and the organic material was extracted with ether. Titration of the aqueous phase (Volhard) indicated that about 50% dehydrochlorination had been effected. The ether extract was washed with dilute hydrochloric acid to remove collidine and upon evaporation a crude residue (260 mg.) was obtained. This was dissolved in 5 cc. of acetic acid and a solution of 150 mg. of 2,4-dinitrophenylhydrazine in 5 cc. of acetic acid was added. After standing overnight the brick-red 2,4-dinitrophenylhydrazone was filtered, m.p. 219–220° (ethanol–ethyl acetate). The product was identical in m.p., mixed m.p. and infrared spectrum with testosterone acetate 2,4-dinitrophenylhydrazone.

Anal. Calcd. for $C_{27}H_{34}O_6N_4$: C, 63.51; H, 6.71. Found: C, 63.87; H, 6.65.

Dehydrobromination of 4-Bromotestane-17β-ol-3-one Acetate.—A solution of 50 mg. of bromoketone and 25 mg. of 2,4-dinitrophenylhydrazine in 3 cc. of acetic acid was heated on the steam-bath for one hour. After cooling, 55 mg. of pure testosterone acetate 2,4-dinitrophenylhydrazone, m.p. 219–220°, identical with the product described above, was obtained.

DETROIT, MICHIGAN
CAMBRIDGE, MASS.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. XLV.[1] Introduction of the 11-Keto and 11α-Hydroxy Groups into Ring C Unsubstituted Steroids (Part 8).[2] Performic Acid Oxidation of 7,9(11)-Dienes[3]

BY CARL DJERASSI,[4] O. MANCERA, J. ROMO AND G. ROSENKRANZ

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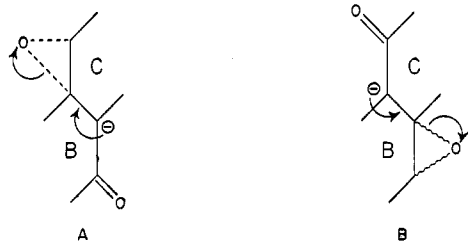
As illustrated with $\Delta^{7,9(11)}$-dienes of the 20β-hydroxy, 20-keto and 16α,17α-oxido-20-ketoallopregnane series as well as with a sapogenin derivative, performic acid oxidation leads to 9α,11α-oxido-7-ketones which are useful intermediates for the synthesis of 11-keto and 11α-hydroxy steroids.

During the past two years there have been developed a number of syntheses of 11-oxygenated steroids, notably cortisone, from ring C unsubstituted precursors which occur abundantly in a variety of plant sources. All of these methods[5] proceed through some type of oxidation of a steroidal $\Delta^{7,9(11)}$-diene I followed by appropriate manipulations leading eventually to the desired 11-ketosteroid. One of the methods developed in this Laboratory involves performic acid oxidation of such dienes and the present paper is concerned with a description of the experimental details in four different series.[6]

The starting material for our initial experiments was $\Delta^{7,9(11)}$-allopregnadiene-3β,20β-diol diacetate (IA)[7] since it was felt that the absence of carbonyl groups (aside from the acetate functions) would facilitate infrared examination of the oxidation products. The diacetate IA proved indeed a fortuitous choice since all of the subsequent transformation products were nicely crystalline. Oxidation of the diene IA with hydrogen peroxide in formic acid solution, with or without an additional solvent,[8] resulted in the introduction of two oxygen atoms. Since the product exhibited no ultraviolet absorption and showed no infrared hydroxyl band but did possess carbonyl bands at 1736 cm.$^{-1}$ (acetate) and 1718 cm.$^{-1}$ (unconjugated 6-membered ring carbonyl band), only three possible structures were considered: (a) saturated 7,11-dione; (b) 8,9-oxido-11-ketone, and (c) 9,11-oxido-7-ketone IIA. The subsequent transformations[9] served to establish the correctness of the last structure IIA. Thus mild alkaline treatment resulted in saponification *cum* rearrangement yielding a trihydroxy ketone, which formed a triacetate and exhibited a pronounced ultraviolet absorption maximum at 254 mμ (log ε 4.11). Such a reaction excludes a 7,11-dione structure and can be rationalized only with an epoxyketone (A or B) rearranging to an unsaturated ketol.



A B

Catalytic hydrogenation with palladized charcoal resulted in smooth reduction of the double bond and a modified[10] Wolff–Kishner reduction produced a triol which could be oxidized to the known allopregnane-3,11,20-trione (VIIIa).[11] The oxidation to the ketone demonstrated that the triol was allopregnane-3β,11α,20β-triol (VIIa), the 11α-configuration being proved by the facile preparation of a 3,11,20-triacetate VIIb. This in turn requires the placement of the reactive (to Wolff–Kishner conditions and Girard complex formation) keto

(1) Paper XLIV, F. Sondheimer, G. Rosenkranz, O. Mancera and C. Djerassi, THIS JOURNAL, **75**, 2601 (1953).

(2) Part 7, F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, *ibid.*, **75**, 1282 (1953).

(3) We are greatly indebted to Dr. Gilbert Stork of Columbia University for valuable suggestions.

(4) Department of Chemistry, Wayne University, Detroit 1, Michigan.

(5) For a recent review, see L. Velluz, A. Petit and J. Mathieu, *Bull. soc. chim. France*, 1 (1952).

(6) Part of this material has been announced in a preliminary Communication to the Editor (G. Stork, J. Romo, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 3546 (1951)).

