ether and acidified with concentrated hydrochloric acid. The vigorous evolution of gas on acidification indicated decarboxylation of the intermediate malonic acid. The organic layer was separated and the aqueous phase extracted with ether. The combined ether solutions were washed with water to neutrality and dried over anhydrous magnesium sulfate. Ether was removed, the residue heated at 180° for one-half hour (practically no evolution of gas) and distilled; yield, 21.0 g. (83.2%) of a yellow oil which boiled at 161–166° (3 mm.) and crystallized to a waxy solid melting at 60–65°.

2-Diethylaminoethyl α-(2-Cyclopenten-1-yl)-2-thienylacetate Hydrochloride.—A solution of 6.305 g. (0.0303 mole) of α-(2-cyclopenten-1-yl)-2-thienylacetic acid and 4.11 g. (0.0303 mole) of 2-diethylaminoethyl chloride in 80 ml. of absolute isopropyl alcohol was refluxed for 48 hours, cooled, filtered and evaporated to a sirup *in vacuo*.[15] Ether was added to the sirup and crystallization soon started. The mixture was placed in the refrigerator and after several hours the white crystalline mass was filtered off, washed with ether and dried *in vacuo;* yield 8.6 g. (82.7%), m.p. 120–125°. After two recrystallizations from an isopropyl alcohol–ether mixture the compound melted at 130–132°.

Acknowledgment.—The author is indebted to Mr. Leon Simet for technical assistance in the preparation of a number of the intermediates and basic-ester hydrochlorides described.

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NEW YORK 11, N. Y.

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

Steroids. XXXI.[1] Introduction of the 11-Keto and 11α-Hydroxy Groups into Ring C Unsubstituted Steroids (Part 4).[2] Saturated 7,11-Diones

BY J. ROMO, GILBERT STORK,[3a] G. ROSENKRANZ AND CARL DJERASSI[3b]

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As exemplified in the allopregnane and 22-isoallospirostan series, steroidal Δ^8-11α-ol-7-ones can be isomerized smoothly with potassium *t*-butoxide to saturated 7,11-diones, which represent important intermediates in the synthesis of cortisone. The 7-keto group in 7,11-diones as well as in 7-one-11α-ols can be removed readily by conversion to the 7-cycloethylenemercaptol followed by desulfurization.

It was reported recently,[4,5] that performic acid oxidation of steroidal $\Delta^{7,9(11)}$-allodien-3β-ols leads to 9α,11α-oxido-7-ketones, which upon mild treatment with carbonate or alkali hydroxide[4,5] are isomerized smoothly to the corresponding Δ^8-11α-ol-7-ones (*e.g.*, I). Catalytic reduction of the 8,9-double bond followed by Wolff–Kishner reduction of the 7-keto function affords 11-oxygenated steroids, which are convertible to cortisone and related adrenal steroids.[6] Since Δ^8-11α-ol-7-ones (*e.g.*, I) are now readily available, it was of interest to study further reactions of this interesting ketol system with a view to develop alternate approaches to 11-oxygenated steroids.

