5 hour, 12.3 ml. of hydrogen had been absorbed and the uptake ceased. The colorless solution was filtered and the methanol removed *in vacuo* to give 203 mg. of crude XI, m.p. 207–213°. One recrystallization raised the m.p. to 212–216°, $[\alpha]^{25}D$ + 157° (0.78),[35] λ_{max} 256 mμ (ϵ 8,175); $\lambda\lambda_{max}^{CHCl_3}$ 2.85–2.92, 5.72(sh), 5.79, 5.85, 6.01 and 6.21 μ.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.69; H, 7.29.

The m.p. of the material above was not depressed when mixed with $\Delta^{8(9)}$-pregnene-17α,21-diol-3,11,20-trione 21-acetate, m.p. 210–216°, isolated as a by-product in the conversion of pregnane-3α,17α-diol-11,20-dione to cortisone acetate[15]; the infrared spectra were identical.

A sample of XI on base hydrolysis and reacetylation resulted in recovery of XI unchanged.

$\Delta^{8(14)}$-Pregnene-11β,17α,21-triol-3,20-dione 21-Acetate (XIII).—A slurry consisting of 3.62 g. of $\Delta^{4,8(14)}$-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate (III), 2.5 g. of 5% palladium-on-barium sulfate and 130 ml. of methanol was purged with hydrogen and hydrogenated with magnetic stirring at atmospheric pressure. The steroid dissolved during the hydrogenation. The uptake of hydrogen amounted to 103% of the theoretical amount of 1 mole per mole of steroid. The mixture was filtered, the filtrate evaporated to dryness *in vacuo* and the crystalline material dried for 1 hr. at 100° and 0.1 mm. The product, m.p. 188–199°, was obtained in quantitative yield. Three crystallizations from acetone–hexane yielded material, m.p. 195–197°, $[\alpha]^{25}D$ +165° (1.0), no maximum in the ultraviolet; $\lambda\lambda_{max}^{CHCl_3}$ 2.8, 2.92, 5.75(sh), 5.80 and 5.87 μ.

Anal. Calcd. for $C_{25}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.16; H, 7.88.

Attempted hydrogenation of XIII over platinum-in-methanol and over platinum-in-acetic acid resulted in no further hydrogen uptake. Reduction of XIII with lithium aluminum hydride followed by attempted oxidation with selenium dioxide[31] produced no change in the ultraviolet spectrum.

$\Delta^{8(14)}$-Pregnene-11β,17α,21-triol-3,20-dione 11β-Mesylate 21-Acetate (XIIIa).—To a solution of 0.404 g. (1.0 millimole) of $\Delta^{8(14)}$-pregnene-11β,17α,21-triol-3,20-dione 21-acetate (XIII) in 5 ml. of pyridine cooled to 0° was added dropwise with cooling 1.0 ml. of methanesulfonyl chloride (13 millimoles). The mixture was allowed to stand at 0° for 24 hours. To the mixture was added 10 g. of ice and

(35) On several occasions the hydrogenation product exhibited unusual behavior. Paper-strip analysis indicated a less polar constituent as the major product separable by chromatography on neutral alumina, having a m.p. 173–177° and infrared ($CHCl_3$) and ultraviolet the same as XI with slightly lower extinction. This compound changed on standing in the solid state to the more polar XI, m.p. 212–216°. This behavior might be interpreted as the consequence of a boat ⇌ chair conformational transition induced by lattice forces.

after 15 minutes the product was extracted with ethyl acetate. The ethyl acetate extract was washed successively with water, 1.6% phosphoric acid, 5% sodium bicarbonate solution, water, dried over magnesium sulfate and concentrated to dryness *in vacuo*. The residue was crystallized from acetone–hexane to yield 0.255 g. (53%) of XIIIa, m.p. 142–144° dec., $[\alpha]^{25}D$ +131.5° (1.0).

Anal. Calcd. for $C_{24}H_{34}O_8S$: C, 59.71; H, 7.10; S, 6.64. Found: C, 59.76; H, 6.82; S, 6.72.

