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

Steroids. LXX.[1] Removal of the 17-Hydroxyl Group from 17α,21-Dihydroxy-20-ketopregnane Derivatives[2]

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A convenient and simple two-step sequence for removing the 17α-hydroxy group from 17α,21-dihydroxy-20-ketopregnane derivatives is described, which involves formation of the 21,21-dibenzyloxy-20-ketone followed by catalytic hydrogenolysis. The method was first studied with Δ⁵-pregnene-3β,17α,21-triol-20-one (I), which yielded allopregnane-3β,21-diol-20-one (III), and has been used to prepare Reichstein's Substance N (IXa) and R (IXb) from cortisone (IVa) and hydrocortisone (IVb), respectively. The conversion of Reichstein's Substance S (IVc) to desoxycorticosterone (XII) shows that the Δ⁴-3-keto system may be left intact if it is protected by ketalization.

In these laboratories certain naturally occurring 11-oxygenated pregnan-20-one-21-ol derivatives, especially allopregnane-3β,21-diol-11,20-dione (Reichstein's substance N) (IXa) and allopregnane-3β,11β,21-triol-20-one (Reichstein's substance R) (IXb) were required. These compounds previously had been synthesized from corticosterone,[3] but in view of the ready commercial availability of cortisone (IVa) and hydrocortisone (IVb) it seemed highly desirable to convert these latter substances to IXa and IXb, respectively, through removal of the 17α-hydroxy group and reduction of ring A. The present paper describes the realization of this objective.

The removal of the 17α-hydroxy group from a 17α,21-dihydroxy-20-ketopregnane was studied first with Δ⁵-pregnene-3β,17α,21-triol-20-one (I).[4] A possible method seemed to be one involving reaction of I with methanol in the presence of anhydrous hydrogen chloride to give the 21,21-dimethoxy-20-ketone (IIa) with the 17-hydroxy group eliminated, as described by Mattox[5] in other series, followed by hydrolysis to the 20-keto-21-aldehyde (or its hydrate) and reduction at C-21. The hydrolysis of 21,21-dimethoxy-20-ketones of type IIa, however, proved to be very complex[6] and none of the 20-keto-21-alcohol III could be isolated after reduction, despite the fact that both steps were carried out under a variety of conditions.

The above difficulty was overcome by substituting the 21,21-dibenzyl acetal IIb for the dimethyl acetal, since it is known that benzyl ethers may be cleaved readily, *e.g.*, through catalytic reduction. The crystalline dibenzyl ether IIb was obtained smoothly in *ca.* 70% yield by treating the triol I with dry hydrogen chloride in benzyl alcohol for 5 days at room temperature. The structural assignment was based on the analogous dimethoxy acetals obtained by Mattox[5] with hydrogen chloride in methanol and was confirmed by the elementary analysis, the comparatively low polarity and the negative reaction with triphenyltetrazolium chloride.

The catalytic hydrogenolysis of the dibenzyl acetal IIb was studied with a number of different catalysts. The best conditions were found to be hydrogenation in ethanol solution over a 10% palladium–charcoal catalyst at room temperature and atmospheric pressure, when *ca.* 4 moles of hydrogen was absorbed and allopregnane-3β,21-diol-20-one (III) (identified by comparison with an authentic sample) was produced in 64% yield. Catalytic hydrogenation of the 21,21-dibenzyloxy-20-ketone system present in IIb therefore yields the 21-hydroxy-20-ketone directly in one step (in the case studied the Δ⁵-double bond was reduced as well) and a simple two-step method for removing the 17-hydroxy grouping from 17α,21-dihydroxy-20-ketones had been found.

