STUDIES IN SYNTHESES OF STEROID METABOLITES. PART IV.

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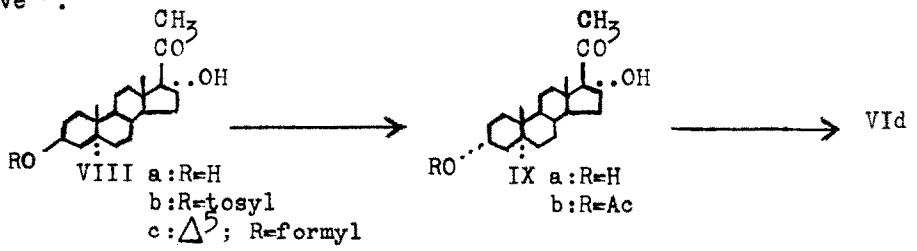
Palladium on charcoal hydrogenation of Reichstein's Compound S acetate[30] afforded the 5α-dihydro derivative I as the minor, and the 5β-dihydro derivative II as the major, product. Raney nickel hydrogenation of the former gave Reichstein's Compound P acetate (IIIa), which was converted into allo-THS (VIa). Raney nickel hydrogenation of the 5β compound II gave a mixture of THS 21-acetate (Vb) and its 3β epimer IVb. The 5α-dihydro derivative X of DOCA was hydrogenated in a similar fashion to afford the 3β compound XIa which was transformed into allo-tetrahydrodesoxy-corticosterone (XVa). Raney nickel hydrogenation of the 5β-dihydro derivative XII gave a mixture of tetrahydrodesoxycorticosterone 21-acetate (XIIIb) and its 3β epimer XIVb. The presence of a 17α-hydroxyl and of a 16α,17α-epoxy group in several 5β-3-keto steroids increases the ratio of 3α to 3β alcohols produced by Raney nickel hydrogenation.

In previous papers of this series hydrogenations of hydrocortisone,[1,2] cortisone[2], corticosterone[3] and/or their acetates were described, the formation of 5β isomers was emphasized and the practical significance of these findings in relation to syntheses of steroid metabolites was pointed out. The present paper is a report of hydrogenation studies of derivatives of Reichstein's Compound S and of derivatives of desoxy-corticosterone, ultimately leading to syntheses of several 11-desoxy metabolites.

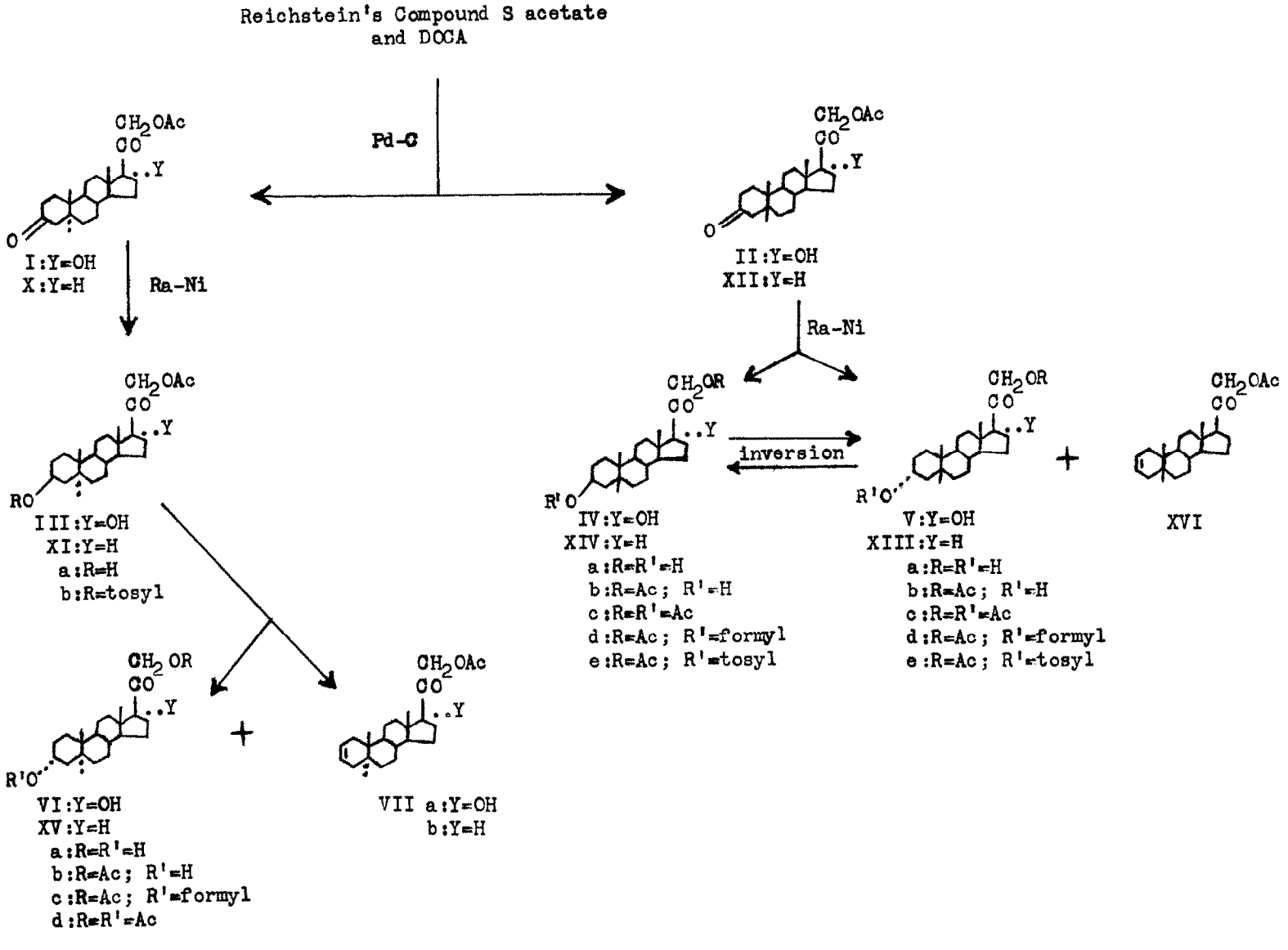
Results of palladium hydrogenations of several steroids, possessing the Δ^4-3-keto group and devoid of an oxygen function at position 11, were summarized by Wettstein and Hunziker[4] who showed the predominance of 5β-dihydro compounds as reduction products. Related results were now

