acetic acid added slowly during the course of 0.5 hour keeping the temperature below 15°. After stirring for 100 minutes at 20°, the mixture was poured into water and the steroid extracted with ether. The ether was washed well with water only and evaporated *in vacuo* with stirring to a heavy, gummy, yellowish residue. This was dissolved in 125 ml. of *t*-butyl alcohol, 125 ml. of 5% aqueous sodium bicarbonate was added and the mixture mechanically shaken overnight. On dilution with water and addition of ether 3.1 g. of crystalline material separated immediately. Evaporation of the ethereal layer and crystallization from ether gave 6.8 g. more of crystalline 3-acetoxy product. The over-all yield without regard to recovered starting material was 51%; the yield corrected for recovered starting material, 65%. The m.p. determined at a moderate heating rate was 185–191°; however, on slow heating a double melting was observed. The flattened needles melted at 173.5°, solidified to quadrilateral forms which reliquefied at 203–205° giving a doubly refracting melt when observed through polarizing filters, $[\alpha]^{25}D$ −26°; $\lambda^{227}_{max.}$ mμ 9880, log 4.0; $\lambda_{max.}$ 1677 cm.$^{-1}$ (CS_2).

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.00, 70.91; H, 8.15, 7.83.

An aliquot containing 1 g. of the gummy yellowish residue described above was dissolved in 25 ml. of *t*-butyl alcohol, 1 g. of KOH in 1 cc. of H_2O was added and the mixture was stirred for 3 hours at 25°. The mixture of products was isolated with ether, washed with 5% hydrochloric acid, 5% sodium bicarbonate, dried and evaporated. The residue was a black tar yielding no crystallizable matter.

Another 1-g. aliquot in benzene solution was adsorbed on activated alumina overnight. Chloroform eluted 0.22 g. and methanol eluted 0.78 g. of glassy materials showing only moderate infrared absorption near 1677 cm.$^{-1}$ These materials could not be crystallized.

3β-Acetoxy-13α-hydroxy-16α,17α-epoxy-12-carboxy-12,13-*seco*-allopregnane-20-one 12,13-Lactone (IV). (a) From II.—From Δ 16-20-ketone II, 9.8 g., in 660 ml. of methanol was treated with 37 ml. of 30% hydrogen peroxide at 10° and 4.1 g. of sodium hydroxide in 21 ml. of water added. The mixture was let stand overnight at 10°, diluted with 500 ml. of water containing 3.74 g. of hydrochloric acid, and the solution repeatedly extracted with chloroform until test evaporations of the chloroform showed no residue. A sample of the white crystalline residues in the last extracts was identified as the oxide of the 3β-acetoxy derivative of the 13α-hydroxy-12-carboxylic acid produced by the partial saponification of the lactone, *viz.*, 3β-acetoxy-16α,17α-epoxy-13α-hydroxy-12-carboxy-12,13-*seco*-allopregnane-20-one (III), m.p. 210–213.5°, $[\alpha]^{25}D$ +38.4° (MeOH).

Anal. Calcd. for $C_{23}H_{34}O_7$: C, 65.38; H, 8.11. Found: C, 65.26; H, 8.12.

Treatment of the combined extracts with pyridine–acetic anhydride overnight at room temperature gave ring closure to the lactone IV in 38% yield. The product m.p. 265–267° gave hexagonal scales from ether, m.p. 269–270°, after transition to octagonal forms, $[\alpha]^{25}D$ +17.8°.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.07; H, 8.03.

(b) From 3β-Acetoxy-16-allopregnene-12,20-dione (V).—Two grams of V, m.p. 179–180, *i.e.*, 5.37 millimoles, was mixed at 5° with 44.32 ml. of chloroform containing 21.48 millimoles of perbenzoic acid. One milliter of 10% sulfuric acid in acetic acid was added and the mixture let stand for two weeks. The chloroform was washed with dilute sodium hydroxide and with water and evaporated. The residue was triturated with ether whereupon 190 mg. of a crystalline precipitate formed melting over 300° which was filtered off. The mother liquors deposited 350 mg. of a white crystalline product m.p. 231–241°, which on recrystallization once from acetone melted at 266–270° and had an infrared spectrum essentially identical with that of the preparation described above.

3β-Acetoxy-13α-hydroxy-12,13-*seco*-allopregnane-20-one-12-carboxylate 12,13-Lactone (VI).—Two grams of II in 75 cc. of tetrahydrofuran were shaken with 1 g. of 5% palladium-on-carbon catalyst at three atmospheres for six hours. The catalyst was filtered and washed with acetone. The solvents were evaporated and the resulting glassy residue was crystallized from ether to give 0.4 g. of crystalline material, m.p. 178–183°. This product on slow crystallization from acetone gave large hexagonal tablets having a double melting point 172.5°, 184–189°, $[\alpha]^{25}D$ +60.4°.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.54; H, 8.65.