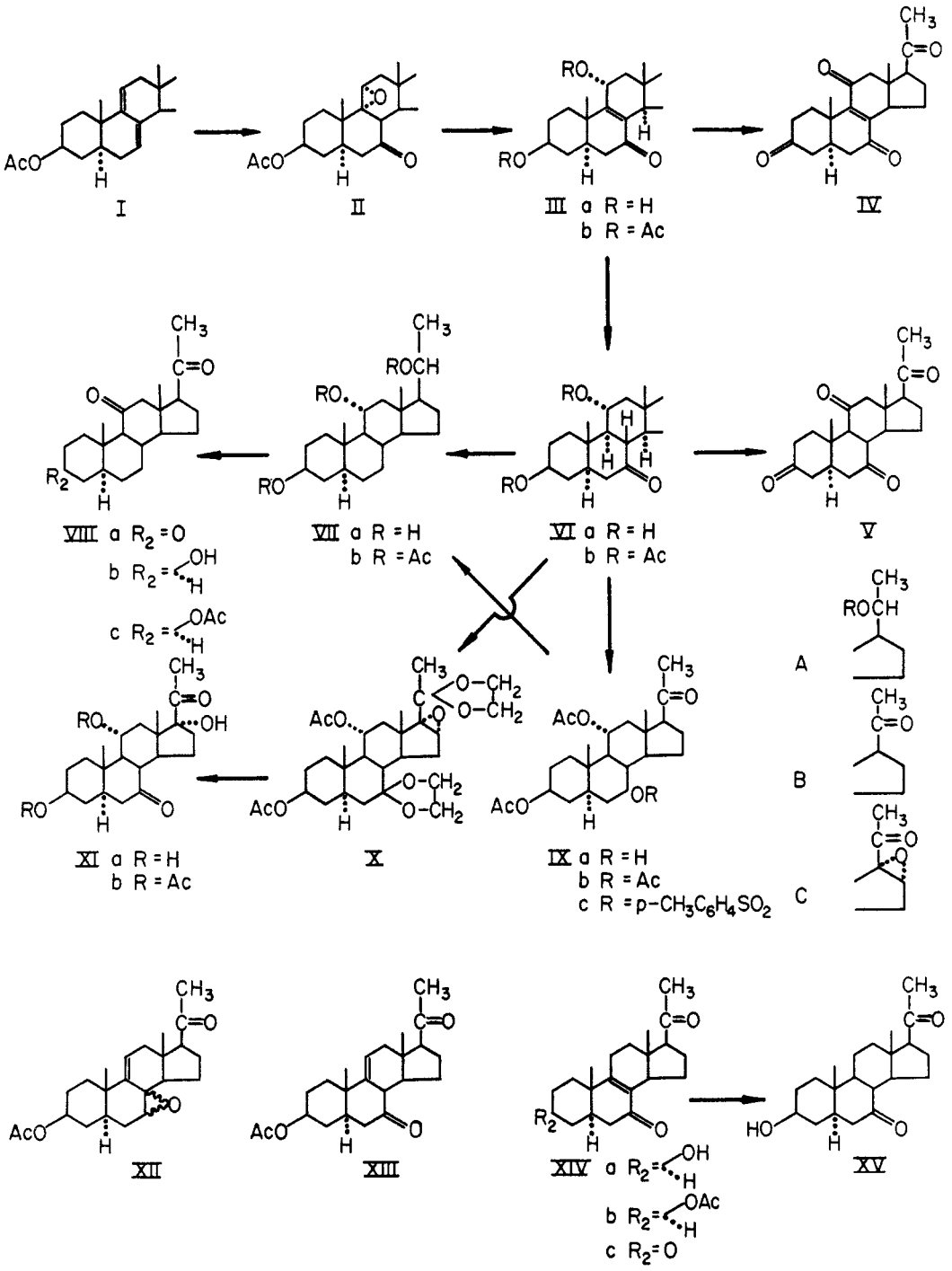
(7) J. Romo, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 5489 (1951).

(8) Similar oxidations recently also have been described in the ergosterol (R. Budziarek, G. T. Newbold, R. Stevenson and F. S. Spring, *J. Chem. Soc.*, 2892 (1952); R. C. Anderson, R. Stevenson and F. S. Spring, *ibid.*, 2901 (1952)) and cholesterol series (L. F. Fieser and J. E. Herz, THIS JOURNAL, **75**, 121 (1953)).

(9) An independent proof of structure has already been presented in the sapogenin series (C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, THIS JOURNAL, **74**, 1712(1952)) where the epoxyketone II was converted to the 7-cycloethylene mercaptal and desulfurized to the known 9α,11α-oxido-22a-5α-spirostan-3β-ol (C. Djerassi, H. Martinez and G. Rosenkranz, *J. Org. Chem.*, **16**, 1278 (1951)).

(10) Huang-Minlon, THIS JOURNAL, **71**, 3301 (1949).

(11) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **21**, 161 (1938), obtained this substance VIIIa by degradation of corticosterone.



group at C-7 and thus leads to the unequivocal assignment of structure IIA for the epoxyketone and IIIA for the rearranged ketol. The 11α-configuration in the triol VIIa applies equally to all intermediates up to and including the epoxyketone IIA and thus affords independent proof for the α-configuration of 9,11-oxides formed by peracid treatment.[12] It is interesting to note that the catalytic hydrogenation of the Δ^8-7-one-11α-ol IIIA leads to a reduction product VIA which is stable to alkali and thus must possess the "normal" 8β,9α-configuration. This direct formation of a *trans* juncture is best rationalized by assuming a 1,4-addition of hydrogen in the reduction step.