The method was next applied to the synthesis of Reichstein's Substance N (IXa) from cortisone (IVa). Treatment of the latter (or of its 21-acetate) with hydrogen chloride in a mixture of chloroform and benzyl alcohol for 2 days yielded the dibenzyl acetal Va, which on hydrogenation over a 10% palladium–charcoal catalyst followed by acetylation and chromatographic purification produced the required allopregnane-3,11,20-trione-21-ol acetate (VIa). The latter was identified with a sample prepared by oxidizing allopregnane-11β,21-diol-3,20-dione 21-acetate (dihydro-allocorticosterone acetate) (VIb)[7] with chromium trioxide. It was expected that the allo (5α) isomer would be produced by reduction of the Δ⁴-double bond of Va, since it is known[7] that 11-keto and 11β-hydroxy-Δ⁴-3-ketones on hydrogenation yield this isomer predominantly.

Unfortunately the yield in the reduction step leading from Va to VIa was low, the over-all yield of VIa from cortisone being only *ca.* 12%. This could be improved by carrying out separately the reduction of the Δ⁴-3-ketone system and that of the 21,21-dibenzyloxy-20-ketone system. Thus, when cortisone acetate was first reduced catalyti-

(1) Paper LXIX, A. Zaffaroni, V. Troncoso and M. Garcia, *Chemistry & Industry*, 534 (1955).

(2) Presented in part at the New York Meeting of the American Chemical Society, September, 1954.

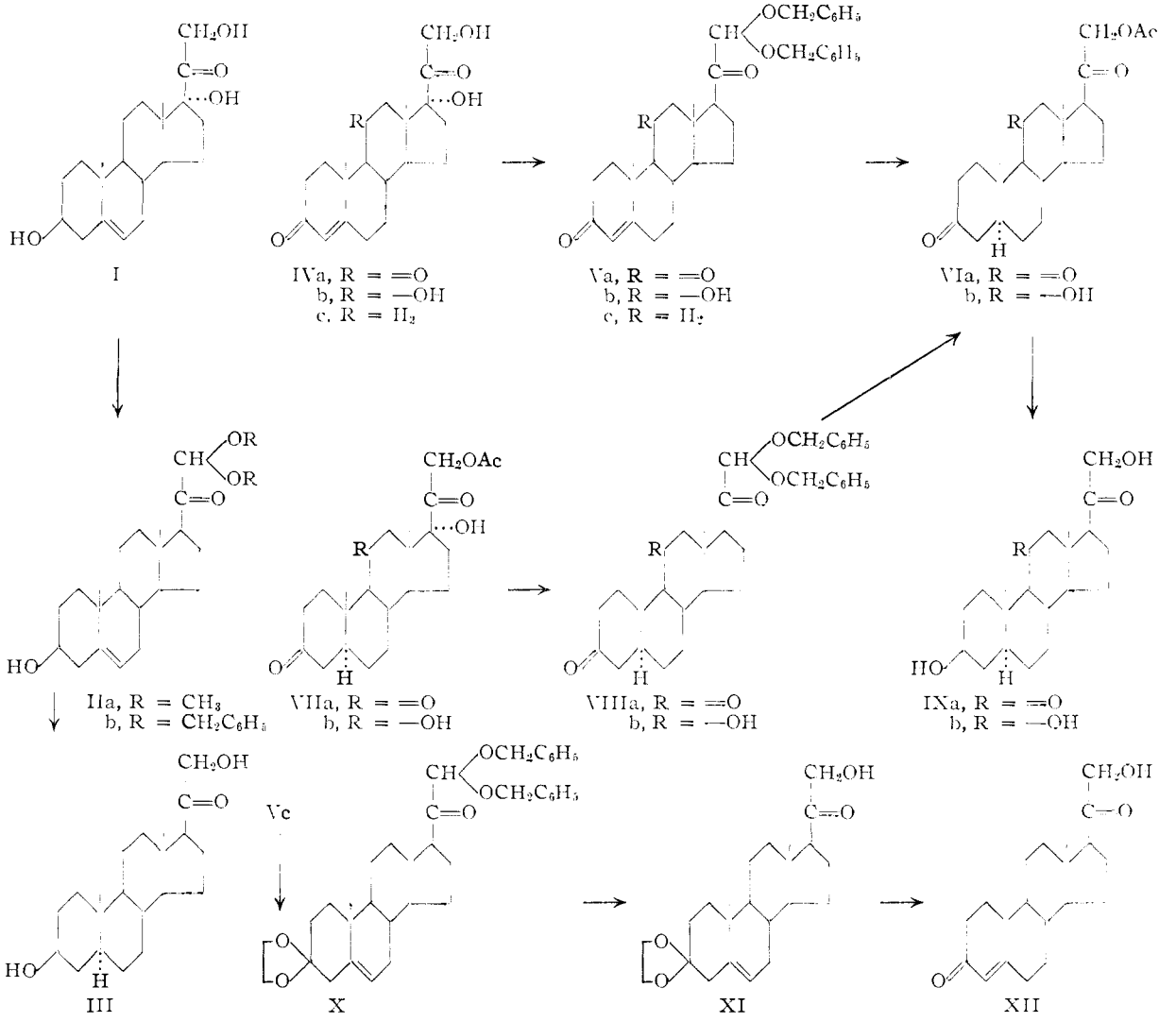
(3) Synthesis of Substance R 21-monoacetate and 3,21-diacetate: J. Pataki, G. Rosenkranz and C. Djerassi, *J. Biol. Chem.*, **195**, 751 (1952). Oxidation of Substance R diacetate to Substance N diacetate: T. Reichstein, *Helv. Chim. Acta*, **21**, 1490 (1938). It is of interest to mention that an indirect path may be traced from cortisone acetate to Substance N diacetate *via* allopregnane-3β,11β,17α,20β,21-pentol (Reichstein's Substance A) 3,20,21-triacetate [C. Djerassi, G. Rosenkranz, J. Pataki and S. Kaufmann, *J. Biol. Chem.*, **194**, 115 (1952); see also L. H. Sarett, M. Feurer and K. Folkers, THIS JOURNAL, **73**, 1777 (1951); P. L. Julian, E. W. Meyer, W. J. Karpel and W. Cole, *ibid.*, **73**, 1982 (1951); T. Reichstein and J. von Euw, *Helv. Chim. Acta*, **24**, 247 E (1941)], 17-iso-allopregnane-3β,11β,21-triol-20-one (iso-R) 3,21-diacetate and 17-isoallopregnane-3β,21-diol-11,20-dione (iso-N) diacetate [C. W. Shoppee and T. Reichstein, *ibid.*, **23**, 729 (1940)].