Acknowledgment—The authors wish to thank Harriet Cooper Amsterdam for technical assistance, C. L. Ogg, Ruth B. Kelley and Dolores McClelland for microanalyses, C. R. Eddy and C. Fenske for infrared spectra.

PHILADELPHIA 18, PENNA.

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Steroidal Sapogenins. XXII.[2] Conversion of Hecogenin Acetate to a Hecololactone Derivative with the Adrenal Cortical Hormone Side Chain *via* Allopregnane-3β,17α,21-triol-12,20-dione Diacetate

BY EDWARD S. ROTHMAN AND MONROE E. WALL

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Allopregnane-3β,17α-diol-12,20-dione 3-acetate is described as having physical properties different from those previously reported. This material was in turn converted to allopregnane-3β,17α,21-triol-12,20-dione 3,21-diacetate, a diketone, which suffers oxidative attack by perbenzoic acid only at the C-12 carbonyl group to form 12-carboxy-12,13-seco-allopregnane-3β,13α,17α,21-tetrol-20-one 12,13-lactone 3,21-diacetate.

In the preceding article of this series[2] the direct degradation of hecololactone acetate to the *seco*-allopregnene derivative 12-carboxy-12,13-*seco*-16-allopregnene-3β,13α-diol-20-one 12,13-lactone 3-acetate was described. The *seco*-allopregnene product presented difficulties in subsequent transformations. In particular the attempted opening of the epoxide ring of its 16α,17α-epoxy derivative did not lead to isolation of crystalline products. For this reason, an alternative approach to our problem of synthesis of hecololactone types having the dihydroxyacetone side chain was considered. The results of this approach involving the lactonization of the C-ring as the *final* reaction step are presented here.

Starting with 16-bromoallopregnane-3β,17α-diol-12,20-dione 3-acetate (I), a compound first synthesized by Mueller, Stobaugh and Winniford,[3] we

(1) A laboratory of the Eastern Utilization Research Branch, Agricultural Research Service, United States Department of Agriculture. Article not copyrighted.

(2) Paper XXI, E. S. Rothman and M. E. Wall, THIS JOURNAL, **77**, 2228 (1955).

(3) G. P. Mueller, R. E. Stobaugh and R. S. Winniford, *ibid.* **75**, 4888 (1953).