By analogy to the conversion of Δ^4-cholesten-3-one-6β-ol to cholestane-3,6-dione,[7] Δ^8-allopregnene-3β,11α,20β-triol-7-one[4] (Ia) (ultraviolet absorpation maximum at 254 mμ) was refluxed with methanolic hydrochloric acid, but the resulting product exhibited maxima at 226 and 298 mμ; elementary analysis indicated the loss of one mole of water. These results coupled with the observation that the product formed a di- rather than triacetate and an oxime clearly confirm the structure of the substance as that of the dehydration product $\Delta^{8,11}$-allopregnadien-3β,20β-diol-7-one (IV). Similarly, attempts to prepare the enol acetate of the triacetate Ib followed by alkaline saponification resulted in dehydration and isolation of the dienone IV. While ordinary alkaline saponification conditions suffice to accomplish the isomerization of the Δ^4-3-one-6β-ol system to the corresponding saturated 3,6-dione,[7,8] the 6α-ol isomer is much more resistant[8] to such treatment. This is also true of the Δ^8-11α-ol-7-ones (I, VII), since they are, in fact, products of the alkaline treatment of epoxyketones.[4,5] It is significant that the hydrogen atom which is difficult to remove by base is polar in both the 6α- and 11α-hydroxyl compounds. It was found, however, that if the Δ^8-allopregnene-3β,11α,20β-triol (Ia) was refluxed with potassium *t*-butoxide in anhydrous *t*-butyl alcohol, there was obtained in over 90% yield an isomeric substance, which exhibited no selective absorption in the ultraviolet and whose infrared spectrum showed only the presence of saturated carbonyl and free hydroxyl groups. The subsequent transformations of this substance established its constitution as the desired isomerization product allopregnane-3β,20β-diol-7,11-dione (IIa). Thus it formed a diacetate (IIb), a monooxime (IIc) and a monocycloethylenemercaptol (IId), which upon desulfurization with Raney nickel afforded allopregnane-3β,20β-diol-11-one diacetate (IIe). The structure of the desulfurization product IIe was proved by saponification to the 3,20-diol-11-one (IIf), which still showed an infrared carbonyl band, and by oxidation to the known allopregnane-3,11,-20-trione (VI).[4,9] This reaction sequence (*t*-butoxide isomerization, mercaptol formation and desulfuri-

(1) Paper XXX, J. Pataki, G. Rosenkranz and C. Djerassi, *J. Biol. Chem.*, **195**, 751 (1952).

(2) Part 3, C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, THIS JOURNAL, **74**, 1712 (1952).

(3) (a) Department of Chemistry, Harvard University, Cambridge, Mass.; (b) Department of Chemistry, Wayne University, Detroit, Michigan.

(4) G. Stork, J. Romo, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 3546 (1951).

(5) C. Djerassi, O. Mancera, G. Stork and G. Rosenkranz, *ibid.*, **73**, 4496 (1951).

(6) G. Rosenkranz, C. Djerassi, R. Yashin and J. Pataki, *Nature*, **168**, 28 (1951); J. M. Chemerda, E. M. Chamberlain, E. H. Wilson and M. Tishler, THIS JOURNAL, **73**, 4053 (1951); G. Rosenkranz, J. Pataki and C. Djerassi, *ibid.*, **73**, 4055 (1951); C. Djerassi, G. Rosenkranz, J. Pataki and St. Kaufmann, *J. Biol. Chem.*, **194**, 115 (1952).