(4) J. Heer and K. Miescher, *ibid.*, **34**, 359 (1951).

(5) V. R. Mattox, THIS JOURNAL, **74**, 4340 (1952).

(6) *Cf.* H. Reich and T. Reichstein, *Helv. Chim. Acta*, **22**, 1124 (1939).

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



cally to dihydro-allocortisone acetate (VIIa) (72% yield)[8] and the latter then converted to the dibenzyl acetal VIIIa, catalytically reduced and acetylated, allopregnan-21-ol-3,11,20-trione acetate (VIa) was obtained in 24% over-all yield. Finally preferential reduction of VIa at C-3 through hydrogenation over a Raney nickel catalyst (as had been described for the corresponding 11β-hydroxy derivative VIb),[7] followed by saponification with sodium carbonate, afforded Reichstein's Substance N (IXa) in 52% yield.

In analogous fashion, for the synthesis of Reichstein's Substance R (IXb), hydrocortisone (IVb) was transformed to the non-crystalline benzyl acetal Vb,[9] which on hydrogenation over a 10% palladium–charcoal catalyst followed by acetylation produced the known dihydro-allocorticosterone acetate (VIb)[7] in 16% over-all yield. Again the yield could be improved to 26% by first hydrogenating hydrocortisone acetate to the dihydro-allo compound VIIb[7] (81%) and then carrying out the benzyl acetal formation, catalytic hydrogenation and acetylation with this substance. The preferential reduction of VIb at C-3 by means of hydrogen over Raney nickel has been described previously[7] and saponification of the resulting Substance R 21-acetate with sodium carbonate furnished Substance R.