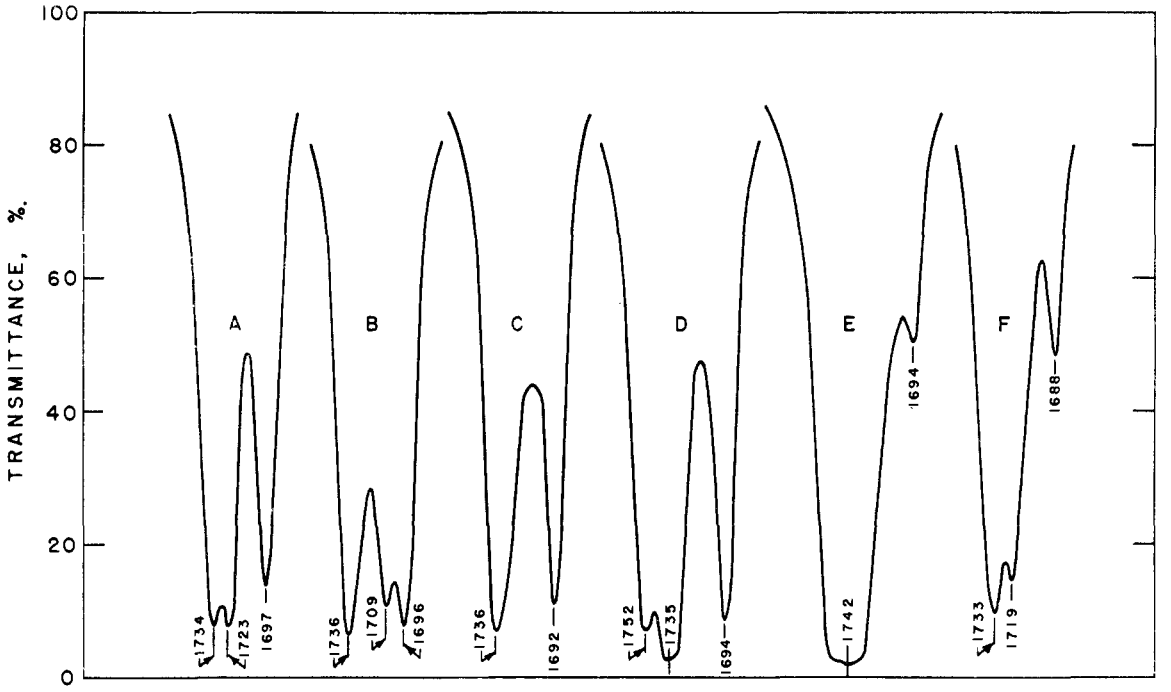


Fig. 1.—Characteristic ketone and acetate bands of 12-keto and C-ring lactone steroids, CS_2 solution, 10 g./l., 1 mm. cell: A, 16-bromoallopregnane-3β,17α-diol-12,20-dione 3-acetate (I); B, allopregnane-3β,17α-diol-12,20-dione 3-acetate (II); C, 21-bromoallopregnane-3β,17α-diol-12,20-dione 3-acetate (III); D, allopregnane-3β,17α,21-triol-12,20-dione 3,21-diacetate (IV); E, 12-carboxy-12,13-seco-allopregnane-3β,13α,17α,21-tetrol-20-one 12,13-lactone 3,21-diacetate (V); F, 16-bromoallopregnane-3β,17α-diol-20-one 3-acetate.

obtained by debromination using Raney nickel–alcohol, and also using palladium–calcium carbonate-catalyzed hydrogenolysis, a substance that is presumably allopregnane-3β,17α-diol-12,20-dione 3-acetate (II). The melting point and rotation values differ, however, from those reported for this compound by Mueller, *et al.*[4] The variability in their results and ours regarding the nature of the products obtained in this debromination step may be due to differences in the preparation of the Raney nickel.[5] With W-7 Raney nickel we observed no debromination whatsoever. Use of Adkins Raney nickel[6] gave a mixture of several substances including allopregnane-3β-ol-12,20-dione 3-acetate and 16α,17α-epoxy-allopregnane-3β-ol-12,20-dione 3-acetate, but the desired product II predominated. In our hands, debromination of I by means of zinc and acetic acid did not give the desired product but gave instead about a 50% yield of crystalline 16α,17α-epoxyallopregnane-3β-ol-12,20-dione 3-acetate. The mother liquors did not crystallize but had an infrared spectrum essentially identical with that of allopregnane-3β-ol-12,20-dione 3-acetate.[7] The use of 5% palladium-on-charcoal and hydrogen gave no debromination; however, the use of palladium-on-calcium carbonate[5,8] converted I in 96% yield to II with no side-reaction interference. The product, m.p. 130–131°, α +43 ($CHCl_3$), shows a *strong* carbonyl interaction band[9] *vide infra* (see Fig. 1B). This result is in agreement with other findings that 17α-hydroxy-12,20-diketones show a strong interaction peak near 1693 $cm.^{-1}$, *e.g.*, see Fig. 1 A, C, D, E, F.

This interaction may be so complete that no absorption band may occur between 1700 and 1725 $cm.^{-1}$ even though C-12 carbonyl is present, *e.g.*, see Fig. 1C.[10]

Using II, m.p. 130–131°, as starting material we obtained by monobromination and acetolysis allopregnane-3β,17α,21-triol-12,20-dione 3,21-diacetate. This substance, in the presence of sulfuric acid catalyst, consumed in about 70 hours one equivalent of perbenzoic acid to form 12-carboxy-12,13-*seco*-allopregnane-3β,13α,17α,21-tetrol-

(4) After our work was completed there came to our attention a recent publication by W. J. Adams, D. N. Kirk, D. K. Patel, V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.*, 2209 (1954), in which they describe the independent synthesis of this compound and other intermediates in an attempt to prepare 4-allopregnene-17α,21-diol-3,12,20-trione. The debromination product of these workers, m.p. 131–133°, α + 55° ($CHCl_3$), is apparently similar to our product, m.p. 130–131°, α +43° ($CHCl_3$), and non-identical with the compound described by Mueller, *et al.*

(5) W. J. Adams, D. K. Patel, V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.*, 1825 (1954), also report erratic results with Raney nickel.

(6) H. Adkins, "Reactions of Hydrogen," Univ. of Wisconsin Press, Madison, Wis., 1937, p. 21.

(7) This substance was the main constituent of the mixture obtained by Stobaugh and Mueller in some experiments (private communication).