obtained with Reichstein's Compound S acetate, the ratio of 5β to 5α-dihydro compounds (II and I) obtained being slightly over 3:2.

Raney nickel hydrogenation of the 5α isomer I in dioxane furnished the expected 3β-hydroxy derivative IIIa (Reichstein's Compound P 21-acetate) in 72% yield. Its tosylate IIIb was heated in dimethylformamide[5] and from the resulting mixture there were isolated, by crystallization and chromatography, three compounds: the elimination product VIIa (14%), the 3α-formate VIc (61%) and the 3α-ol VIb (6%). Mild hydrolysis of VIc or VIb with potassium bicarbonate gave, in over 75% yield, 5α-pregnane-3α,17α,21-triol-20-one (allo-THS) (VIa) which was recently prepared by v. Euw, Neher and Reichstein[6]. This compound was identified in human urine after administration of 5-pregnene-3β,17α,21-triol-20-one to a normal subject[7]. Recently Finkelstein and Shoenberger identified allo-THS in the urine of a boy aged 4 with an adrenogenital syndrome associated with hypertension[28]. Rumney found evidence for the presence of allo-THS in the urine of a $2\frac{1}{2}$ year old child with congenital adrenal hyperplasia and hypertension whose sex chromatin was found to be positive[29].



It is of incidental interest that the intermediates IXb and IXa[8], used by the Swiss workers[6] to prepare allo-THS diacetate (VId) and by Fukushima and Meyer[9] to synthesize 5α-pregnane-3α,17α,20β-triol, were now prepared by epimerization of 5α-pregnane-3β,17α-diol-20-one (VIIIa) via its 3-tosylate VIIIb, followed by hydrolysis and acetylation.


Reichstein's Compound S acetate
and DOCA
Pd-C
I:Y=OH
X:Y=H
Ra-Ni
II:Y=OH
XII:Y=H
Ra-Ni
inversion
III:Y=OH
XI:Y=H
a:R=H
b:R=tosyl
IV:Y=OH
XIV:Y=H
a:R=R'=H
b:R=Ac; R'=H
c:R=R'=Ac
d:R=Ac; R'=formyl
e:R=Ac; R'=tosyl
V:Y=OH
XIII:Y=H
a:R=R'=H
b:R=Ac; R'=H
c:R=R'=Ac
d:R=Ac; R'=formyl
e:R=Ac; R'=tosyl
XVI
VI:Y=OH
XV:Y=H
a:R=R'=H
b:R=Ac; R'=H
c:R=Ac; R'=formyl
d:R=R'=Ac
VII a:Y=OH
b:Y=H

In the 5β series, hydrogenation of dihydro Reichstein's Compound S acetate (II) with Raney nickel afforded a mixture which was purified by chromatography to afford a 24% yield of the 3β-ol IVb and a 60% yield of THS 21-acetate (Vb)[10]. Mild hydrolysis of IVb gave the free triolone IVa; this compound was previously obtained by Ungar and Dorfman[11] by incubation of 5β-dihydro Reichstein's Compound S with rat liver. The structure of this triolone was established by (a) degradation with sodium borohydride - sodium periodate to 5β-androstane-3β-ol-17-one; and (b) conversion of THS 21-acetate (Vb) to its tosylate Ve and epimerization in dimethylformamide. Chromatography of the resulting mixture gave three compounds: the 3β-formate IVd (67%) which, like Vb, could be hydrolyzed to the triolone IVa, identical with a sample described above; the 3β-ol IVb (5%); and the unepimerized 3α-ol Vb (5%).