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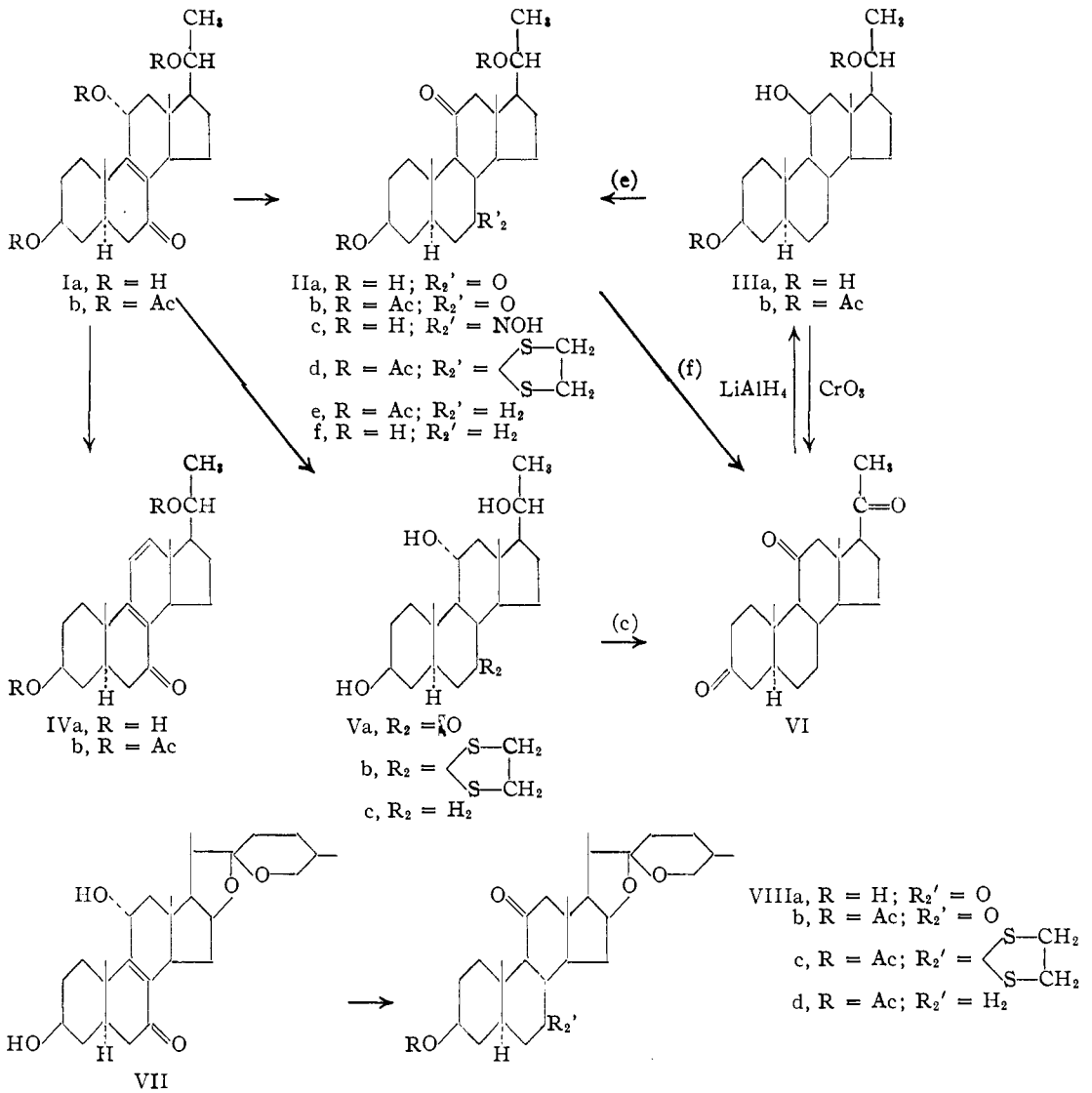
(8) P. T. Herzig and M. Ehrenstein, *J. Org. Chem.*, **16**, 1050 (1951).

(9) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **21**, 161 (1938).



zation) is equally applicable to sapogenins as demonstrated with Δ^8-22-isoallospirosten-3β,11α-diol-7-one (VII)[2]; the resulting known 22-isoallospirostan-3β-ol-11-one acetate (VIIId)[2,10,11] has already been converted[6,10] into cortisone. Saturated 7,11-diones are the key intermediates in two procedures[10,12] for the introduction of an 11-keto group into ring C unsubstituted steroids, and the presently described isomerization of Δ^8-11α-ol-7-ones represents still another route[5,10,12,12a] to these important substances.

The earlier described[4] synthesis of allopregnane-3β,11α,20β-triol (Vc) involved as the last step Huang-Minlon's modification[13] of the Wolff–Kishner reduction of allopregnane-3β,11α,20β-triol-7-one (Va). The alternate procedure, namely, reductive removal of the 7-keto group *via* the 7-cycloethylenemercaptol, which has served so well with 7,11-diones of the allo (*vide supra*) and normal[12] series, has now proved equally satisfactory in the transformation of allopregnane-3β,11α,20β-triol-7-one (Va) to allopregnane-3β,11α,20β-triol (Ve). The isomeric 3β,11β,20β-triol (IIIa) was synthesized by lithium aluminum hydride reduction of allopregnane-3,11,20-trione (VI) and, in accordance with that formulation, IIIa formed only a 3,20-diacetate (IIIb); oxidation of the latter led to the above described allopregnane-3β,20β-diol-11-one diacetate (IIb).