Allopregnane-3,11,20-trione (VIIIa) obtained in the above synthesis was reduced selectively at C-3 by means of Raney nickel catalyst and the resulting allopregnan-3β-ol-11,20-dione (VIIIb) was converted by methods already described[13-15] to corti-

(12) H. Heymann and L. F. Fieser, THIS JOURNAL, **73**, 5252 (1951), have furnished rigorous proof for the formation of a 9α,11α-oxide in the peracid oxidation of $\Delta^{9(11)}$-lithocholenic acid.

(13) G. Rosenkranz, C. Djerassi, R. Yashin and J. Pataki, *Nature*, **168**, 28 (1951).

(14) J. M. Chemerda, E. M. Chamberlain, E. H. Wilson and M. Tishler, THIS JOURNAL, **73**, 4053 (1951).

(15) G. Rosenkranz, J. Pataki and C. Djerassi, *ibid.*, **73**, 4055 (1951); J. Pataki, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 5615 (1952).

sone. Since the starting 7,9(11)-diene IA[7] can be synthesized[16] from both Δ^5-22a-spirosten-3β-ol (diosgenin) and Δ^5-pregnen-3β-ol-20-one (and hence stigmasterol) this completes a chemical route from these abundant plant steroids to cortisone.

It appeared of interest to investigate the applicability of this performic acid oxidation to steroidal 7,9(11)-dienes with other side chains. Thus, no difficulty was encountered in isolating the desired epoxyketone, 9α,11α-22a-5α-spirostan-3β-ol-7-one, from the oxidation of the diosgenin derivative $\Delta^{7,9(11)}$-22a-5α-spirostadien-3β-ol acetate[17] and the subsequent transformations of this epoxyketone, constituting an alternate synthesis of cortisone, have already been recorded.[18] Attention was next turned to a 20-ketosteroid, $\Delta^{7,9(11)}$-allopregnadien-3β-ol-20-one acetate (IB).[16] As illustrated in the experimental section, performic acid oxidation produced an analogous epoxyketone IIB, which was saponified and isomerized to the oily ketol IIIBa, characterized by the crystalline 3,11-diacetate IIIBb, and hydrogenated to the saturated allopregnane-3β,11α-diol-7,20-dione (VIBa). The 20β-hydroxy and 20-keto series were interrelated at the Δ^8-ketol IIIAa and IIIBa and saturated ketol VIAa and VIBa stages by oxidation to the corresponding 3,7,11,20-tetrones IV and V.

An alternate interconversion, albeit in poor yield, between the 20β-hydroxy and 20-keto series was accomplished in the following manner. Raney nickel hydrogenation of allopregnane-3β,11α-diol-7,20-dione diacetate (VIBb) resulted in preferential reduction of the 7-keto group IXa, further characterized by the triacetate IXb. Tosylation of IXa led to allopregnane-3β,7,11α-triol-20-one 3,11-diacetate 7-tosylate (IXc) which upon reduction with lithium aluminum hydride[19] furnished allopregnane-3β,11α,20β-triol (VIIa), identical with the material prepared by the first route from VIAa.

In the performic acid oxidation of $\Delta^{7,9(11)}$-allopregnadien-3β-ol-20-one acetate IB it was observed that if the reaction time and temperature were reduced somewhat, it was possible to isolate two isomeric substances, which possessed only one additional oxygen atom and were unsaturated to tetranitromethane but exhibited no selective absorption in the ultraviolet. Both substances on treatment with boiling potassium carbonate solution were isomerized to the same α,β-unsaturated ketone, Δ^8-allopregnen-3β-ol-7,20-dione (XIVa),[20] which could be hydrogenated to the known[21] allopregnan-3β-ol-7,20-dione (XV). The present information is not sufficient to decide among the four possible structures for the two products from the mild performic acid oxidation, *viz.*, the isomeric $\Delta^{9(11)}$-7,8-oxides XII and the epimeric (8α or 8β) $\Delta^{9(11)}$-7-ketones XIII.[22]

Finally, there was also investigated the performic acid oxidation of a 7,9(11)-diene with an α-keto oxide function in the side chain, 16α,17α-oxido-$\Delta^{7,9(11)}$-allopregnadien-3β-ol-20-one acetate (IC).[7] Again, it was possible to isolate the corresponding 9α,11α-oxido-7-ketone IIC, rearrange it to the Δ^8-7-one-11α-ol IIIC and hydrogenate it to 16α,17α-oxido-allopregnane-3β,11α-diol-7,20-dione (VICa). This substance, as the 3,11-diacetate VICb was converted to the 7,20-bis-ethylene ketal X and after reduction with lithium aluminum hydride and acid hydrolysis furnished allopregnane-3β,11α,17α-triol-7,20-dione (XIa) and upon acetylation the 3,11-diacetate XIb.

The performic acid oxidation of $\Delta^{7,9(11)}$-dienes I—when carried out without catalysts as described in the present paper—affords only fair yields of the 9α,11α-oxido-7-ketones II and in terms of over-all yield for 11-ketosteroid synthesis is inferior to the lithium–ammonia reduction method[2,23,24] of Δ^8-11-ketones which are available in two steps from the dienes I. While all of the hitherto described chemical introduction methods of the C-11 oxygen atom are of necessity more complex and hence less desirable than the one-stage microbiological oxidation[25–27] particularly as applied to the synthesis of cortisone[26,27] the presently described performic acid oxidation procedure through epoxyketones was the first to offer a ready path to 11α-hydroxy steroids and has made possible the chemical synthesis of the 11α-epimers of all of the important adrenal hormones.[28]

Experimental[29]

20β-Hydroxy Series (A).