(8) F. B. Colton, W. R. Nes, D. A. Van Dorp, H. L. Mason and E. C. Kendall, *J. Biol. Chem.*, **194**, 235 (1952); J. Romo, A. Zaffaroni, J. Hendricks, G. Rosenkranz, C. Djerassi and F. Sondheimer, *Chem. & Ind.*, 783 (1952).

(9) R. N. Jones, P. Humphries, F. Herling and K. Dobriner, THIS JOURNAL, **74**, 2820 (1952). Note especially their Fig. 1 showing a *weak* 1693 $cm.^{-1}$ band.

(10) Molecular models of 21-bromoallopregnane-3β-17α-diol-12,20-dione 3-acetate indicate the possibility of hydrogen bonding linking the C-17 hydroxyl group to the C-21 bromine atom. In such a case the two ketone groups are held in close contact and the dicarbonyl interaction might be expected to be at maximum.

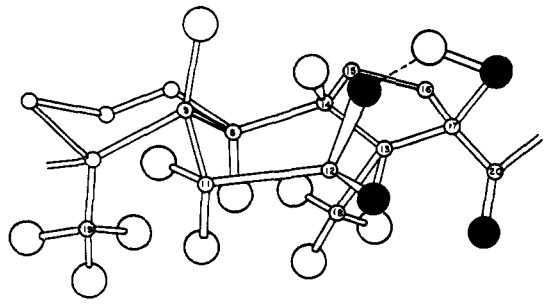


Fig. 2.—Chair-like, A-form of 7-membered ring C lactone, 1/4 view from alpha face.

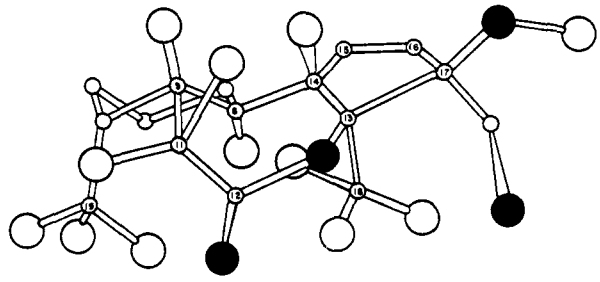


Fig. 3.—Boat-like, B-form of 7-membered ring C lactone, 1/4 view from alpha face. The oxygen (black) and hydrogen atoms (white) are deliberately made larger than the carbon atoms in order to best exemplify the stereochemical features.

20-one 12,13-lactone 3,21-diacetate, V. The product contained bonded hydroxyl and showed bands in the infrared near 3480 and 3570 cm.$^{-1}$, but did not contain C-12 carbonyl since there was no absorption band between 1700 and 1725 cm.$^{-1}$ and only a weak band near 1695 cm.$^{-1}$ (*vide infra*). The intensity of the band near 1240 cm.$^{-1}$ was of the order of that expected for a diacetate,[11] and elementary analysis showed the presence of an additional oxygen atom and was in accord with the above formulation.

The fact that oxidation at C-20 did not occur is noteworthy. Leeds, Fukushima and Gallagher[12] found that the C-20 group of allopregnane-3β,17α-diol-20-one acetate (Reichstein's "L" acetate) was attacked in two days' time by perbenzoic acid to form isoandrosterone acetate even in the absence of acidic catalyst. If toluenesulfonic acid was present the 17-keto group of the product, isoandrosterone acetate, was attacked further to produce isoandrololactone acetate. Antonucci, Bernstein, *et al.*, have reported evidence that the C-20 group of compounds with the adrenal cortical side chain is hindered markedly by the 21-acetoxy group.[13] On this basis, in terms of the hindering effect of the C-21 acetoxy group, the failure of the C-20 group to undergo peracid oxidative cleavage is understandable. The procedure of selective oxidation of C-12 ketones in the presence of the acetylated dihydroxyacetone side chain should enable the preparation of other corticoid hormone analogs in which the C-11 oxygen function is replaced by the ϵ-lactone C-ring. Such experiments are currently in progress and will be reported at a later date.[14]

The stereochemistry of the seven-membered C-ring is interesting. Fisher–Taylor–Hirschfelder models can be constructed in two forms. In form A, see Fig. 2, the C=O bond of the lactone carbonyl group is parallel to the angular methyl group bonds at C-18 and C-19 and is perpendicular to the general plane of the rings. It may then be termed "axial"[15] and, further, "alpha," since it projects below the general plane of the rings. The other construction, B, see Fig. 3, also shows an "axial" C=O bond, but in this case the bond is "beta" oriented. Form A (Fig. 2) seems to be less strained and resembles cyclohexane chair forms; while form B, Fig. 3, has many of the properties of cyclohexane boat forms, *e.g.*, C-8 and C-12 are in close juxtaposition recalling the close approach of C-1 and C-4 atoms in cyclohexane boat forms.

