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

Steroidal Sapogenins. XXII.[1] Steroids. XXXIV.[2] Degradation of 11-Oxygenated Sapogenins. Synthesis of Allopregnane-$3\beta,11\beta$-diol-20-one and Allopregnane-$3\beta,11\alpha$-diol-20-one

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Side chain degradation of 22-isoallospirostan-3β-ol-11-one (11-ketotigogenin) by way of the crystalline "diosone" IIIa led to Δ^{16}-allopregnen-3β-ol-11,20-dione acetate IVa which upon hydrogenation produced the known allopregnan-3β-ol-11,20-dione acetate (Va). Protection of the 20-keto group by means of ketal or hemithioketal formation followed by lithium aluminum hydride reduction and acid or Raney nickel cleavage furnished allopregnane-$3\beta,11\beta$-diol-20-one (VII). The corresponding 11α-epimer (Vb) was prepared by side chain degradation of 22-isoallospirostan-$3\beta,11\alpha$-diol and subsequent hydrogenation of the resulting Δ^{16}-allopregnene-$3\beta,11\alpha$-diol-20-one diacetate.

Allopregnane-$3\beta,11\beta$-diol-20-one (VII) and allopregnane-$3\beta,11\alpha$-diol-20-one (Vf) are potentially important starting materials for the synthesis of 17α-hydroxycorticosterone (Kendall's Compound F) and its 11α-hydroxy epimer, and the present paper is concerned with the preparation of these two previously unknown 20-ketopregnanes from 11-oxygenated sapogenins.

The degradation of the side chain of 22-isoallospirostan-3β-ol-12-one (hecogenin) proceeds in a much poorer yield[4] than that of ring C unsubstituted sapogenins,[5] and it was of interest as well as of practical significance to determine the course and yield of the side chain degradation of 11-oxygenated sapogenins. 22-Isoallospirostan-3β-ol-11-one (Ia) is a key intermediate in certain synthetic sequences from Δ^5-22-isospirosten-3β-ol (diosgenin)[6,7] and 22-isoallospirostan-3β-ol-12-one (hecogenin)[8] to cortisone and the side chain degradation of this 11-keto sapogenin Ia has so far only been reported in a preliminary communication.[6] As described in the experimental section, this reaction proceeds particularly well and just as in the case of Δ^7-22-isoallospirosten-3β-ol[9] yields a rather insoluble "diosone" (IIIa), thus considerably facilitating the isolation of pure intermediates. Hydrolysis of the "diosone" IIIa followed by hydrogenation of the resulting Δ^{16}-20-ketone IVa[10] led to the previously described[6,11] allopregnan-3β-ol-11-20-dione acetate (Va). Conversion of this substance to the desired 11β-hydroxy derivative VII was accomplished by two closely related methods. The first procedure, adapted from one employed recently[12] with pregnan-3α-ol-11,20-dione and involving formation of the 20-ethylene ketal (VIc) followed by reduction with lithium aluminum hydride and acid hydrolysis, was carried out without isolation of intermediates and led directly to the $3\beta,11\beta$-diol-20-one VIIa. The second approach was developed in an attempt to employ a procedure which would obviate the acid hydrolysis once the acid-labile 11β-hydroxy group was formed and took advantage of the recently described[13] Raney nickel hydrolysis of hemithioketals. Allopregnan-3β-ol-11,20-dione acetate (Va) was converted by means of β-mercaptoethanol and zinc chloride into the 20-hemithioketal (VIa) which was reduced with lithium aluminum hydride to the 20-hemithioketal of allopregnane-$3\beta,11\beta$-diol-20-one (VIb) and then treated with Raney nickel in ethanol solution to give allopregnane-3β,11β-diol-20-one (VIIa) further characterized by its 3-monoacetate (VIIb).

The preparation of the epimeric allopregnane-$3\beta,11\alpha$-diol-20-one diacetate Vb was accomplished by degrading 22-isoallospirostan-$3\beta,11\alpha$-diol[14] *via* the oily furosten IIb and "diosone" IIIb directly to Δ^{16}-allopregnene-$3\beta,11\alpha$-diol-20-one diacetate IVb in 45% over-all yield followed by catalytic hydrogenation of the Δ^{16}-double bond. Application of Kritchevsky and Gallagher's enol acetate-peracid method[15] led to allopregnane-$3\beta,11\alpha,17\alpha$-triol-20-one diacetate (VIII).