$\Delta^{8(14),9(11)}$-Pregnadiene-17α,21-diol-3,20-dione 21-Acetate (XIV).—A solution of 100 mg. (0.208 millimole) of $\Delta^{8(14)}$-pregnene-11β,17α,21-triol-3,20-dione 11-mesylate-21-acetate (XIIIa) in 1.0 ml. of pyridine was refluxed for 2 hours. After addition of 10 ml. of water the mixture was extracted with three 10-ml. portions of ethyl acetate. The combined ethyl acetate extracts were washed with water, 1.6% phosphoric acid, 5% sodium bicarbonate solution, water and saturated salt solution, dried over magnesium sulfate and concentrated *in vacuo*. The crude product was treated with decolorizing charcoal and crystallized from acetone–hexane, m.p. 180–185°, $[\alpha]^{24}D$ +79° (1.0), λ_{max} 271 mμ (ϵ 4,600); $\lambda\lambda_{max}^{Nujol}$ 2.91, 5.73, 5.80, 5.85 and 5.91 μ.

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.22; H, 7.88.

Reduction of XIV with lithium aluminum hydride gave an amorphous product, λ_{max} 271 mμ (ϵ 4,210).

$\Delta^{8(14)}$-Pregnadiene-17α,21-diol-3,20-dione 21-Acetate (XV).—A solution of 150 mg. (0.39 millimole) of $\Delta^{8(14),9(11)}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate (XIV) in 10 ml. of chloroform was treated with gaseous hydrogen chloride at 0° for 1 hour. The mixture was evaporated to dryness, treated with decolorizing charcoal and crystallized from acetone–hexane, m.p. 210–214°, $[\alpha]^{23}D$ −26.2° (1.0), λ_{max} 246 mμ (ϵ 21,500); $\lambda\lambda_{max}^{Nujol}$ 2.9, 5.75(sh), 5.79, 5.87, 6.11 and 6.20 μ.

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.46; H, 7.55.

$\Delta^{4,8(14),9(11)}$-Pregnatriene-17α,21-diol-3,20-dione 21-Acetate (XVI).—By a method analogous to the preparation of XIV from XIIIa, $\Delta^{4,8(14)9,(11)}$-pregnatriene-17α,21-diol-3,-20-dione 21-acetate (XVI) was obtained from $\Delta^{4,8(14)}$-pregnadiene-11β,17α,21-triol-3,20-dione 11β-mesylate 21-acetate (IIIb). The product was obtained as needles from acetone, m.p. 182–186°, $[\alpha]^{24}D$ +120° (1.0), λ_{max} 241 mμ (ϵ 21,600), 270 mμ(sh) (ϵ 4,700); $\lambda\lambda_{max}^{CHCl_3}$ 2.85–2.90, 5.73, 5.78, 6.00 and 6.15 μ.

Anal. Calcd. for $C_{23}H_{28}O_5$: C, 71.88; H, 7.30. Found: C, 71.66; H, 7.11.

$\Delta^{4,8,(14)}$-Pregnatriene-17α,21-diol-3,20-dione 21-Acetate (XVII). (A).—By treatment with gaseous hydrogen chloride in chloroform as previously described for conversion of XIV to XV, $\Delta^{4,8(14),9(11)}$-pregnatriene-17α,21-diol-3,20-dione 21-acetate (XVI) was converted to $\Delta^{4,8(9),14}$-pregnatriene-17α,21-diol-3,20-dione 21-acetate, m.p. 188–192°, $[\alpha]^{24}D$ +143°, λ_{max} 242 mμ (ϵ 37,400); $\lambda\lambda_{max}^{CHCl_3}$ 2.90–2.95, 5.73(sh), 5.78, 6.00 and 6.1(sh) μ.

Anal. Calcd. for $C_{23}H_{28}O_5$: C, 71.88; H, 7.30. Found: C, 71.64; H, 7.56.

(B).—The method which employed 60% perchloric acid for conversion of II to III converted 17α-hydroxy-$\Delta^{8(9)}$-dehydrocorticosterone 21-acetate (XXIV) exclusively to $\Delta^{4,8(9),14}$-pregnatriene-17α,21-diol-3,20-dione 21-acetate (XVII) identical with material of method A by mixed m.p. and by ultraviolet spectrum.