It is significant that the 12,20-diketones I, II, III and IV, Fig. 1A, B, C and D, all show a *strong* 1693 cm.$^{-1}$ band[9] rather than the *weak* band noted by Jones, *et al.*, in eleven unsubstituted C-ring compounds bearing the dihydroxyacetone side chain. This strong band is presumably due to the influence of the C-12 ketone function on the C-17 hydroxy-C-20-ketone system since the band is absent in 12,20-diketones lacking 17-hydroxyl. However, with the replacement of the 12-ketone function with the lactone function the 1693 cm.$^{-1}$ band becomes weak again as in the compounds described by Jones, and the spectrum shows two bonded hydroxyl bands at about 3570 and 3480 cm.$^{-1}$ [16]

Examination of molecular models shows that the C-12 lactone carbonyl might conceivably hydrogen-bond with the 17α-hydroxyl in form A. Such bonding can be similarly demonstrated to be impossible in form B (compare Figs. 2 and 3). The infrared spectrum shows that the hydroxyl *is* bonded. Furthermore, models show that the C-20 carbonyl oxygen atom and C-12 lactone carbonyl oxygen atom *cannot contact and interact* either in form A or in form B so that in the lactone series the C-20 carbonyl bonds only weakly[17] with the C-17 hydroxyl group or with the C-21 acetoxy group. The weak peak at 1693 cm.$^{-1}$ in V, see Fig. 1E, probably mirrors this condition of only

(11) It will be recalled, *cf.* E. S. Rothman, M. E. Wall and C. R. Eddy, THIS JOURNAL, **76**, 527 (1954), that the intensity of the 1243 cm.$^{-1}$ band of hecololactone was unaffected by the lactone function and was of the order expected for a monoacetate rather than of a diester.

(12) N. S. Leeds, D. K. Fukushima and T. F. Gallagher, THIS JOURNAL, **76**, 2265 (1954).

(13) R. Antonucci, S. Bernstein, M, Heller, R. Lenhard, R. Littell and J. Williams, *J. Org. Chem.*, **18**, 70 (1953), found that although cortisone formed a 3,20-bis-dioxolane derivative, cortisone acetate formed only a 3-monodioxolane derivative. They observed further that the 3,20-bis-dioxolane derivative of cortisone after *subsequent* acetylation could be selectively cleaved to give the 20-monodioxolane derivative.

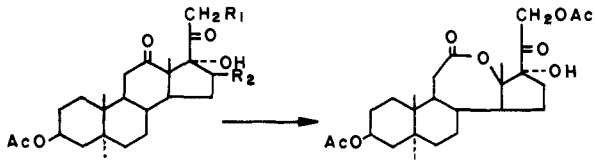
(14) Compound V, the analog of Reichstein's substance D is being tested for physiological activity.

(15) The quotation marks are preserved since these terms are generally used for substituent groups linked to tetrahedral carbon atoms. In the C-ring of hecogenin (chair-form) the C=O bond projects below the plane of the ring in a manner much like the seven-membered ring in Fig. 2. Hecogenin with a boat-form C-ring similarly resembles Fig. 3 strongly.

(16) *Cf.* reference 9 especially p. 2826.

(17) Bonding would be difficult since the chelate ring would consist of four atoms plus a hydrogen atom and would presumably be strained, as in the case of the 12-desoxy compounds described by Jones.[9]

minor bonding effects at C-20.[18] For these reasons we believe that the lactone V exists essentially in the chair-like form A as in Fig. 2.



I R_1 = H ; R_2 = Br V

II R_1 = H ; R_2 = H

III R_1 = Br; R_2 = H

IV R_1 = OAc; R_2 = H

Experimental

All melting points were taken on the Kofler hot-stage and are corrected. Rotations were determined in $CHCl_3$ unless otherwise noted.

16α,17α-Epoxyallopregnan-3β-ol-12,20-dione Acetate.—The general conditions of Mueller, *et al.*,[3] were used but a modification of the workup raised the yield from the reported 50 to an 87% yield; thus 42.5 g. of the crude Δ^{16}-20-ketone gave 14.3 g. of the epoxide acetate, m.p. 229–231°, identified by comparison of its infrared spectrum with that of the authentic compound; however, neutralization of the filtrate with dilute hydrochloric acid, extraction with ether, *reacetylation*, and crystallization from ether gave an additional 24.3 g. of similar material. The total yield was 38.6 g.