Experimental[16]

Δ^{16}Allopregnen-3β-ol-11,20-dione Acetate (IVa).—A solution of 7 g. of 22-isoallospirostan-3β-ol-11-one[6,7,8] in 55 cc. of acetic anhydride was heated in a bomb tube for eight hours at 190°, poured into water, extracted with ether, washed well with sodium carbonate solution, water, dried and evaporated. The resulting oily $\Delta^{20(22)}$-allofurostene-3β,26-diol-11-one diacetate (IIa) was oxidized with chromium trioxide exactly as described in the degradation of

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[1] Paper XXI, G. Diaz, A. Zaffaroni, G. Rosenkranz and C. Djerassi, *J. Org. Chem.*, in press.

[2] Paper XXXIII, J. Pataki, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **74**, 3436 (1952).

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[4] R. B. Wagner, J. A. Moore and R. F. Forker, THIS JOURNAL, **72**, 1856 (1950).

[5] *Cf.* R. E. Marker, *ibid.*, **62**, 3350 (1940).

[6] E. M. Chamberlain, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, *ibid.*, **73**, 2396 (1951).

[7] J. Romo, G. Stork, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 2918 (1952); F. Sondheimer, R. Yashin, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 2696 (1952).

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

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

[10] It is interesting to note that while Δ^{16}-12,20-diones exhibit an abnormally low ultraviolet absorption maximum at 230 mμ (ref. 4), the corresponding 11-keto or 11α-acetoxy derivatives (IVa,b) show maxima at the usual position (237 mμ).

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

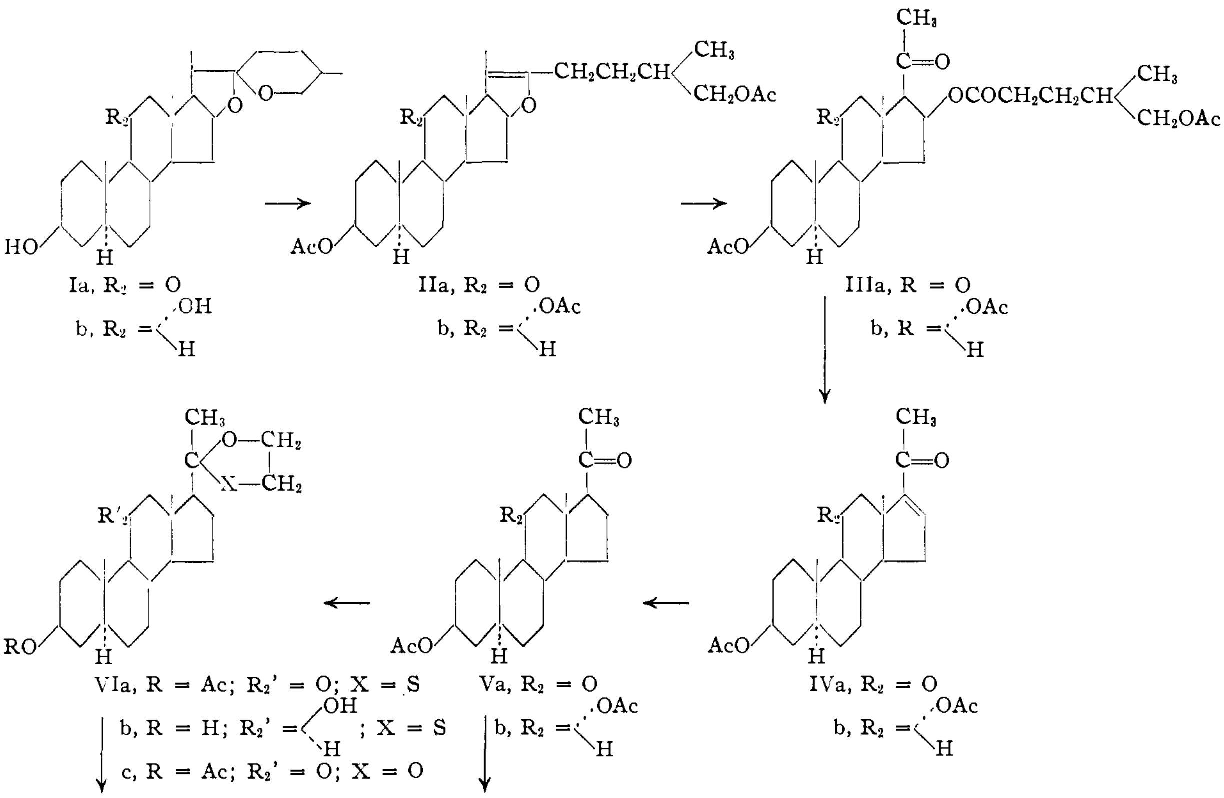
[12] G. Rosenkranz, J. Pataki and C. Djerassi, *J. Org. Chem.*, **17**, 290 (1952).