Finally it has been shown that the above described method for removing the 17-hydroxy group may be carried out without hydrogenating the Δ^4-3-ketone system, if the latter is protected by ketal formation. This was demonstrated by the conversion of Δ^4-pregnene-3,20-dione-17α,21-diol (Reichstein's Substance S) (IVc) to desoxycorticosterone (XII). Substance S (or its acetate) was first transformed in the usual way to the non-crystalline dibenzyl acetal Vc (76%). It was expected that the latter substance on cycloethylene ketalization would be attacked only at C-3 since it

(8) C. Djerassi, G. Rosenkranz, J. Pataki and S. Kaufmann, *J. Biol. Chem.*, **194**, 115 (1952); E. Wilson and M. Tishler, THIS JOURNAL, **74**, 1609 (1952).

(9) It was found that the reaction conditions employed (hydrogen chloride in chloroform and benzyl alcohol at room temperature) did not cause appreciable dehydration of the 11β-hydroxy group. The analogous transformation of hydrocortisone to the dimethyl acetal corresponding to Vb by means of hydrogen chloride in methanol at room temperature now has been described by D. Taub, R. H. Pettibone, N. L. Wendler and M. Tishler (*ibid.*, **76**, 4094 (1954)) and by S. A. Simpson, J. F. Tait, A. Wettstein, R. Neher, J. von Euw, O. Schindler and T. Reichstein, *Helv. Chim. Acta*, **37**, 1163 (1954)).

seemed likely that the 21,21-dibenzyloxy grouping would hinder the C-20 ketone at least as much as a 21-acetoxy grouping, which is known to prevent ketalization at C-20.[10] In fact when the acetal Vc was distilled with methylethyldioxolane in the presence of *p*-toluenesulfonic acid,[11] 60% of the crystalline 3-monocycloethylene ketal X was produced. Hydrogenation of the latter substance in the usual way (10% palladium–carbon catalyst) resulted in the uptake of 3 moles of hydrogen and in the formation of desoxycorticosterone 3-monocycloethylene ketal (XI) (58%). This compound proved to be identical with a sample prepared by saponification of the known acetate[10] and it was smoothly converted to desoxycorticosterone (XII) by treatment with a trace of *p*-toluenesulfonic acid in acetone solution.

After completion of this work there appeared a publication by Taub, Pettebone, Wendler and Tishler[12] describing an elegant method for removing the 17α-hydroxy group from 17α,21-dihydroxy-20-ketopregnanes, which proceeds by a different path from ours.

Experimental[13]

21,21-Dibenzyloxy-Δ⁵-pregnen-3β-ol-20-one (IIb).—A mixture of 2.0 g. of Δ⁵-pregnene-3β,17α,21-triol-20-one (I),[4] 30 cc. of dry chloroform (previously freed of ethanol by washing with concentrated sulfuric acid) and 30 cc. of a 0.7 *N* solution of hydrogen chloride in benzyl alcohol was allowed to stand for 5 days with occasional shaking. At the end of this period a homogeneous solution had resulted from which the solvents were removed by steam distillation. The product was then taken up in ether, the extract was well washed with water, dried and evaporated. Chromatography of the residue on neutral alumina furnished 2.05 g. (68%) of the acetal IIb (eluted with benzene and benzene–ether) as a colorless transparent viscous oil which was suitable for use in the next step. It gave no red color with triphenyltetrazolium chloride and therefore was not contaminated with starting material. A small sample after 3 weeks standing solidified completely to a crystalline mass with m.p. 102–110°. Recrystallization from chloroform–methanol yielded the analytical specimen with m.p. 110–112°, $[\alpha]_D$ +28°, ν_{max} 1700 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{35}H_{44}O_4$: C, 79.46; H, 8.41. Found: C, 79.23; H, 8.19.

A very similar result was obtained when the reaction was run entirely in benzyl alcohol containing hydrogen chloride, the chloroform being omitted.