16-Bromoallopregnane-3β,17α-diol-12,20-dione 3-Acetate (I).—Mueller's conditions[3] were modified by prolonging the reaction time to 16 hours and increasing the quantity of hydrobromic acid twofold. No unreacted oxide contaminated the crude product which separated from small volumes of ether as massive, hexagonal prisms, m.p. 159–162°, yield 88%.

Allopregnane-3β,17α-diol-12,20-dione 3-Acetate (II). Method (a).—A sample of 16-bromoallopregnane-3β,17α-diol-12,20-dione 3-acetate, 390 mg., m.p. 173–176°, in 70 ml. of methanol and 7 ml. of water, was shaken with a commercial 10% palladium-on-calcium carbonate catalyst for five hours. The catalyst was filtered and the methanol concentrated, whereupon 312 mg. (96% yield) of crystalline product, m.p. 127–130°, separated. Recrystallization from petroleum ether raised the m.p. to 130–131°, $[\alpha]^{25}D$ +43° ($CHCl_3$). *Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8,78. Found: C, 71.05; H, 8.76. Bromination of this material gave the same 21-bromo derivative as the bromination of the Raney nickel product.

Method (b).—A sample of 16-bromoallopregnane-3β-17α-diol-12,20-dione 3-acetate, 2.07 g. in 75 ml. of ethanol, was refluxed with Adkins Raney nickel (12 g.) according to the procedure of Mueller, *et al.*[3] On filtering and evaporating the ethanol a crystalline residue, m.p. 114–158°, low in halogen (Beilstein test) was obtained. The residue, crystallized from ether, gave a mass of blunt, pointed clusters of crystals, m.p. 144–159°. A crystallization from ether raised the m.p. to 170–179°. Further recrystallization from methanol gave large pointed hexagonal prisms, m.p. 183–185° (some few surviving at 188°). This insoluble material was identified as allopregnane-3β-ol-12,20-dione 3-acetate.

The infrared spectrum showed no hydroxyl bands. The spectrum of the mother liquor fraction which contained II, 1.69 g., showed the presence of hydroxyl at 3520 $cm.^{-1}$ and the characteristic strong carbonyl interaction band at 1693 $cm.^{-1}$ and was essentially identical to that of the material prepared in part a.

(18) Mueller, *et al.*,[3] have discussed dicarbonyl interaction effects in accounting for the unusual 227 mμ ultraviolet absorption maximum of 16-allopregnene-3β-ol-12,20-dione acetate. This same value is obtained with the analogous lactonic compound 12-carboxyl-2,13-seco-16-allopregnene-3β,13α-diol-20-one 12,13-lactone 3-acetate.[2] Since the side chain in the latter compound is copolanar with the D-ring there is closer approach between the C-12 lactonic carbonyl and C-20 carbonyl than is permitted in V and the interaction again is possible.

21-Bromoallopregnane-3β,17α-diol-12,20-dione 3-Acetate (III).—To 1 g. of allopregnane-3β,17α-diol-12,20-dione 3-acetate in 25 ml. of carbon tetrachloride was added dropwise and with stirring 10.43 ml. of a solution of 409 mg. of bromine in carbon tetrachloride. The mixture was chilled initially but the rate of bromine uptake was so slow that the mixture was allowed to warm to room temperature. The colorless mixture was decanted from traces of a brown gum coating the reaction flask, was washed well with water and evaporated *in vacuo* at 35°. The colorless frothy solid dissolved in a little ether but quickly precipitated a crop of colorless crystals, short blades, 645 mg., m.p. 155–169°. Concentration gave further crops, total yield 819 mg., 68%. The product was recrystallized from cyclohexane giving pointed blades, m.p. 176–178°, $[\alpha]^{25}D$ +52.4°.

Anal. Calcd. for $C_{23}H_{33}O_5Br$: C, 58.85; H, 7.09; Br, 17.04. Found: C, 58.66; H, 7.05; Br, 17.06.