The 9α,11α-Oxidoallopregnane-3β,20β-diol-7-one Diacetate (IIA).—A starting solution of 10.0 g. of the $\Delta^{7,9(11)}$-allopregnadiene-3β,20β-diol diacetate (IA)[7] in 250 cc. of 90% formic acid was treated with stirring with 10 cc. of 30% hydrogen peroxide at 15° for one hour and for an additional two hours at 25–30°. After dilution with water, extraction with chloroform, washing until neutral, evapora-

(16) C. Djerassi, J. Romo and G. Rosenkranz, *J. Org. Chem.*, **16**, 754 (1951).

(17) G. Rosenkranz, J. Romo, E. Batres and C. Djerassi, *ibid.*, **16**, 298 (1951).

(18) C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, THIS JOURNAL, **74**, 1712 (1952).

(19) *Cf.* P. Karrer, H. Asmis, K. N. Sareen and R. Schwyzer, *Helv. Chim. Acta*, **34**, 1022 (1951).

(20) C. Djerassi, O. Mancera, M. Velasco, G. Stork and G. Rosenkranz, THIS JOURNAL, **73**, 4496 (1951); **74**, 3321 (1952), have described a procedure for converting such Δ^8-7-ketones into 11-oxygenated steroids.

(21) W. Klyne, *J. Chem. Soc.*, 3449 (1951).

(22) L. F. Fieser, J. C. Babcock, J. E. Herz, W. Huang and W. P. Schneider, THIS JOURNAL, **73**, 4053 (1951), have isolated one of the $\Delta^{9(11)}$-7-ketones in the dichromate oxidation of methyl 3α-acetoxy-$\Delta^{7,9(11)}$-choladienate.

(23) F. Sondheimer, R. Yashin, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 2696 (1952).

(24) E. Schoenewaldt, L. Turnbull, E. M. Chamberlain, D. Reinhold, A. E. Erickson, W. V. Ruyle, J. M. Chemerda and M. Tishler, *ibid.*, **74**, 2696 (1952).

(25) D. H. Peterson and H. C. Murray, *ibid.*, **74**, 1871 (1952).

(26) O. Mancera, A. Zaffaroni, B. A. Rubin, F. Sondheimer, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 3711 (1952); **75**, 1286 (1953).

(27) J. Fried, R. W. Thoma, J. R. Gerke, J. E. Herz, M. N. Donin and D. Perlman, *ibid.*, **74**, 3962 (1952).

(28) (a) 11α-Hydroxyprogesterone: O. Mancera, J. Romo, F. Sondheimer, G. Rosenkranz and C. Djerassi, *J. Org. Chem.*, **17**, 1066 (1952); (b) 11α,17α-dihydroxyprogesterone: J. Romo, G. Rosenkranz, C. Djerassi and F. Sondheimer, THIS JOURNAL, **75**, 1277 (1953); (c) 11α,21-dihydroxyprogesterone (11-epicorticosterone): ref. 1; (d) 11α,17α,21-trihydroxyprogesterone (11-epi Compound F): J. Romo, A. Zaffaroni, J. Hendrichs, G. Rosenkranz, C. Djerassi and F. Sondheimer, *Chemistry and Industry*, 783 (1951), and ref. 28b.

(29) Melting points are uncorrected. Unless noted otherwise, rotations were determined in chloroform and ultraviolet absorption spectra in 95% ethanol solution. Appreciation is expressed to Srta. Paquita Revaque and staff for carrying out these numerous measurements and for the infrared absorption spectra (Perkin-Elmer model 12C single beam spectrometer with sodium chloride optics) and to Srta. Amparo Barba and staff for the microanalyses.

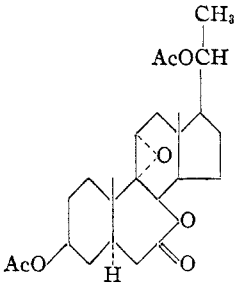
tion to dryness and crystallization from methanol there was isolated 4.3 g. of colorless crystals with m.p. 260–268°. This material was subjected to a Girard separation with 5 g. of Girard reagent T, 50 cc. of absolute ethanol and 5 cc. of glacial acetic acid. Recrystallization of the ketonic fraction from chloroform–methanol furnished 3.1 g. of the **epoxyketone** IIA with m.p. 238–240°,[30] $[\alpha]^{20}D$ −54°, no selective absorption in the ultraviolet, λ_{max}^{Nujol} 1736 and 1718 cm.$^{-1}$, but no free hydroxyl band.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.03; H, 8.54.

The non-ketonic fraction from the Girard separation after recrystallization from chloroform–methanol yielded colorless needles with m.p. 325–327°, $[\alpha]^{20}D$ −39°, λ_{max}^{Nujol} 1736 and 1720 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 66.76, 66.89; H, 8.18, 8.26.

This non-ketonic by-product is presumably the **diacetoxy oxido-lactone** formed by opening of ring B, but no further work has been done to prove this structure.



Alkaline saponification followed by acidification and recrystallization from methanol–acetone led to the free **dihydroxy oxido-lactone** with m.p. 276–278°, $[\alpha]^{20}D$ −46°, no selective absorption in the ultraviolet.

Anal. Calcd. for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.29; H, 8.99.