Allopregnane-3β,21-diol-20-one (III).—A solution of 2 g. of the acetal IIb in 40 cc. of ethanol (previously distilled over Raney nickel) was shaken in hydrogen over 0.5 g. of a 10% palladium–charcoal catalyst at 24° and 592 mm. After 24 hours, hydrogen equivalent to 4.1 moles had been absorbed and uptake had ceased. The product, after removal of catalyst and solvent, gave a strong red color with triphenyltetrazolium chloride and after two crystallizations from acetone–hexane furnished 0.81 g. (64%) of allopregnane-3β,21-diol-20-one with m.p. 171–172°, $\nu_{max.}$ 1700 cm.$^{-1}$ and free hydroxyl band. An authentic specimen (obtained by saponification of the diacetate) showed m.p. 169–171° (reported[14] m.p. 170–171°) and identity was demonstrated through mixture m.p. determination and infrared comparison.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.30; H, 10.55.

The diacetate exhibited m.p. 150–152°, $\nu_{max.}$ 1736, 1718 and 1700 cm.$^{-1}$, no hydroxyl band and was identified with an authentic sample of m.p. 149–150° by mixture m.p. and infrared comparison.

Allopregnan-21-ol-3,11,20-trione Acetate (VIa). (a) From Cortisone (IVa).—A mixture of 2 g. of free cortisone (Δ⁴-pregnene-17α,21-diol-3,11,20-trione, IVa), 40 cc. of alcohol-free chloroform and 40 cc. of a 0.5 *N* solution of hydrogen chloride in benzyl alcohol was allowed to stand at room temperature for 50 hours, by which time an aliquot gave only a very weak color with triphenyltetrazolium chloride. Steam distillation, followed by ether extraction and chromatography of the product on neutral alumina yielded 2.38 g. (79%) of the crude acetal Va as a colorless oil (eluted with benzene and benzene–ether) which was employed for the subsequent step. After standing for several days the substance partially crystallized. Crystallization of a sample from acetone–ether gave material with m.p. 132–140° and on repeated recrystallization from this solvent pair, from acetone–hexane and from chloroform–methanol the m.p. gradually rose until it reached the constant value of m.p. 180–182°, $\lambda_{max.}$ 238 mμ, log ε 4.24, $\nu_{max.}$ 1702 and 1660 cm.$^{-1}$, no free hydroxyl band.

Anal. Calcd. for $C_{35}H_{40}O_5$: C, 77.75; H, 7.46. Found: C, 77.57; H, 7.63.

Identical results were obtained when the reaction was carried out with cortisone 21-acetate.

A solution of 1 g. of the crude acetal Va in 30 cc. of ethanol was hydrogenated over 0.25 g. of a 10% palladium–charcoal catalyst at 22° and 586 mm. After 20 hours 3.9 moles of gas had been taken up and absorption stopped. The catalyst and solvent were removed and the amorphous residue was acetylated with acetic anhydride–pyridine for 40 minutes at 90°. Chromatography of the product on neutral alumina, followed by crystallization of the fractions eluted with benzene–ether from acetone–hexane, produced 0.11 g. (15%) of allopregnan-21-ol-3,11,20-trione acetate with m.p. 164–166°. Further crystallization led to the analytical sample with m.p. 173–174°, $[\alpha]_D$ +113°, $\nu_{max.}$ 1736, 1718 and 1700 cm.$^{-1}$, no free hydroxyl band.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.52; H, 8.23.

(b) From Allopregnane-17α,21-diol-3,11,20-trione 21-Acetate (VIIa).—The benzyl alcohol reaction was carried out with 2 g. of dihydro-allocortisone acetate (VIIa),[8] 30 cc. of alcohol-free chloroform and 40 cc. of a 0.4 *N* solution of hydrogen chloride in benzyl alcohol for 90 hours at room temperature. Isolation as before produced 2.4 g. (89%) of the crude acetal VIIIa as a light yellow oil which was not purified further. It gave a negative reaction with triphenyltetrazolium chloride.