8ξ,14ξ-Oxido-Δ^4-pregnene-17α,21-diol-3,11,20-trione 21-Acetate (XIX). (A) By Perbenzoic Acid Oxidation of the Dienedione IV.—A solution of 801 mg. (2.0 millimoles) of the dienedione IV in 20 ml. of chloroform was treated with 17.25 ml. of 0.348 *M* perbenzoic acid in benzene (6.0 millimoles) and the mixture stored overnight at 0°. During this time rosettes of needles had separated and were removed by filtration and washed once with ether, once with 10% aqueous sodium thiosulfate, three times with water, three times with ether and dried *in vacuo*, wt. 756.4 mg. (90.8%), m.p. 247.5–260° dec. Extraction of the filtrate and washings was effected with ethyl acetate, the extracts were washed with water, aqueous sodium thiosulfate and aqueous sodium bicarbonate in the usual manner, and afforded an additional 115 mg. of crude product. Recrystallization of this latter sample from methanol gave 39.4 mg. (4.6%), m.p. 249–262° dec. A sample prepared for analysis by recrystallization from acetone–methanol had the m.p. 245–250° dec. (the m.p. of this oxide was dependent on the state of subdivision and the rate of heating), λ_{max} 238 mμ (ϵ 14,600); $\lambda\lambda_{max}^{Nujol}$ 2.9, 5.74, 5.80, 5.90 and 6.04 μ.

Anal. Calcd. for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78; acetyl, 10.30. Found: C, 66.10; H, 6.59; acetyl, 9.72.

(B) Pyridine–Chromium Trioxide Oxidation of 8ξ,14ξ-Oxido-Δ^4-pregnene-11β,17α,21-triol-3,20-dione 21-Acetate.—Oxidation of 126 mg. (0.30 millimole) of the oxide of III, m.p. 203–206° dec., with chromium trioxide in pyridine (see oxidation of III to IV) afforded, after one crystallization from acetone, 88 mg. of XIX, m.p. 242–254° dec., undepressed on admixture with material prepared in (A) above. The infrared spectra were identical.

The 21-alcohol of the oxide XIX was prepared as follows: a 208.2-mg. (0.50 millimole) sample of XIX in 75 ml. of dioxane was mixed with 25.0 ml. of 2.0 *N* aqueous perchloric acid and the mixture stored at 25° for 6 days; 200 ml. of saturated salt solution was added and the organic material extracted with three portions of ethyl acetate. The combined extracts were washed with water until neutral, then with saturated salt solution, filtered through anhydrous magnesium sulfate and the solvents removed to give a granular crystalline residue, weight 180 mg., m.p. 210–225° dec. Recrystallization twice from acetone–ether afforded 92.5 mg. of micro-needles, m.p. 222–226° dec., λ_{max} 240 mμ (ϵ 12,700); $\lambda\lambda_{max}^{Nujol}$ 2.78, 3.04, 5.83, 5.89 and 6.07 μ; $\lambda\lambda_{max}^{CHCl_3}$ 5.84, 5.99 and 6.1 μ.

Anal. Calcd. for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.59; H, 6.80.

In order to prove that no changes other than hydrolysis had occurred, a 30-mg. sample of the 21-alcohol was acetylated with acetic anhydride and pyridine at 25°. Within 10 minutes the solution had deposited crystalline material. After standing overnight at 25°, ice and water were added and the excess acetic anhydride decomposed. Filtration gave 31 mg. of XIX, m.p. 252–260° dec., undepressed on admixture with authentic material. Comparison of the infrared spectra confirmed the identity.

A number of unsuccessful experiments were performed in an effort to transform the oxide XIX into other products. These are briefly as follows: (1) an attempt to epimerize XIX at C-9 on special alumina[5b] gave unchanged starting material; (2) treatment with excess ozone in ethyl acetate at −80° gave 25% of unchanged XIX and an amorphous mixture of unidentified products; (3) subjection of a sample of XIX to the action of osmium tetroxide in pyridine–benzene gave 62% recovery of starting material with no other products isolated; (4) on treatment with periodic acid in dilute aqueous dioxane, XIX was recovered unchanged; and (5) heating a sample of XIX with lithium chloride in dimethylformamide for two hours at 100° again gave unchanged starting material. Under more strongly acidic conditions, however, the oxide XIX was not recovered, but no pure products could be isolated. The acidic conditions employed were as follows: (1) acetic acid, acetic anhydride and *p*-toluenesulfonic acid at 25° overnight; (2) treatment of a chloroform solution of XIX with 60% aqueous perchloric acid at 0° for 15 minutes; and (3) the action of dry hydrogen chloride in chloroform at 0° for one hour.