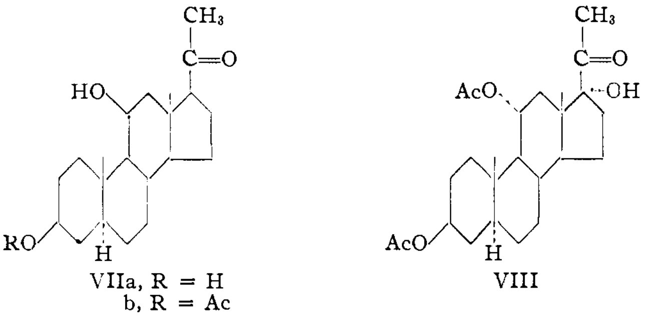
[13] J. Romo, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 4961 (1951).

[14] C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, *ibid.*, **74**, 1712 (1952).

[15] T. H. Kritchevsky and T. F. Gallagher, *J. Biol. Chem.*, **179**, 507 (1949); THIS JOURNAL, **73**, 184 (1951).

[16] All melting points are uncorrected. Unless noted otherwise, rotations were determined in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Srta. Paquita Revaque for these measurements and to Srta. Amparo Barba for the microanalyses. Acknowledgment is also due to Srta. Josefina Gatica for assistance in certain phases of the experimental work.





Δ^7-22-isoallospirosten-3β-ol[8] and after two recrystallizations from methanol afforded 5.02 g. (56%) of **allopregnane-3β,16β-diol-11,20-dione 3-acetate 16-γ-methyl-δ-acetoxyvalerate (IIIa)** with m.p. 128–130°, $[\alpha]^{20}_D$ +47°, no selective absorption in the ultraviolet.

Anal. Calcd. for $C_{31}H_{46}O_8$: C, 68.10; H, 8.48. Found: C, 68.26; H, 8.25.

Separate bicarbonate saponification[8] of the mother liquors of IIIa and of the crystalline "diosone" IIIa followed by recrystallization from methanol–chloroform furnished a total of 3.24 g. (53% over-all yield based on 22-isoallospirostan-3β-ol-11-one) of **Δ^{16}-allopregnen-3β-ol-11,20-dione acetate (IVa)** with m.p. 184–185°, $[\alpha]^{20}_D$ +66°, λ_{max}^{EtOH} 237 and 312 mμ, log ε 4.13, 1.85; reported,[6] m.p. 183–185°, $[\alpha]^{20}_D$ +64.5°.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.75; H, 8.46.

Allopregnan-3β-ol-11,20-dione Acetate (Va).—The catalytic hydrogenation of the Δ^{16}-dione IVa was accomplished in 86% yield at room temperature and atmospheric pressure (1 hour) employing ethyl acetate as the solvent and 5% palladized charcoal as the catalyst. Recrystallization from hexane–acetone gave colorless crystals with m.p. 143–145°, $[\alpha]^{20}_D$ +86.5°; lit.[6,11] m.p. 141–143°, 143–145°, $[\alpha]_D$ +88°.

Allopregnan-3β-ol-11,20-dione 3-Acetate 20-Ethylenehemithioketal (VIa).—The hemithioketal was prepared in the usual fashion[13] from 1.0 g. of the dione Va, 1.5 cc. of β-mercaptoethanol, 5 g. of anhydrous sodium sulfate and 5 g. of freshly fused zinc chloride in 15 cc. of dioxane. Recrystallization from chloroform–methanol afforded 0.8 g. of brilliant plates with m.p. 191–193°, $[\alpha]^{20}_D$ +35° (dioxane).

Anal. Calcd. for $C_{25}H_{38}O_4S$: C, 69.09; H, 8.81. Found: C, 69.46; H, 8.97.