The crude acetal VIIIa (2.4 g.) in 300 cc. of ethanol (previously distilled over Raney nickel) was hydrogenated over 0.8 g. of a 10% palladium–charcoal catalyst at 25° and 590 mm. Uptake had practically stopped after 2.9 moles of hydrogen had been absorbed. The catalyst and solvent were removed and the non-crystalline residue was acetylated as before. Crystallization from acetone–hexane then furnished 0.35 g. of allopregnan-21-ol-3,11,20-trione acetate with m.p. 170–172°. Chromatography of the mother liquors on alumina produced another 0.31 g. with m.p. 166–169° (38% total yield). Identity with the compound prepared by method (a) was established by mixture m.p. and infrared comparison.

(c) From Allopregnane-11β,21-diol-3,20-dione 21-Acetate (VIb).—A solution of 0.42 g. of chromium trioxide in 1 cc. of water and 10 cc. of acetic acid was added dropwise and with stirring to a solution of 2 g. of dihydro-allocorticosterone 21-acetate (VIb)[7] in 100 cc. of acetic acid, the temperature being kept at 20° through ice cooling. After being allowed to stand for 1 hour at room temperature, a few drops of methanol were added, the solution was concentrated to *ca.* 40 cc. and diluted with water. The precipitate was collected, washed well with water, dried and crystallized

(10) R. Antonucci, S. Bernstein, R. Lenhard, K. J. Sax and J. H. Williams, *J. Org. Chem.*, **17**, 1369 (1952).

(11) *Cf.* H. Dauben, B. Löken and H. J. Ringold, THIS JOURNAL, **76**, 1359 (1954).

(12) D. Taub, R. H. Pettebone, N. L. Wendler and M. Tishler, *ibid.*, **76**, 4094 (1954); see also W. Schindler, H. Frey and T. Reichstein, *Helv. Chim. Acta*, **24**, 360 (1941).

(13) Melting points are uncorrected. Unless noted otherwise rotations were determined at 20° in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are indebted to Mrs. P. Lopez and Miss T. Cardinas for these measurements as well as for the infrared spectra which were determined in chloroform solution on a Perkin–Elmer model 12C single beam spectrophotometer with sodium chloride prism. We also would like to thank Mrs. A. Gonzalez for the microanalyses and Miss M. Velasco for valuable assistance.

(14) J. J. Schneider, *J. Biol. Chem.*, **199**, 235 (1952).

from chloroform–hexane. The oxidized compound VIa thus obtained weighed 1.66 g. (83%) and showed m.p. 170–171°, $[\alpha]D$ +115°. It was identified with the substances obtained by routes a and b through non-depression of m.p. on admixture and through infrared comparison.

Allopregnane-3β,21-diol-11,20-dione (Reichstein's Substance N) (IXa).—A solution of 8.8 g. of allopregnan-21-ol-3,11,20-trione acetate (VIa) in 300 cc. of dioxane (distilled over sodium) was shaken in hydrogen at 22° and 590 mm. with *ca.* 20 g. of W-4 Raney nickel. After 4 hours, absorption of gas was complete. The metal was removed, most of the solvent was evaporated and the residue was diluted with water. The precipitate on collection, drying and crystallization from acetone–hexane furnished 6.70 g. (76%) of crude Substance N 21-acetate with m.p. 160–162°.

This material was dissolved in 280 cc. of methanol, the solution was cooled in ice and nitrogen was bubbled through it for a few minutes. Saponification was effected by addition of an ice-cold solution of 2.8 g. of potassium carbonate in 28 cc. of distilled water (previously boiled to expell air) through which nitrogen also had been passed. The resulting solution was allowed to stand at room temperature for 1.5 hours under nitrogen and glacial acetic acid was then added until the liquid was just acid. Evaporation to small volume *in vacuo*, dilution with iced water and crystallization of the precipitate from methanol–ether produced 4.12 g. (69%) of Reichstein's Substance N (IXa) with m.p. 187–189°, $[\alpha]D$ +97° (ethanol), ν_{max}^{mull} 1702 cm.$^{-1}$ and free hydroxyl band; reported[15] m.p. 189–191°, $[\alpha]D$ +94° (ethanol).