Δ^8-Allopregnene-3β,11α,20β-triol-7-one (IIIAa).—A solution of 3.80 g. of the above epoxyketone IIA in 50 cc. of ethanol was refluxed with 1.0 g. of potassium hydroxide and 5 cc. of water for one hour and the mixture was concentrated to a small volume *in vacuo*. Addition of water, extraction with chloroform, drying, evaporation and crystallization of the residue from acetone–hexane gave 2.54 g. of the unsaturated ketol IIIAa with m.p. 250–252°, $[\alpha]^{20}D$ −25° (ethanol), λ_{max}^{EtOH} 254 mμ, log ϵ 4.11, λ_{max}^{Nujol} 1662 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.37; H, 9.25. Found: C, 72.52; H, 8.97.

Acetylation (acetic anhydride–pyridine, 1 hour, steam-bath) and recrystallization from acetone–hexane produced the **3,11,20-triacetate** IIIAb in nearly quantitative yield; m.p. 203–205°, $[\alpha]^{20}D$ +23°, λ_{max}^{EtOH} 252 mμ, log ϵ 4.04.

Anal. Calcd. for $C_{27}H_{38}O_7$: C, 68.32; H, 8.07. Found: C, 68.21; H, 8.06.

Allopregnane-3β,11α,20β-triol-7-one (VIAa).—The catalytic hydrogenation of 3.0 g. of the Δ^8-triol-7-one IIIA in 200 cc. of ethanol with 0.8 g. of 10% palladized charcoal at room temperature and atmospheric pressure (560 mm.) ceased after 1.5 hours when the hydrogen up-take corresponded to one mole. Filtration of the catalyst, evaporation to dryness and recrystallization from methanol–acetone yielded 2.3 g. of colorless crystals with m.p. 246–248°, $[\alpha]^{20}D$ −112° (ethanol), λ_{max}^{Nujol} 1718 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.77. Found: C, 71.58; H, 10.01.

Allopregnane-3β,11α,20β-triol (VIIa).—The above trihydroxy ketone VIAa (0.73 g.) was refluxed for 1 hour with 20 cc. of ethylene glycol and 0.8 cc. of hydrazine hydrate. At the end of this period, a solution of 1.5 g. of potassium hydroxide in 2 cc. of water was added, the mixture was heated without a condenser until the temperature of the vapor rose to 190° and was then refluxed for 4 hours. Dilution with water, collection of the precipitate and recrystallization from methanol–acetone yielded 0.59 g. of the triol VIIa with m.p. 253–255°, $[\alpha]^{20}D$ −28° (ethanol), no carbonyl absorption in the infrared. The removal of the 7-keto group by desulfurization of the 7-cycloethylene mercaptal has already been described earlier.[31]

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.63; H, 10.83.

The **triacetate** VIIAb after recrystallization from methanol–water showed m.p. 162–164°, $[\alpha]^{20}D$ −16°.

Anal. Calcd. for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15. Found: C, 70.47; H, 9.26.

Allopregnane-3,11,20-trione (VIIIa).—The above triol VIIa (0.75 g.) in 35 cc. of glacial acetic acid was oxidized at room temperature for 2.5 hours with a solution of 0.8 g. of chromium trioxide in 2 cc. of water. The product was isolated by chloroform extraction and after two recrystallizations from acetone–hexane furnished the analytical sample (0.49 g.) with m.p. 211–213°, $[\alpha]^{20}D$ +129° (ethanol); reported[11] m.p. 212–216°, $[\alpha]D$ +133° (ethanol). A mixture melting point determination, kindly carried out by Prof. T. Reichstein of the University of Basle, showed no depression.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.19; H, 9.39.

Allopregnan-3β-ol-11,20-dione (VIIIb).—One-half gram of the trione VIIIa in 100 cc. of ethanol was shaken in an atmosphere of hydrogen at room temperature and atmospheric pressure with 3 g. of prereduced W-2 Raney nickel catalyst for 2 hours, whereupon slightly more than one mole of hydrogen was consumed. After proceeding in the usual manner, the residue was recrystallized from hexane–acetone to yield 0.4 g. of crystals with m.p. 192–194°, $[\alpha]^{20}D$ +99°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.48; H, 9.53.

The **acetate** VIIIc was recrystallized from methanol–water; m.p. 143–144°, $[\alpha]^{20}D$ +89°, $\lambda_{max}^{CS_2}$ 1736 and 1710 cm.$^{-1}$ but no free hydroxyl band.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.28; H, 8.88.

20-Keto Series (B)

The 9α,11α-Oxidoallopregnan-3β-ol-7,20-dione Acetate (IIB).—The preparative performic acid oxidation was carried out with 10 g. of the $\Delta^{7,9(11)}$-allopregnadien-3β-ol-20-one acetate (Ib)[16] in 200 cc. of 90% formic acid and 8 cc. of 30% hydrogen peroxide for 2 hours at 40°. Dilution with water, extraction with ether, and recrystallization of the ether residue from hexane–acetone produced 2.61 g. of colorless crystals with m.p. 205–212°. Further recrystallization from methanol raised the m.p. to 219–220°, $[\alpha]D$ −36°, $\lambda_{max}^{CHCl_3}$ 1728 and 1700 cm.$^{-1}$ but no free hydroxyl band, no color with tetranitromethane.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.06; H, 8.46.