Allopregnane-3β,11β-diol-20-one 20-Ethylenehemithioketal (VIb).—A solution of 0.4 g. of the above hemithioketal VIa in 30 cc. of tetrahydrofuran was added dropwise to a mixture of 200 mg. of lithium aluminum hydride in 20 cc. of ether and the mixture was refluxed for 20 minutes. After decomposition with water, evaporation of the ether and addition of Rochelle salt solution, the product was filtered and recrystallized from methanol–water yielding 350 mg. of colorless crystals with m.p. 175–178°, $[\alpha]^{20}_D$ +28° (dioxane).

Anal. Calcd. for $C_{23}H_{38}O_3S$: C, 70.01; H, 9.70. Found: C, 69.69; H, 9.78.

Allopregnane-3β,11β-diol-20-one (VIIa) (a) From Allopregnane-3β,11β-diol-20-one 20-Ethylenehemithioketal (VIb).—An acetone solution of 300 mg. of the hemithioketal VIb was refluxed for 2 hours with 3 g. of W-2 Raney nickel,[17] the catalyst was filtered, the solvent was evaporated to dryness and the crystalline residue was recrystallized from hexane–acetone furnishing 190 mg. of **allopregnane-3β,11β-diol-20-one (VIIa)** with m.p. 232–234°, $[\alpha]^{20}_D$ +114°.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C; 75.54; H, 10.26.

Acetylation with acetic anhydride–pyridine (1 hour, steam-bath) followed by recrystallization from dilute methanol produced shiny crystals of the **3-monoacetate VIIb** with m.p. 180–182°, $[\alpha]^{20}_D$ +102°, $\lambda_{max}^{CHCl_3}$ 1722 cm.$^{-1}$ (acetate), 1700 cm.$^{-1}$ (20-ketone) and free hydroxyl band.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.40; H, 9.69.

(b) **From Allopregnan-3β-ol-11,20-dione 3-Acetate 20-Ethyleneketal (VIc).**—A benzene solution of 0.8 g. of the dione acetate Va was converted in the usual manner[12] with ethylene glycol into the ethylene ketal VIc which without purification was reduced in ether solution with lithium aluminum hydride in the above described manner. The crude reduction product was dissolved in 50 cc. of acetone and left at room temperature with 200 mg. of *p*-toluenesul-

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

fonic acid for 20 hours in order to cleave the ketal grouping. Dilution with water, extraction with chloroform, washing with water, drying, evaporating and recrystallizing from acetone–hexane furnished 0.42 g. of the diol VIIa with m.p. 231–234°. The monoacetate VIIb melted at 180–182° and the infrared curves of both products proved to be identical with those of specimens prepared according to (a).

Δ^{16}-Allopregnene-3β,11α-diol-20-one Acetate (IVb).—The degradation of the side chain of 22-isoallospirostan-3β,11α-diol (Ib)[14] was carried out exactly as described for the 11-keto analog Ib except that the furosten IIb and the "diosone" IIIb were not isolated. Crystallization from ether–hexane afforded between 43–47% of the Δ^{16}-diacetate IVb with m.p. 156–158°, $[\alpha]^{20}\text{D}$ −10°, $\lambda_{\max}^{\text{EtOH}}$ 237 mμ, log ϵ 4.12, $\lambda_{\max}^{\text{CHCl}_3}$ 1724 and 1668 cm.$^{-1}$, but no free hydroxyl band.

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.09; H, 8.49.

Allopregnane-3β,11α-diol-20-one Diacetate (Vb).—The catalytic hydrogenation of the Δ^{16}-derivative IVb was performed as described for the 11-keto analog IVa and proceeded in 90% yield; m.p. 171–173°, $[\alpha]^{20}\text{D}$ +44°, $\lambda_{\max}^{\text{CHCl}_3}$ 1724 cm.$^{-1}$ (acetate) and 1702 cm.$^{-1}$ (saturated 20-ketone).

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.97; H, 9.19.

Allopregnane-3β,11α,17α-triol-20-one 3,11-Diacetate (VIII).—The above diacetate Vb was converted into its enol acetate and treated with peracid exactly as described for allopregnan-3β-ol-20-one[15] except that monoperphthalic acid[18] rather than perbenzoic acid[15] was used. The crude product from the alkaline saponification of the epoxide was directly acetylated with pyridine–acetic anhydride and after recrystallization from hexane–acetone afforded in 65–73% yield the diacetate VIII with m.p. 180–182°, $[\alpha]^{20}\text{D}$ −28°, $\lambda_{\max}^{\text{CHCl}_3}$ 1726, 1704 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.34; H, 8.87.