Allopregnane-3β,17α,21-triol-12,20-dione 3,21-Diacetate (IV). (a) Method of Kritchevsky.[19]—A solution of 3.51 g. of 21-bromoallopregnane-3β,17α-diol-12,20-dione 3-acetate in 1700 ml. of 95% ethanol at 26° was treated with 1700 ml. of 0.1 *N* NaOH at 17°. On mixing the solutions, the temperature rose to 28°. After 10 min., 1700 ml. of 0.1 *N* HCl at 17° was added, and the mixture was extracted with ether. The ether was washed with 50 ml. of 5% sodium hydroxide and with saturated sodium chloride. This material reduced Fehling solution and gave a positive silver mirror test. The volume was reduced to 100 ml. and the mixture was acetylated overnight at room temperature with 40 ml. of pyridine and 50 ml. of acetic anhydride. The mixture was shaken well with water, 300 ml. of ether was added and the ether layer collected. The ether was washed with 5% hydrochloric acid containing sodium chloride, with 5% sodium hydroxide, and with saturated sodium chloride. On evaporation, 2.46 g. of a semi-crystalline residue was obtained. On trituration with ether 1.16 g. of crystals, m.p. 145–160°, was obtained. An additional 0.82 g., m.p. 145–160°, was obtained with difficulty from the filtrate after long standing by slow evaporation of the ether; combined yield 59%. The analytical sample was obtained by recrystallization from ether, m.p. 164–165°, $[\alpha]^{25}D$ +40.9°.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 67.00; H, 8.32.

(b) Method of Levin.[20]—21-Bromoallopregnane-3β,17α-diol-12,20-dione 3-acetate (III) (3.3 g.), acetone (210 ml.), potassium iodide (48 mg.), dry potassium acetate (13.4 g.) and 2.1 ml. of acetic acid were refluxed with stirring for 16 hours. The solids were filtered, washed with acetone and the filtrate was concentrated to a small volume under reduced pressure. Water was added and the crystalline product, 2.9 g., m.p. 162–165°, was isolated, 93% yield. This product always contained halogen traces (positive Beilstein flame test) and occasionally infrared spectra showed greater hydroxyl absorption than expected for a pure sample and showed weak indications of carbonyl peaks near 1710 $cm.^{-1}$ indicating that some loss of 21-acetoxyl had occurred. Reacetylation always gave a compound whose infrared absorption spectrum was like that of authentic material. Although this procedure gives a somewhat less pure product, it is nevertheless to be preferred to the preceding procedure both in yield and ease of isolation of the product.

12-Carboxy-12,13-*seco*-allopregnane-3β,13α,17α,21-tetrol-20-one 12,13-Lactone 3,21-Diacetate (V).—A sample of III, 2.91 g., in 20 ml. of chloroform was chilled, treated with 42 ml. of perbenzoic acid in chloroform (1 ml. = 7.7 ml. of 0.10 *N* $Na_2S_2O_3$) and with 1.33 ml. of 10% sulfuric acid in acetic acid, and was stored at 25° for 92 hours, during which time approximately one equivalent of perbenzoic acid was consumed. The chloroform solution was washed with 5% aqueous sodium hydroxide, dried and was evaporated *in vacuo* to give a glassy residue which was partition-chromatographed on silica gel, 27 g. impregnated with 10 ml. of ethanol.[21] The elution was carried out with 98% dichloromethane–2% ethanol moving phase. The product was eluted very quickly in less than 100 ml. of solvent. Crystallization from ether gave 1.09 g., 36% yield, of ortho-

(19) *Cf.* T. H. Kritchevsky, D. L. Garmaise and T. F. Gallagher, THIS JOURNAL, **74**, 483 (1952).

(20) R. H. Levin, *et al.*, *ibid.*, **76**, 546 (1954).

(21) E. R. Katzenellenbogen, K. Dobriner and T. H. Kritchevsky, *J. Biol. Chem.*, **207**, 315 (1954).

gonal prisms softening and sweating at 205° and subliming incompletely above 217° to little squares. A characteristic melting with transition within the melt to thick quadrilaterals remelting from 219–220° occurred. The analytical sample obtained by ether recrystallization showed a double m.p. 203–205, 209–220°, $[\alpha]^{25}D$ +13°.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 64.63; H, 7.81. Found: C, 64.30; H, 7.55.

The hydroxyl group was not acetylatable under mild conditions (pyridine–acetic anhydride 16 hours, 25°). Attempts at saponification gave non-crystalline material soluble in aqueous alkali.

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Steroidal Cyclic Ketals. XIV.[1] The Preparation of Pregnane-5α,21-diol-3,20-dione and Pregnane-5α,11β,17α,21-tetrol-3,20-dione

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Pregnane-5α,21-diol-3,20-dione (VIIa) and pregnane-5α,11β,17α,21-tetrol-3,20-dione (XIa) have been prepared for evaluation of the biological influence of the substitution of a 3-keto-5α-hydroxyl group for the Δ⁴-3-ketone group in desoxycorticosterone (I) and hydrocortisone.