(10) E. M. Chamberlain, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, THIS JOURNAL, **73**, 2396 (1951).

(11) C. Djerassi, H. J. Ringold and G. Rosenkranz, *ibid.*, **73**, 5513 (1951).

(12) L. F. Fieser, J. E. Herz and W. Huang, *ibid.*, **73**, 2397 (1951); L. F. Fieser, J. C. Babcock, J. E. Herz, W. Huang and W. P. Schneider, *ibid.*, **73**, 4053 (1951).

(12a) NOTE ADDED IN PROOF: R. C. Anderson, R. Budziarek, G. T. Newbold, R. Stevenson and F. S. Spring, *Chem. ent. Int.*, 1035 (1951), have outlined a similar method to the presently described one in the ergosterol series.

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

Experimental[14]

$\Delta^{8,11}$-Allopregnadiene-3β,20β-diol-7-one (IVa).—A mixture of 1.0 g. of Δ^8-allopregnene-3β,11α,20β-triol-7-one (Ia),[4] 2 cc. of concentrated hydrochloric acid and 80 cc. of

(14) Melting points are uncorrected. Unless noted otherwise, rotations were determined in chloroform and ultraviolet absorption spectra in 95% ethanol solution. The infrared spectra were obtained on a Perkin–Elmer model 12C spectrometer with sodium chloride prism. We are indebted to Srta. Paquita Revaque and staff for the physical measurements and to Srta. Amparo Barba for the microanalyses.

methanol was refluxed for one hour, concentrated to one-half its volume, diluted with water and filtered; yield 0.33 g., m.p. 220–223°. The analytical sample crystallized as colorless plates from hexane–acetone with m.p. 228–229°, $[\alpha]^{20}D$ −31° (ethanol), $\lambda_{max.}^{EtOH}$ 226 and 298 mμ, log ε 4.30, 3.81, $\lambda_{max.}^{nujol}$ 1660 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.48; H, 9.10.

The identical dehydration product (mixed m.p., analysis, infrared spectrum of free diol and diacetate) was isolated in 50% yield when a solution of 2.5 g. of Δ^5-allopregnene-3β,-11α,20β-triol-7-one triacetate (Ib) and 0.25 g. of *p*-toluenesulfonic acid in 200 cc. of acetic anhydride was slowly concentrated over a period of 5 hours to a volume of 40 cc. and the resulting product saponified with methanolic sodium hydroxide solution.

The diacetate IVb exhibited m.p. 160–162°, $[\alpha]^{20}D$ −1°, $\lambda_{max.}^{EtOH}$ 226 and 297 mμ, log ε 4.33, 3.88, $\lambda_{max.}^{nujol}$ 1736 and 1666 cm.$^{-1}$ no free hydroxyl band.

Anal. Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.68; H, 8.55.

$\Delta^{5,11}$-Allopregnadiene-3β,20β-diol-7-one oxime, prepared in pyridine solution, was recrystallized from methanol whereupon it showed m.p. 228–229°, $\lambda_{max.}^{EtOH}$ 228 and 298 mμ, log ε 4.30, 3.72.

Anal. Calcd. for $C_{21}H_{31}O_3N$: C, 73.02; H, 9.04; N, 4.05. Found: C, 73.10; H, 9.28; N, 4.22.