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[18] G. Rosenkranz, J. Pataki, St. Kaufmann, J. Berlin and C. Djerassi, THIS JOURNAL, **72**, 4081 (1950).

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Many-Membered Carbon Rings. V. Cyclodecyne, *cis*- and *trans*-Cyclodecene and Related Compounds[1]

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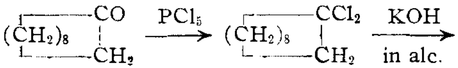
The synthesis of the ten-membered cyclic hydrocarbons cyclodecyne, *cis*-cyclodecene and *trans*-cyclodecene has been achieved. Cyclodecyne was obtained by the oxidative decomposition of 1,2-cyclodecanedione dihydrazone with yellow mercuric oxide. Hydrogenation of cyclodecyne in the presence of a palladium catalyst led to *cis*-cyclodecene which was also obtained by dechlorination of 1-chlorocyclodecene using sodium in liquid ammonia. *trans*-Cyclodecene was produced by dehydration of cyclodecanol, by the action of zinc on 2-bromocyclodecanol acetate, and by the thermal decomposition of cyclodecyltrimethylammonium hydroxide. Certain physical properties of these cyclic hydrocarbons and many of their cyclic intermediates have been determined. The infrared spectra of these compounds show that there is a close correspondence in characteristic absorptions for various atomic groupings in acyclic and C_{10}-carbocyclic compounds. A comparison of the properties of the isomeric cyclodecenes indicates that both forms are probably strainless with *trans*-cyclodecene being the more stable thermally.

The development of the acyloin condensation as a useful method for the synthesis of carbocyclic compounds[3,4,5] has encouraged a study of the chemistry of simple functional derivatives of many-membered carbon rings in the intermediate range, *i.e.*, carbocycles having 9 to 12 members. The extensive work of Ruzicka and others has shown that derivatives of carbocycles containing 15 or more ring members may be obtained by transformations applicable to open-chain molecules of comparable size and, further, the properties of such compounds are also similar to those of analogous acyclic molecules. However, in the intermediate range of carbocycles methods of synthesis as well as chemical and physical properties appear not to correspond closely to acyclic analogs.

The present article describes observations pertaining to certain unsaturated hydrocarbons having a ten-membered carbon ring. The considerable interest in corresponding derivatives of the eight-membered carbocycle stimulated these particular studies.[6,7]

Sebacoin, obtained in improved yield (55%) by certain modifications of methods previously described,[3,4,5] was used as the starting material for all syntheses. Since the application of infrared spectrophotometry proved to be of great value in following the purification of many of the ten-membered ring compounds and in their ultimate characterization, infrared absorption curves for some of the compounds studied are presented. No data up to the present time have been published on the infrared spectra of carbocycles containing more than eight members.

Cyclodecyne.—In view of Domnin's report of a successful synthesis of cycloöctyne[8] it seemed reasonable to apply his method to the synthesis of cyclodecyne (V) from cyclodecanone (I) as outlined in the following diagram.



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[1] For the preceding paper in this series see A. T. Blomquist, *et al.*, THIS JOURNAL, **73**, 5510 (1951).

[2] Abstracted from the dissertations presented by Arthur C. Sucsy in February, 1949, and Robert E. Burge, Jr., in February, 1952, to the Graduate Faculty of Cornell University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[3] V. L. Hansley, U. S. Patent 2,228,268, Jan., 1941; *C. A.*, **35**, 2534 (1941).

[4] V. Prelog, L. Frenkiel, M. Kobelt and P. Barman, *Helv. Chim. Acta*, **30**, 1741 (1947).

[5] M. Stoll and J. Hulstkamp, *ibid.*, **30**, 1815 (1947); M. Stoll and A. Rouve, *ibid.*, **30**, 1822 (1947).

[6] K. Ziegler and H. Wilms, *Ann.*, **567, 1** (1950).

[7] L. E. Craig, *Chem. Revs.*, **49**, 103 (1951).

[8] N. A. Domnin, *J. Gen. Chem.* (*U. S. S. R.*), **8,** 851 (1938); *C. A.*, **33,** 1282 (1939).