On carrying out the oxidation as above but in half as strong a solution below 30° for 20–25 minutes (at which time a test portion did not give any more the red color with tetranitromethane characteristic of the starting diene IB) there was isolated after repeated crystallization from ether and methanol 1.45 g. of crystals with m.p. 210–213°, $[\alpha]D$ −35°, $\lambda_{max}^{CHCl_3}$ 1718 and 1700 cm.$^{-1}$, yellow color with tetranitromethane. A very satisfactory analysis could not be obtained.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.43; H, 8.79.

Chromatography of the mother liquors on 300 g. of ethyl acetate-washed alumina and recrystallization of the benzene–hexane (25/75) eluates from methanol and acetone–hexane furnished 1.05 g. of crystals with m.p. 139–142°, $[\alpha]^{20}D$ +37°, $\lambda_{max}^{CHCl_3}$ 1728 and 1700 cm.$^{-1}$, yellow color with tetranitromethane.

(30) The melting point 260–262° reported in our original Communication to the Editor (ref. 6) refefred to material which was not purified by Girard separation and which still contained some of the high-melting by-product.

(31) J. Romo, G. Stork, G. Rosenkranz and C. Djerassi, THIS JOURNAL, 74, 2918 (1952).

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.49; H, 9.03.

As pointed out in the discussion, these products may be the isomeric $\Delta^{9(11)}$-7,8-oxides XII and/or 7-ketones XIII.

Δ^8-Allopregnen-3β-ol-7,20-dione (XIVa).—Either one of the above two products (m.p. 213° or 142°) upon refluxing for 30 minutes with half its weight of potassium carbonate in methanol–water solution produced after recrystallization from acetone in *ca.* 75% yield **Δ^8-allopregnen-3β-ol-7,20-dione** (XIVa) with m.p. 192–194°, $[\alpha]^{20}D$ −5°, λ_{max}^{EtOH} 252 mμ, log ϵ 4.10, λ_{max}^{Nujol} 1700 and 1656 cm.$^{-1}$ and free hydroxyl band. Its conversion to Δ^8-allopregnen-3β,11α-diol-7,20-dione diacetate (IIIBb) has already been reported.[20]

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.40; H, 9.29.

From a preparative viewpoint, it was not necessary to isolate the intermediate performic acid oxidation products (XII and/or XIII) since the entire crude oxidation mixture could be treated with carbonate directly.

The **acetate** XIVb was recrystallized from hexane–acetone; m.p. 162–164°, $[\alpha]^{20}D$ −12°.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.13; H, 8.91.

Chromium trioxide oxidation of XIVb in the usual manner followed by recrystallization from chloroform–methanol afforded **Δ^8-allopregnene-3,7,20-trione** (XIVc) with m.p. 280–282°, $[\alpha]^{20}D$ +0°, λ_{max}^{EtOH} 252 mμ, log ϵ 4.10.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.35; H, 8.26.

Allopregnan-3β-ol-7,20-dione (XV).—Catalytic hydrogenation of 0.3 g. of the unsaturated ketone XIVa with 50 mg. of 10% palladized charcoal in ethanol solution was complete after 15 minutes; yield 0.21 g., m.p. 203–205°, $[\alpha]^{20}D$ ±0°, no selective absorption in the ultraviolet, lit.[21] m.p. 209–211° (cor.), $[\alpha]D$ +2°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.26; H, 9.89.

Δ^8-Allopregnene-3β,11α-diol-7,20-dione Diacetate (IIIBb).—Five grams of the epoxyketone IIB in 200 cc. of methanol was refluxed for 30 minutes with 4.0 g. of potassium carbonate and 40 cc. of water. The resulting oily ketol IIIBa (4.8 g.), λ_{max}^{EtOH} 252 mμ, log ϵ 4.01, which could not be crystallized, was directly acetylated with acetic anhydride and pyridine to yield 4.5 g. of the 3,11-diacetate IIIBb with m.p. 210–214°. The analytical sample, after recrystallization from hexane–acetone and high vacuum sublimation, exhibited the following constants: m.p. 216–218°, $[\alpha]^{20}D$ +55°, λ_{max}^{EtOH} 252 mμ, log ϵ 4.07, $\lambda_{max}^{CHCl_3}$ 1728, 1700 and 1670 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.65; H, 7.98.

Δ^8-Allopregnene-3,7,11,20-tetrone (IV).—Chromium trioxide oxidation at room temperature for 2 hours in acetic acid solution of either the crystalline ketol IIIAa or the oily ketol IIIBa gave after recrystallization from ether–hexane in *ca.* 55% yield yellowish crystals of the unsaturated tetrone IV with m.p. 226–228°, λ_{max}^{EtOH} 268 mμ, log ϵ 3.94.

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.68; H, 7.78.

Allopregnane-3β,11α-diol-7,20-dione (VIBa).—The catalytic hydrogenation of 1.5 g. of the oily ketol IIIBa was carried out in the usual manner with 10% palladized charcoal and required two hours. Recrystallization from hexane–acetone yielded 1.2 g. of the saturated diol-dione VIBa with m.p. 240–241°, $[\alpha]D$ −15°, no selective absorption in the ultraviolet.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.52; H, 9.50.

The **diacetate** VIBb, prepared either by acetylation of VIBa or by hydrogenation of the unsaturated acetate IIIBb, was obtained as colorless needles from acetone–hexane with m.p. 156–157°, $[\alpha]^{20}D$ ±0°, $\lambda_{max}^{CS_2}$ 1736, 1718 and 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.37; H, 8.52.

Allopregnane-3,7,11,20-tetrone (V).—Chromium trioxide oxidation of either VIAa, VIBa or allopregnane-3β,20β-diol-7,11-dione[31] gave the identical tetrone V with m.p. 256–258°, λ_{max}^{EtOH} 292 mμ, log ϵ 2.03.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 73.47; H, 8.33.