Allopregnane-3β,20β-diol-7,11-dione (IIa).—To a solution of 8.0 g. of potassium in 500 cc. of anhydrous *t*-butyl alcohol was added 7.0 g. of Δ^5-allopregnene-3β,11α,20β-triol-7-one (Ia)[4] and the mixture was refluxed for 30 minutes[15] at which time it had assumed a reddish color. On addition of 600 cc. of water and acidifying with dilute hydrochloric acid, the solution turned yellowish and was concentrated *in vacuo* until all the alcohol had distilled. The collected precipitate after recrystallization from methanol–acetone afforded 6.5 g. of colorless needles with m.p. 280–281°, $[\alpha]^{20}D$ −23° (ethanol), $\lambda_{max.}^{EtOH}$ 294, mμ, log ε 1.90.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.40; H, 9.47.

The diacetate IIb was obtained in nearly quantitative yield; m.p. 125–126°, $[\alpha]^{20}D$ −15°, $\lambda_{max.}^{CHCl_3}$ 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, 69.34; H, 8.21.

The mono-oxime IIc had m.p. 313–315°, $[\alpha]^{20}D$ −56° (ethanol), no selective absorption in the ultraviolet.

Anal. Calcd. for $C_{21}H_{33}O_4N$: C, 69.38; H, 9.15; N, 3.85. Found: C, 69.76; H, 9.45; N, 4.30.

Allopregnane-3β,20β-diol-7,11-dione 7-Cycloethylenemercaptol Diacetate (IId).—The mercaptol was prepared in the usual fashion[16] by allowing a mixture of 1.5 g. of dioldione diacetate IIb, 1.5 cc. of ethanedithiol, 10 g. of anhydrous zinc chloride, 10 g. of anhydrous sodium sulfate and 30 cc. of dioxane to stand at room temperature for 18 hours. Dilution with water, filtration and recrystallization from methanol yielded 1.3 g. of the mercaptol IId as needles with m.p. 207–209°, $[\alpha]^{20}D$ −10° (dioxane).

Anal. Calcd. for $C_{27}H_{40}O_5S_2$: C, 63.75; H, 7.92; S, 12.58. Found: C, 64.03; H, 8.12; S, 12.57.

Allopregnane-3β,20β-diol-11-one Diacetate (IIe) (a) By Desulfurization of Allopregnane-3β,20β-diol-7-11-dione 7-Cycloethylenemercaptol Diacetate (IId).—One gram of the above mercaptol in 300 cc. of ethanol was refluxed for two hours with *ca.* 10 g. of W-2 Raney nickel catalyst.[17] After filtration of the catalyst, evaporation to dryness and recrystallization from methanol–water there was isolated 0.72 g. of diacetate IIe with m.p. 154–156°, $[\alpha]^{20}D$ +32°, $\lambda_{max.}^{CHCl_3}$ 1726 (acetate) and 1710 cm.$^{-1}$ (11-ketone).

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.90; H, 8.93.

(b) **By Oxidation of Allopregnane-3β,11β,20β-triol 3,-20-Diacetate (IIIb)**.—The pure diacetoxy ketone IIe was isolated in 70% yield on oxidizing 0.5 g. of the triol diacetate IIIb with 0.5 g. of chromium trioxide in 30 cc. of 90% acetic acid for one hour at room temperature. The identity of the acetate, m.p. 155–157°, $[\alpha]^{20}D$ +33°, with that prepared according to (a) was established by infrared comparison.

Allopregnane-3β,20β-diol-11-one (IIf) was obtained upon alkaline saponification of the above diacetate; m.p. 239–240°, $[\alpha]^{20}D$ +34° (ethanol). Chromium trioxide oxidation led in 75% yield to the known[4,9] allopregnane-3,11,20-trione (VI).

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.60; H, 10.23.

Allopregnane-3β,11α,20β-triol (Vc).—Allopregnane-3β,-11α,20β-triol-7-one (Va)[4] was converted in the above described manner to the **mercaptol** Vb; yield 78%, m.p. 281–283°, $[\alpha]^{20}D$ +6.2° (dioxane).