$\Delta^{4,6,8(14)}$-Pregnatriene-17α,21-diol-3,11,20-trione (XX).[25]—A suspension of 521 mg. (1.25 millimoles) of the oxide XIX in a mixture of 75 ml. of tetrahydrofuran and 25 ml. of methanol was placed under a nitrogen atmosphere and 4.16 ml. of 0.376 *N* sodium methoxide in methanol (1.56 millimoles) added with stirring. After 7 minutes, the solid had dissolved to give a pale purple-yellow solution and after 8 minutes, the reaction was quenched by the addition of 0.20 ml. of glacial acetic acid. The solvents were removed *in vacuo* at 25° and the sirupy residue taken up in ethyl acetate. After washing the solution with water, 5% aqueous sodium bicarbonate solution, water and saturated salt solution, it was filtered through anhydrous magnesium sulfate and the ethyl acetate removed *in vacuo* to give a yellow amorphous solid, weight 445 mg., $\lambda\lambda_{max}$ 237 mμ, $E_{1cm.}^{1\%}$ 279 and 336 mμ, $E_{1cm.}^{1\%}$ 270. Two crystallizations from acetone afforded 89.5 mg. (19%) of XX, m.p. 225–235° dec., λ_{max} 337 mμ (ϵ 25,800); $\lambda\lambda_{max}^{Nujol}$ 3.0, 5.82, 6.1 and 6.26 μ; $\lambda\lambda_{max}^{CHCl_3}$ 3.0, 5.82, 6.02 and 6.23 μ.

Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.49; H, 7.04.

A sample of the trienedione XX prepared above was acetylated with acetic anhydride and pyridine at 25° overnight. Isolation in the usual manner gave the **21-acetate** of XX, m.p. 218–225° dec., λ_{max} 334 mμ (ε 27,500), $\lambda\lambda_{max}^{CHCl_3}$ 3.0, 5.72(sh), 5.79, 6.01 and 6.22 μ; $\lambda\lambda_{max}^{Nujol}$ 2.95, 5.74, 5.80, 5.85, 6.0 and 6.23 μ.

Anal. Calcd. for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58. Found: C, 69.06; H, 6.83.

The disposition of double bonds in the trienedione XX was ascertained by reduction with lithium aluminum hydride. A 40-mg. (0.122 millimole) sample of XX in 10 ml. of tetrahydrofuran was added over 20 minutes to a stirred solution of 106 mg. (2.8 millimoles) of lithium aluminum hydride in 10 ml. of tetrahydrofuran. The addition was carried out in an atmosphere of nitrogen. After heating under reflux for 1.5 hours, the reaction was worked up by adding ethyl acetate, saturated aqueous sodium sulfate and anhydrous magnesium sulfate. Filtration and removal of the solvents afforded a gummy residue. This was dissolved in ethyl acetate, the solution washed twice with water, once with saturated salt solution, dried, filtered and the solvent removed *in vacuo* to give 20.9 mg. of amorphous solid XXI, λ_{max} 284.5 mμ (ε 19,150).

Hydrogenation of 132 mg. (0.37 millimole) of XX over 50 mg. of palladium-on-barium sulfate in 10 ml. of methanol also was carried out. The absorption of hydrogen continued at a steady rate until 18.4 ml. had been consumed (0.74 millimole or 2 moles/mole). The solution was filtered and the methanol removed *in vacuo*. Acetylation with acetic anhydride in pyridine at 60–70° for one hour followed by isolation in the usual manner gave 160 mg. of amorphous solid exhibiting only end absorption in the ultraviolet. This product was chromatographed on neutral alumina and the fractions eluted with 20 and 30% chloroform in benzene were combined, weight 104 mg. Two crystallizations, from ether–Skellysolve **B** and then from acetone–ether, gave 14.5 mg. of crystals, m.p. 193–203° with previous softening; $\lambda\lambda_{max}^{CHCl_3}$ 2.76, 2.84–2.97, 5.72(sh), 5.79(sh) and 5.83 μ. A mixture with the $\Delta^{8(14)}$-enedione XXII was depressed.