Androstane-5α-ol-3,17-dione, androstane-5α,17β-diol-3-one and 17α-methylandrostane-5α,17β-diol-3-one have recently been prepared for evaluation as possible metabolic precursors of their corresponding Δ⁴-3-ketonic hormones.[2] In all three cases, the substitution of the 3-ketone-5α-ol group for the usual Δ⁴-3-ketone group resulted in an appreciable decrease in androgenicity (subcutaneous injection-capon assay), and, consequently, this possible metabolic pathway was discounted.[2] Notwithstanding these results, it was of interest to us to extend this work to the pregnane series, and more particularly to the 5α-hydroxy analog of desoxycorticosterone and hydrocortisone.[3] We have succeeded in preparing pregnane-5α,21-diol-3,20-dione (VIIa) and pregnane-5α,11β,17α,21-tetrol-3,20-dione (XIa) by a pathway which capitalized on the fact that during the formation of an ethylene ketal of a Δ⁴-3-ketosteroid the double bond migrates from the C-4 to C-5 position.[4] The preparative details for these compounds (VIIa and XIa), and their biological activities form the basis of this paper.

Desoxycorticosterone (I, Flow Sheet A) on ketalization with ethylene glycol was converted into the expected Δ⁵-3,20-bis-ethylene ketal (IIa). Acetylation gave the Δ⁵-21-acetate 3,20-bis-ethylene ketal (IIb). Epoxidation of IIb in benzene with a solution of perbenzoic acid in ethyl acetate afforded a product which consisted of the α-oxide IIIa and presumably the β-oxide IIIb. On the basis of solubility in acetone–petroleum ether, the mixture was separated into two fractions, 1 and 2, the former being the more insoluble fraction.

Fraction 1 in tetrahydrofuran–ether on treatment with lithium aluminum hydride gave a product which proved difficult to purify by recrystallization. It therefore was hydrolyzed under acidic conditions for the removal of the ketal groups. This afforded what is probably pregnane-5α,6β,21-triol-3,20-dione (Va) in a practically pure state. Its 6,21-diacetate Vb was obtained analytically pure.[5]

Fraction 2 on similar reaction with lithium aluminum hydride, followed by acetylation, resulted in a complex mixture which was resolved in the following way. Chromatography on alumina gave three fractions in order of increasing polarity, called 2A, 2B and 2C.

Fraction 2A on saponification, chromatography and acid hydrolysis gave pregnane-5α,21-diol-3,20-dione (VIIa). Fraction 2B on purification by recrystallization gave pregnane-5α,21-diol-3,20-dione 21-acetate 3,20-bis-ethylene ketal (VIb). Fraction 2C on purification also by recrystallization gave pregnane-5α,21-diol-3,20-dione 3,20-bis-ethylene ketal (VIa). The presence of this compound may be ascribed to incomplete acetylation or saponification during the chromatography on alumina.

Hydrolysis of the 5α,21-diol 3,20-bis-ethylene ketal (VIa) in methanol with sulfuric acid resulted in a mixture of pregnane-5α,21-diol-3,20-dione (VIIa) and desoxycorticosterone (I), which were separated by fractional recrystallization.[6] The

(1) Paper XIII, S. Bernstein and R. H. Lenhard, THIS JOURNAL, **77**, 2331 (1955).

(2) (a) S. A. Julia, Pl. A. Plattner and H. Heusser, *Helv. Chim. Acta*, **35**, 665 (1952); (b) S. A. Julia and H. Heusser, *ibid.*, **35**, 2080 (1952).

(3) The Swiss workers[2a] have indicated a forthcoming communication dealing with the 5α-oxy-compounds in the pregnane and 21-oxy-pregnane series; but this work has not appeared as yet.

(4) E. Fernholz and H. E. Stavely, Abstracts of the 102nd Meeting of the American Chemical Society, Atlantic City, N. J., September 8–12, 1941, p. M39; E. Fernholz, U. S. Patents 2,356,154 (August 22, 1944) and 2,378,918 (June 26, 1945); R. Antonucci, S. Bernstein, R. Littell, K. J. Sax and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952); and G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(5) The 5α,6β,21-triols appear to have been derived at some stage principally from the β-oxide IIIb. Theoretically, the β-oxide IIIb on treatment with lithium aluminum hydride would give rise predominantly to allopregnane-6β,21-diol-3,20-dione 3,20-bis-ethylene ketal (IV); none of this compound was isolated. In this connection, see Pl. A. Plattner, H. Heusser and M. Feurer, *Helv. Chim. Acta*, **32**, 587 (1949), for the definitive publication on the reduction of 5,6-oxides with lithium aluminum hydride.

(6) See S. A. Julia, Pl. A. Plattner and H. Heusser (ref. 2a) and references cited therein which deal with the elimination of water from 3-keto-5α-oxysteroids to afford Δ⁴-3-ketosteroids.