Allopregnane-3β,7,11α-triol-20-one 3,11-Diacetate (IXa).—The selective reduction of the 7-keto group of VIBb (1.0 g.) was accomplished in 1.5 hours with 5.0 g. of pre-reduced W-2 Raney nickel catalyst in 100 cc. of ethanol at room temperature and atmospheric pressure; yield 0.76 g., m.p. 156–157° (after high vacuum sublimation), $[\alpha]^{20}D$ +62°, $\lambda_{max}^{CHCl_3}$ 1724 and 1700 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.36; H, 8.82.

The **triacetate** IXb after recrystallization from acetone–hexane exhibited m.p. 175–177°, $[\alpha]^{20}D$ +65°, $\lambda_{max}^{CS_2}$ 1736 and 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 68.26; H, 8.30.

The crystalline **tosylate** IXc (m.p. 182–183° dec.) could be obtained in only 30% yield after treatment of the 7-hydroxy diacetate IXb with *p*-toluenesulfonyl chloride in pyridine solution at room temperature overnight followed by crystallization from ether.

Anal. Calcd. for $C_{32}H_{44}O_8S$: C, 65.30; H, 7.48; S, 5.44. Found: C, 65.51; H, 7.60; S, 5.37.

Reduction of 0.4 g. of the tosylate IXc with 0.3 g. of lithium aluminum hydride in 50 cc. of ether for 20 hours afforded 0.03 g. (13%) of allopregnane-3β,11α,20β-triol (VIIa) with m.p. 251–254°, undepressed upon admixture with a sample prepared by Wolff–Kishner reduction of VIAa; the infrared spectra of the two specimens were identical.

16α,17α-Oxido-20-keto Series (C)

9α,11α,16α,17α-Dioxidoallopregnan-3β-ol-7,20-dione (IIC).—Two grams of 16α,17α-oxido-$\Delta^{7,9(11)}$-allopregnadien-3β-ol-20-one acetate (IC)[7] was oxidized with performic acid at 40° exactly as described for IB; yield 0.49 g., m.p. 248–249° (after recrystallization from methanol and from acetone–hexane), $[\alpha]^{20}D$ +55°, $\lambda_{max}^{CHCl_3}$ 1728 and 1704 cm.$^{-1}$, no color with tetranitromethane.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 69.00; H, 7.74.

16α,17α-Oxido-Δ^8-allopregnene-3β,11α-diol-7,20-dione (IIICa).—Potassium carbonate treatment of 1.0 g. of the epoxyketone IIC in the manner described above (for IIB) followed by recrystallization from hexane–ethyl acetate led to 0.6 g. of colorless crystals with m.p. 120–128° (gas evolution) which retained solvent tenaciously. After drying at 100° and 0.001 mm. for three days, the m.p. was 144–146°, $[\alpha]^{20}D$ +150°, λ_{max}^{EtOH} 254 mμ, log ϵ 4.02, λ_{max}^{Nujol} 1700 and 1656 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 70.08; H, 7.64.

The **diacetate** IIICb possessed m.p. 199–200°, $[\alpha]^{20}D$ +163°, λ_{max}^{EtOH} 252 mμ, log ϵ 4.07.

Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.30; H, 7.01.

The 16α,17α-Oxidoallopregnane-3β,11α-diol-7,20-dione (VICa).—The palladium catalyzed hydrogenation of the unsaturated ketol IIICa (3.0 g.) was carried out in the manner described above and afforded after recrystallization from ethyl acetate–hexane 2.48 g. of the saturated analog VICa with m.p. 187–189°, $[\alpha]^{20}D$ −41°, $\lambda_{max}^{CHCl_3}$ 1704 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.65; H, 8.27.

The **diacetate** VICb had m.p. 170–172°, $[\alpha]^{20}D$ −35°.

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67. Found: C, 67.33; H, 7.84.

16α,17α-Oxidoallopregnane-3β,11α-diol-7,20-dione 3,11-Diacetate 7,20-Biscycloethylene Ketal (X).—A mixture of 1.0 g. of the diacetate VICb, 1 cc. of ethylene glycol, 68 mg. of *p*-toluenesulfonic acid and 35 cc. of dry benzene was refluxed for 12 hours using a water separator. The cooled yellow solution was poured into sodium bicarbonate solution, extracted with ether, washed until neutral, dried,

evaporated and crystallized from methanol; yield 0.32 g., m.p. 203–204°, $[\alpha]^{20}D$ −6°, $\lambda_{max}^{CS_2}$ 1736 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{42}O_9$: C, 65.16; H, 7.92. Found: C, 65.39; H, 7.63.

Allopregnane-3β,11α,17α-triol-7,20-dione (XIa).—A solution of 1.0 g. of the bisketal X and 1.0 g. of lithium aluminum hydride in 80 cc. of tetrahydrofuran was refluxed for 15 minutes and the product was isolated by chloroform extraction. The semi-solid residue obtained after evaporation of the chloroform was dissolved in 50 cc. of acetone containing 0.1 g. of *p*-toluenesulfonic acid and the mixture was allowed to stand overnight in order to cleave the ketal groupings. Dilution with water, extraction with chloroform, evaporation to dryness and recrystallization from ethyl acetate–hexane furnished 0.35 g. of the triol XIa with m.p. 185–187°, $[\alpha]D$ −47°, $\lambda_{max}^{CHCl_3}$ 1704 and free hydroxyl band.