$\Delta^{8(14)}$-Pregnene-17α,21-diol-3,11,20-trione 21-Acetate (XXII). (A) By Hydrogenation of IV.—A solution of 400.5 mg. (1.0 millimole) of the dienedione IV in 20 ml. of methanol was stirred in a hydrogen atmosphere at 25° and atmospheric pressure in the presence of 100 mg. of 5% palladium-on-barium sulfate. In 1.5 hours, the absorption of hydrogen ceased, 23.2 ml. having been taken up. The solution was filtered and the solvent removed *in vacuo* to give an amorphous residue. This material exhibited only end absorption in the ultraviolet. One recrystallization from ethyl acetate afforded 330 mg. of XXII, m.p. 196–198.5°, $\lambda\lambda_{max}^{Nujol}$ 2.85, 5.73, 5.79 and 5.86 μ; $[\alpha]^{25}D$ +306 (0.8). This material was identical by mixed m.p. and infrared spectrum with material prepared by oxidation of XIII (see below).

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.37; H, 7.37.

A 100-mg. (0.25 millimole) sample of XXII in 2.5 ml. of tetrahydrofuran and 1.5 ml. of methanol was placed under a nitrogen atmosphere and treated with 4.64 ml. of 0.118 *N* sodium methoxide in methanol (1.10 millimoles). The amber solution was held at 23° for 1 hour, then neutralized with 0.2 ml. of glacial acetic acid. The residue on concentration to dryness *in vacuo* was treated with 1.0 ml. of acetic anhydride and 2.0 ml. of pyridine and allowed to stand overnight at room temperature (23°). After concentration to dryness *in vacuo* 101 mg. of yellow crystalline material was obtained. Paper chromatographic analysis and the infrared spectrum showed the material to be essentially unchanged. One recrystallization from ethyl acetate–ether yielded colorless needles which did not depress the m.p. of starting material.

A sample of XXII was dissolved in chloroform and gaseous hydrogen chloride was bubbled through the solution for 1 hour at room temperature. The product after concentration to dryness showed an ultraviolet spectrum unchanged from that of starting material.

A sample of XXII together with 3 equivalents of lithium chloride were dissolved in dimethylformamide. The mixture was heated on the steam-bath under nitrogen for 2 hours, then cooled to room temperature, diluted with water and saturated salt solution and the product obtained by filtration. The product, m.p. 188–191°, did not depress the m.p. of starting material. The ultraviolet spectra of the product and the starting material were identical.

(B) By Oxidation of XIII.—To a solution at 0° consisting of 0.404 g. (1.0 millimole) of $\Delta^{8(14)}$-pregnene-11β,17α,21-triol-3,20-dione 21-acetate (XIII) in 4 ml. of pyridine was added dropwise with cooling 0.333 g. of chromium trioxide (3.33 millimoles) dissolved in 0.33 ml. of water and 0.50 ml. of pyridine. The mixture was allowed to stand for 18 hours at room temperature. After dilution with 80 ml. of water and 20 ml. of ethyl acetate the mixture was filtered. The residue was washed with ethyl acetate and the aqueous phase extracted with ethyl acetate. The ethyl acetate phase was washed successively with water, 0.5 *N* phosphoric acid and water, then filtered through anhydrous magnesium sulfate. The crude product after concentration *in vacuo* amounted to 0.361 g. (90%). Two recrystallizations from ethyl acetate–ether yielded a product identical with that of method A by m.p. 194–198°, mixed m.p., infrared spectrum and paper-strip comparison.

$\Delta^{8(9)}$-14-Isopregnene-17α,21-diol-3,11,20-trione 21-Acetate (XXIII). (A) By Hydrogenation of the Dienedione VI.—A solution of 800 mg. (2.0 millimoles) of VI in 40 ml. of methanol was hydrogenated as described above in the presence of 100 mg. of 5% palladium-on-barium sulfate. The absorption of hydrogen ceased in *ca.* 15 minutes, 49 ml. having been taken up. After filtration to remove the catalyst, the solvent was removed *in vacuo* to yield a colorless crystalline residue, weight 815 mg., m.p. 177–181°. One recrystallization from ethyl acetate–ether gave 750 mg. (93%) of XXIII, m.p. 178–181°, λ_{max} 248 mμ (ε 8,450), $\lambda\lambda_{max}^{CHCl_3}$ 2.85, 2.95, 5.73, 5.79, 5.83, 6.0 and 6.18 μ.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.56; H, 7.49.