Anal. Calcd. for $C_{23}H_{38}O_3S_2$: C, 64.74; H, 8.97; S, 15.03. Found: C, 65.04; H, 9.20; S, 15.44.

Desulfurization of the mercaptol (0.3 g.) with 3.0 g. of W-2 Raney nickel catalyst[17] afforded 0.18 g. of the desired **allopregnane-3β,11α,20β-triol (Vc)** with m.p. 252–254°, undepressed on admixture with a sample[4] prepared by Huang-Minlon reduction[13] of Va, $[\alpha]^{20}D$ −23° (ethanol).

Allopregnane-3β,11β,20β-triol (IIIa)—Allopregnane-3,11,20-trione (VI)[4,9] (0.4 g.) was refluxed for 20 minutes with 0.4 g. of lithium aluminum hydride in 60 cc. of tetrahydrofuran. The usual work-up followed by recrystallization from hexane–acetone yielded 0.3 g. of colorless crystals with m.p. 203–205°, $[\alpha]^{20}D$ +41° (ethanol), free hydroxyl band in the infrared. Chromium trioxide oxidation regenerated the starting trione VI.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.74; H, 10.79.

Acetylation in the usual manner (acetic anhydride–pyridine, 1 hour, steam-bath) and recrystallization from pentane–ether produced small prisms of the **triol diacetate (IIIb)** with m.p. 180–182°, $[\alpha]^{20}D$ +34°, free hydroxyl as well as acetate bands in the infrared.

Anal. Calcd. for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59. Found: C, 71.73; H, 9.53.

22-Isoallospirostan-3β-ol-7,11-dione (VIIIa).—To a solution of 15 g. of potassium in 500 cc. of *t*-butyl alcohol was added a warm solution of 15.0 g. of Δ^5-22-isoallospirosten-3β,11α-diol-7-one (VII)[2] in 500 cc. of the same solvent and the mixture was refluxed for 30 minutes. The light red solution was worked up exactly as described above for the potassium *t*-butoxide isomerization of Ia and afforded 9.6 g. (64%) of 22-isoallospirostan-3β-ol-7,11-dione (VIIIa) with m.p. 273–275° (Kofler block; the crystal form seemed to change at about 245°), $[\alpha]^{20}D$ −54°, no selective absorption in the ultraviolet. From the mother liquors, there was isolated nearly 1 g. of recovered starting material.

Anal. Calcd. for $C_{27}H_{40}O_5$: C, 72.94; H, 9.07. Found: C, 73.19; N, 9.41.

The acetate VIIIb was obtained in nearly quantitative yield, m.p. 235–237°, $[\alpha]^{20}D$ −82°, and proved to be identical (infrared spectrum) with a specimen prepared by an alternate procedure.[2]

22-Isoallospirostan-3β-ol-7,11-dione 7-cycloethylenemercaptol acetate (VIIIc) was obtained in the usual manner (*vide supra*[16]) in 87% yield; m.p. 295–296°, $[\alpha]^{20}D$ −79° (dioxane).

Anal. Calcd. for $C_{31}H_{46}O_5S_2$: C, 66.16; H, 8.23; S, 11.37. Found: C, 66.55; H, 8.09; S, 11.51.

Desulfurization of the above mercaptol (1.0 g.) with 15 g. of W-2 Raney nickel catalyst[17] in ethanol solution (2 hours refluxing) produced 0.6 g. of **22-isoallospirostan-3β-ol-11-one acetate (VIIId)** with m.p. 222–225°, which proved to be identical (infrared spectrum) with an authentic specimen.[2,11]

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(15) The same yield was obtained if the reaction time was increased to 2 hours.

(16) H. Hauptmann, THIS JOURNAL, **69**, 562 (1947).

(17) H. Adkins and A. Pavlic, *ibid.*, **69**, 3039 (1947).