Allopregnane-11β,21-diol-3,20-dione 21-Acetate (VIb).

(a) From Hydrocortisone (IVb).—The Mattox reaction with benzyl alcohol was carried out with 2 g. of hydrocortisone as described above for cortisone, the same amounts of reagents being employed. After 5 days at room temperature the product was isolated as before and chromatographed on neutral alumina. A mixture of benzene and ether eluted 2.61 g. (87%) of the acetal Vb as a colorless oil, λ_{max} 240 mμ, log ε 4.24, negative reaction with triphenyltetrazolium chloride.

A solution of 1 g. of the acetal Vb in 60 cc. of ethanol was hydrogenated over 0.4 g. of a 10% palladium–charcoal catalyst at 24° and 582 mm. After 28 hours 4.1 moles of gas had been absorbed. The product was acetylated with acetic anhydride and pyridine (overnight at room temperature) and then chromatographed on neutral alumina. The fractions eluted with ether were crystallized from acetone–hexane and furnished 0.13 g. (18%) of dihydro-allocorticosterone 21-acetate (VIb) with m.p. 186–188°. Further purification gave a specimen with m.p. 191–192°, $[\alpha]D$ +138° (acetone), $\nu_{max.}$ 1736, 1718 and 1700 cm.$^{-1}$ and free hydroxyl band, which was identified (mixture m.p., infrared comparison) with an authentic sample [m.p. 190–192°, $[\alpha]D$ +135° (acetone)] obtained[7] by catalytic hydrogenation of corticosterone acetate.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.44; H, 8.54.

(b) From Allopregnane-11β,17α,21-triol-3,20-dione 21-Acetate (VIIb).—Dihydro-allohydrocortisone 21-acetate (VIIb)[7] (1.2 g.) in 16 cc. of alcohol-free chloroform was allowed to react with 24 cc. of an 0.3 *N* solution of hydrogen chloride in benzyl alcohol for 90 hours at room temperature. The crude acetal VIIIb was isolated in the usual way and without purification was dissolved in 250 cc. of ethanol and hydrogenated over 0.6 g. of a 10% palladium–charcoal catalyst at room temperature and atmospheric pressure. The uptake ceased after 2.9 moles of hydrogen had been absorbed and the product was acetylated at room temperature overnight as above. Direct crystallization from acetone–hexane produced 0.31 g. of dihydro-allocorticosterone 21-acetate (VIb) with m.p. 185–187°, while chromatography of the mother liquors on alumina furnished another 0.06 g. of material with the same m.p. (32% total yield from VIIb). A further purified sample exhibited m.p. 189–191° and was identified with an authentic specimen[7] in the usual way.

Allopregnane-3β,11β,21-triol-20-one (Reichstein's Substance R) (IXb).—Allopregnane-11β,21-diol-3,20-dione 21-acetate (VIb) was preferentially reduced at C-3 with Raney nickel in dioxane as described previously[7] and produced Substance R 21-acetate with m.p. 186–189° in about 70% yield. The acetate (3.5 g.) was dissolved in 250 cc. of methanol and saponified with 1.4 g. of potassium carbonate in 25 cc. of air-free water under nitrogen, as described above for Substance N 21-acetate. Crystallization of the product from acetone–ether yielded 2.95 g. (94%) of Substance R with m.p. 198–200°, $[\alpha]D$ +110° (ethanol), $\nu_{max.}$ 1700 cm.$^{-1}$ and free hydroxyl band; reported[16] m.p. 202–204°.