(B) By Isomerization of the Enedione XI.—Treatment of 100 mg. of XI with anhydrous hydrogen chloride in ethanol-free chloroform at 0° for one hour as described above for the conversion of V to VI gave 97 mg. of crude product, m.p. 161–190°. Crystallization from ethyl acetate–ether gave 30 mg., m.p. 198–208°, which on recrystallization had the m.p. 206–213°, undepressed on admixture with the starting enedione XI. The mother liquor of the 30 mg. sample on concentration and seeding with XXIII prepared by hydrogenation afforded 17 mg. of crystals, m.p. 174–180°, undepressed on admixture with authentic XXIII and possessing an identical infrared spectrum.

A sample of the low-melting, less polar form of XI[24] described above gave essentially the same results on isomerization with hydrogen chloride in chloroform.

The enedione XXIII was stable to the action of hydrogen chloride in chloroform at 0° for one hour, the conditions under which it is formed from XI.

(C) By Isomerization of the Enedione XXII.—Isomerization of XXII with hydrogen bromide–lithium chloride–dimethylformamide exactly as described above for the conversion of IV to VI (method C) gave on dilution with water essentially pure XXIII, m.p. 176–178°, λ_{max} 248 μ (ε 8,400). The m.p. was undepressed on admixture with material prepared by hydrogenation and the infrared spectra were identical. The above isomerization occurred also when the lithium chloride was omitted.

$\Delta^{4,8(9)}$-Pregnadiene-11β,17α,21-triol-3,20-dione 21-Acetate (17α-Hydroxy-$\Delta^{8(9)}$-dehydrocorticosterone 21-Acetate) (XXIV).—A solution consisting of 62.0 g. (0.128 mole) of 9α-bromo-17α-hydroxycorticosterone 21-acetate (I, X = Br) and 400 ml. of tetrahydrofuran was added to 400 ml. of *N*-ethylpiperidine and the mixture refluxed for 7.5 hours. The mixture was concentrated *in vacuo* to about 450 ml., filtered and the precipitate washed with three 50-ml. portions of distillate. The precipitate was then washed with water until free of bromide ion; the water washes were caught separately and discarded. The residue amounting to 39.0 g. (75.5%) was chiefly 9β,11β-oxido-Δ^4-pregnene-17α,21-diol-3,20-dione 21-acetate (II), as determined by m.p., mixed m.p. and paper-strip analysis.

The filtrate upon concentration to dryness *in vacuo* yielded 16.74 g. of a steroid mixture. Of this mixture, a 5.00-g. aliquot was chromatographed on neutral alumina. Fractions were eluted with mixtures of benzene and chloroform and the composition of these determined by paper chromatography. $\Delta^{4,8(9)}$-Pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate (XXIV) shows an R_f of 0.09 (benzene–formamide). In this system, cortisone 21-acetate and 9β,-

11β-oxido-Δ^4-pregnene-17α,21-diol-3,20-dione 21-acetate (II) show R_f 0.33 and 0.50, respectively. Fractions amounting to 2.04 g., rich in product were rechromatographed on neutral alumina to yield 0.667 g. of purified compound, m.p. 195–215° dec. Treatment with decolorizing charcoal and three crystallizations from acetone–hexane yielded analytical material, m.p. 213–216° dec., $[\alpha]^{24}D$ +219° (1.0), λ_{max} 238 mμ (ε 16,400); $\lambda\lambda_{max}^{Nujol}$ 2.82, 2.89, 5.81, 6.00 and 6.19 μ.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.69; H, 7.51. Found: C, 68.65; H, 7.58.

$\Delta^{4,8(9)}$-Pregnadiene-11β,17α,21-triol-3,20-dione 11β,21-Diacetate (XXIVa).—A solution consisting of 102.5 mg. (0.255 millimole) of $\Delta^{4,8(9)}$-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate (XXIV), 1 ml. of pyridine and 1 ml. (10.6 millimoles) of acetic anhydride was allowed to stand for 1 week at room temperature (24°). The mixture was diluted with 20 ml. of water, filtered and the residue washed with water. The precipitate amounting to 81.5 mg. (71.4%) was recrystallized from acetone–hexane to yield 65.4 mg. (57.3%) of product, m.p. 201–204°, $[\alpha]^{26}D$ +224° (1.0), λ_{max} 237 mμ (ε 16,000); $\lambda\lambda_{max}^{Nujol}$ 2.96, 5.79, 5.97 and 6.13 μ.

Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.52; H, 7.51.

$\Delta^{4,7,9(11)}$-Pregnatriene-17α,21-diol-3,20-dione 21-Acetate (XXV).—To a solution of 304 mg. (0.756 millimole) of 17α-hydroxy-$\Delta^{8(9)}$-dehydrocorticosterone 21-acetate (XXIV) and 3.75 ml. of pyridine cooled to 0° was added dropwise with cooling 0.75 ml. (10 millimoles) of methanesulfonyl chloride. The mixture was allowed to stand at 0° for 24 hours. To the mixture was added 10 g. of ice and after 15 minutes the product was extracted with ethyl acetate. Concentration of the washed, dried extract yielded 189 mg. (64.9%) of crude triene. The crude material was treated with decolorizing charcoal and crystallized twice from acetone–hexane to yield 85 mg. (29%) of pale yellow needles, m.p. 199–203°, $[\alpha]^{27}D$ +236° (1.0); $\lambda\lambda_{max}$ 242.5 mμ (ε 26,200), 237.5(sh) and 250(sh) mμ (ε 24,900 and 22,100), $\lambda\lambda_{max}^{CHCl_3}$ 2.9, 5.74(sh), 5.78, 6.0 and 6.12 μ.

Anal. Calcd. for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.53; H, 7.31.

Reduction of XXV with lithium aluminum hydride in tetrahydrofuran yielded an amorphous product; $\lambda\lambda_{max}$ 237, 244 mμ (ε 7,780, 8,510), 251(sh) mμ (ε 6,130).

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[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, INDIAN ASSOCIATION FOR THE CULTIVATION OF SCIENCE]

Synthetic Studies in Resin Acids. II[1]

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The conversion of $>C=O$ to $>C<^{CH_3}_{CO_2H}$ has been studied for the case of cyclohexanone and 10-methyldecalone. Two successful methods were achieved for cyclohexanone and one of these was also effective for the decalone system. The second procedure, involving action of methylmagnesium iodide on ethyl 10-methyldecalidene-1-cyanoacetate, failed because reduction rather than addition occurred. The significance of the above syntheses for the preparation of diterpenoid resin acids is noted.

In the synthesis of compounds related to diterpenoid resin acids, the conversion of the tricyclic ketones[1,4] to the corresponding *gem*-methylcarboxylic acids, is of considerable importance. The purpose of the present investigation was to seek suitable means for this conversion, using cyclohexanone and 10-methyldecalone as model compounds. In this communication the essential steps for two procedures, which were successful for the synthesis of 1-methyl-1-carboxy-cyclohexane VII are described. A recent publication,[5] which appeared subsequent to our preliminary communication[6] embodying these methods, has also supported these results.

In procedure I, ethyl cyclohexane-1-carbethoxy-1-acetate obtained from the dicyano-ester[7] was the starting material. The silver salt of the monoester IV afforded the bromoester V on treatment with bromine. Hunsdiecker degradation promised to be a useful route to rather inaccessible bromides of the neopentyl type and hence it has been utilized successfully to build up the quaternary methyl group. The bromide V on reduction with zinc and acetic acid yielded VI, from which VII was obtained on alkaline hydrolysis. VII was further characterized by conversion to its amide.[8] In procedure II, VIII was obtained through the conjugate addition[9] of methyl Grignard reagent to III in the presence of cuprous iodide.[10] The controlled hydrolysis of VIII and pyrolysis of the acidic product yielded the nitrile IX. Attempts at acidic or alkaline hydrolysis of the nitrile were unsuccessful. The nitrile IX was then allowed to react with phenylmagnesium bromide leading to X, which on further reaction with the same reagent gave a mixture of the corresponding carbinol and the dehydrated product. This mixture was directly oxidized to VII.

With the idea that these two procedures in the case of unsymmetrical ketones should lead to dif-

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(3) Communications regarding this paper may be sent to this author.

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