Anal. Calcd. for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 68.90; H, 8.63.

The **diacetate** XIb was recrystallized from ether whereupon it exhibited m.p. 170–172°, $[\alpha]^{20}D$ −32°.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 66.91; H, 7.84.

9α,11α-Oxido-22a-5α-spirostan-3β-ol-7-one Acetate.[32]—A solution of 20 g. of $\Delta^{7,9(11)}$-22a-5α-spirostadien-3β-ol acetate[17] in 100 cc. of chloroform and 500 cc. of 90% formic acid was heated with stirring to 60°, an additional 500 cc. of formic acid was added followed by 40 cc. of 30% hydrogen peroxide, the temperature being maintained between 40–60°. After standing at room temperature for 2 hours, ice-water was added, the product was extracted with ether, washed until neutral, dried and evaporated. Crystallization from ether afforded 6.72 g. with m.p. 270–284°, which upon one recrystallization from chloroform–ether yielded 6.05 g. of the epoxyketone with m.p. 290–295°, $[\alpha]D$ −127°, satisfactory for subsequent transformations.[18] The analytical sample exhibited m.p. 297–299° (Kofler), $[\alpha]^{20}D$ −128°, λ_{max}^{Nujol} 1736 and 1718 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{42}O_6$: C, 71.57; H, 8.70. Found: C, 71.74; H, 8.94.

(32) We are indebted to Sr. Enrique Batres for carrying out this experiment.

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Ouabagenin. I. The Relationship between Ouabagenin Monoacetonide and "Anhydroöuabagenin"[1]

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Cleavage of the glycoside, ouabain, by the action of hydrochloric acid in acetone furnishes the aglycone, ouabagenin, as a sparingly soluble monoacetonide, variously reported as melting between 200 and 255°. Pure material is obtained as prisms, m.p. 300–303° (dec.), by recrystallization of the crude product from a large volume of acetone. On solution in hot nitrobenzene, ouabagenin monoacetonide yields a substance, hitherto designated as "anhydroöuabagenin," which separates from the warm solution as plates, melting point when pure, 303–305° (dec.). Carbon and hydrogen analyses do not serve to distinguish this substance from its precursor. Both compounds yield the same diacetyl derivative on acetylation and show identical absorption in the infrared. X-Ray powder diagrams of "anhydroöuabagenin" and of ouabagenin monacetonide are likewise indistinguishable. These and other considerations indicate that the two substances in spite of differences in crystal habit, are nevertheless identical.

Ouabain, also known as *g*-strophanthin, constitutes the active principle of a preparation long employed by East African aborigines as an arrow poison. The substance was first isolated in pure form from the roots and bark of *Acokanthera ouabaio* by Arnaud in 1888.[2] Arnaud recognized the glycosidic nature of the material and identified the sugar residue as rhamnose, but was unsuccessful in his attempts to prepare the free genin, owing to extensive decomposition resulting from the vigorous conditions required for hydrolysis of the glycoside.[3] Jacobs and Bigelow[4] in subsequent work established the empirical formula $C_{29}H_{44}O_{12}$ for ouabain and on the basis of this result proposed the formula $C_{23}H_{34}O_8$ for the then unknown aglycone.

Early investigation of the properties of ouabain[5] revealed the existence of a close relationship between this substance and the steroid glycosides of the heart poison group. The presence of the characteristic butenolide system was deduced from a positive Legal test and was later confirmed by degradative work and by ultraviolet absorption studies of various derivatives.[6,7] Conversion of the glycoside into an iso compound by the action of alcoholic potassium hydroxide provided evidence, based upon analogy, for the presence of a tertiary hydroxyl group at C_{14}.[4] Other transformations, notably acetolysis of the tetrahydro derivative of heptaacetylanhydroöuabain with loss of a carbon atom as formaldehyde,[4] led Fieser and Newman[8] to the tentative conclusion that one of the hydroxyl functions of the genin is incorporated in a hydroxymethyl group located at an angular position, probably C_{10}.

A major advance in the structural problem was the discovery of Mannich and Siewert[9] in 1942 that cleavage of ouabain may be accomplished without destruction of the resulting aglycone by treatment of the glycoside with small amounts of concentrated hydrochloric acid in acetone solution. The principal cleavage product, which crystallizes directly from the reaction mixture, is an extremely insoluble monoacetonide of the free genin. The crude ma-

(1) This investigation was supported by a research grant, H-1084, from the National Heart Institute, of the National Institutes of Health, Public Health Service.

(2) A. Arnaud, *Compt. rend.*, **106**, 1011 (1888).

(3) A. Arnaud, *ibid.*, **126**, 346, 1208 (1898).

(4) W. A. Jacobs and N. M. Bigelow, *J. Biol. Chem.*, **96**, 647 (1932); *ibid.*, **101**, 15 (1933).

(5) A review of the early literature has been given by T. Reichstein and H. Reich, *Ann. Revs. Biochem.*, **15**, 155 (1946); see also L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd ed., Reinhold Publ. Corp., New York, N. Y., 1949, p. 548.

(6) A. Meyrat and T. Reichstein, *Helv. Chim. Acta*, **31**, 2104 (1948).

(7) R. F. Raffauf and T. Reichstein, *ibid.*, **31**, 2111 (1948).

(8) L. F. Fieser and M. S. Newman, *J. Biol. Chem.*, **114**, 705 (1936).

(9) C. Mannich and G. Siewert, *Ber.*, **75**, 737 (1942).