21,21-Dibenzyloxy-Δ⁴-pregnene-3,20-dione (Vc).—This compound was prepared from 5.0 g. of Δ⁴-pregnene-17α,21-diol-3,20-dione (Reichstein's Substance S) (IVc) in 50 cc. of pure chloroform through treatment with 35 cc. of an 0.5 *N* solution of hydrogen chloride in benzyl alcohol for 56 hours at room temperature. Isolation in the usual way followed by chromatography on neutral alumina and combination of the fractions eluted with benzene–hexane yielded the acetal Vc (5.8 g., 76%) as a colorless oil, $\lambda_{max.}$ 240 mμ, log ε 4.23, negative reaction with triphenyltetrazolium chloride, which could not be induced to crystallize.

When the reaction was carried out as above with Substance S 21-acetate, the yield of oily acetal was only 58% and 21% of unchanged starting material was recovered.

3-Ethylenedioxy-21,21-dibenzyloxy-Δ⁵-pregnen-20-one (X).—A mixture of 7.9 g. of the acetal Vc and 0.1 g. of *p*-toluenesulfonic acid dihydrate in 140 cc. of methylethyldioxolane was heated to boiling (580 mm.) and then slowly distilled during 5.5 hours to half its volume. The cooled solution was diluted with ether and washed with sodium carbonate solution and water. Drying, evaporation (under vacuum after the ether had been removed) and crystallization of the residue from chloroform–methanol produced 5.13 g. (60%) of the 3-ketal X with m.p. 117–123°. Further purification yielded the analytical specimen with m.p. 126–128°, $[\alpha]D$ +37° (chloroform containing one drop of pyridine).

Anal. Calcd for $C_{37}H_{46}O_5$: C, 78.86; H, 8.12. Found: C, 78.57; H, 8.37.

3-Ethylenedioxy-Δ⁵-pregnen-21-ol-20-one (3-Cycloethylene Ketal of Desoxycorticosterone) (XI).—The acetal-ketal X (1.5 g.) was dissolved in 400 cc. of ethanol (previously distilled over Raney nickel) and hydrogenated over 0.4 g. of a 10% palladium–charcoal catalyst at 23° and 582 mm. After 20 hours 3.1 moles of hydrogen had been absorbed and uptake was very slow. The catalyst and solvent were removed and the residue was crystallized from acetone–hexane (containing one drop of pyridine). This procedure furnished 0.44 g. of the ketal XI with m.p. 176–180° and chromatography of the mother liquors gave another 0.13 g. with m.p. 180–182° (58% total yield). The analytical sample exhibited m.p. 186–187°, no high intensity absorption in the ultraviolet, ν_{max}^{mull} 1700 cm.$^{-1}$ and free hydroxyl band, strong positive reaction with triphenyltetrazolium chloride.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.50; H, 9.42.

An authentic specimen was made by saponification of the known 21-acetate[10] by means of methanolic potassium hydroxide at room temperature for 2 hours under nitrogen. It showed m.p. 185–187° and was identified with XI prepared as above through mixture m.p. determination and infrared comparison.

Desoxycorticosterone (XII).—The 3-monoketal XI (130 mg.) of m.p. 176–180°, obtained by hydrogenation of X, was dissolved in 10 cc. of acetone and treated with 30 mg. of *p*-toluenesulfonic acid dihydrate at room temperature for 16 hours. Addition of water and collection of the precipitate produced 75 mg. of desoxycorticosterone with m.p. 137–140°, $[\alpha]D$ +181° (ethanol), λ_{max} 240 mμ, log ε 4.23. Another 15 mg. of m.p. 138–140° (78% total yield) was obtained by chloroform extraction of the filtrate, followed by crystallization from acetone–hexane. An authentic sample of desoxycorticosterone showed m.p. 139–141°, $[\alpha]D$ +177° (ethanol), and identity was demonstrated through mixture m.p. determination.

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(15) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **21**, 546 (1938).

(16) T. Reichstein and J. von Euw, *ibid.*, **21**, 1197 (1938); T. Reichstein, *ibid.*, **21**, 1490 (1938).