Wettstein and Hunziker[4] reduced desoxycorticosterone acetate (DOCA) in alcohol in the presence of palladium on calcium carbonate and isolated a small amount of the 5α-dihydro compound X, in addition to the major 5β product XII. Essentially the same results were now obtained when ethyl acetate and palladium on charcoal were employed in the hydrogenation. Raney nickel in dioxane hydrogenation of X afforded the 3β alcohol XIa in 73% yield. In analogy with the 17-hydroxylated series, epimerization of the 3β-tosylate XIb in dimethylformamide, followed by a combination of crystallization and chromatography, gave the unsaturated acetate VIIb (17%), the 3α-formate XVc (65%) and the 3α alcohol XVb (7%). Mild hydrolysis of XVb or XVc afforded allo-tetrahydrodesoxycorticosterone (XVa) in 80% yield. Acetylation of XVa furnished the diacetate XVd which previously had

been obtained by Schneider[12a] by (a) incubation of desoxycorticosterone with rat liver slices, followed by acetylation and separation of products, and (b) acetoxylation of 5α-pregnane-3α-ol-20-one acetate with lead tetraacetate.

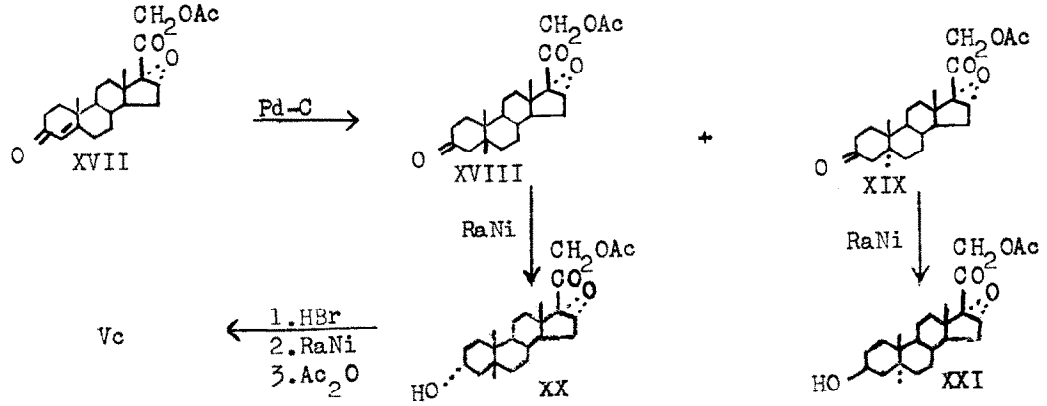
Next the Raney nickel hydrogenation of the 5β-dihydro derivative XII was investigated. The products were separated by chromatography and proved to be the known 3β and 3α epimers XIVb[13,14] and XIIIb[13,15], respectively, in the ratio of 7.6:1. Hydrolysis of the 3α isomer XIIIb gave tetrahydrodesoxycorticosterone (XIIIa). Since the ratio of the epimers XIVb and XIIIb obtained by hydrogenation was unfavorable for a practical synthesis of tetrahydrodesoxycorticosterone, use was made of the 3β isomer as well. Its tosylate XIVe was treated with dimethylformamide and the products were separated by chromatography. The olefin XVI was isolated in 34% yield; the 3α-formate XIIId in 20% yield; and the 3α-ol XIIIb in 12% yield. Hydrolysis of the formate, like that of XIIIb, afforded the diolone XIIIa. It was observed that when the hydrolysis of XIIId with potassium bicarbonate was interrupted before completion, there was obtained a mixture of the diolone XIIIa and its acetate XIIIb, the formate ester at position 3 being hydrolyzed faster than the 21-acetate.

On the basis of Raney nickel in dioxane hydrogenation experiments of the 5β-dihydro derivatives 1 - 4 listed in Table I it appears that while hydrogenations of dihydrodesoxycorticosterone acetate and of its 11β-hydroxy derivative (compounds 1 and 3) lead to the predominant formation of the 3β isomers, the presence of a hydroxyl group in position 17 (compounds 2 and 4) reverses the effect and makes the 3α alcohols the major products.

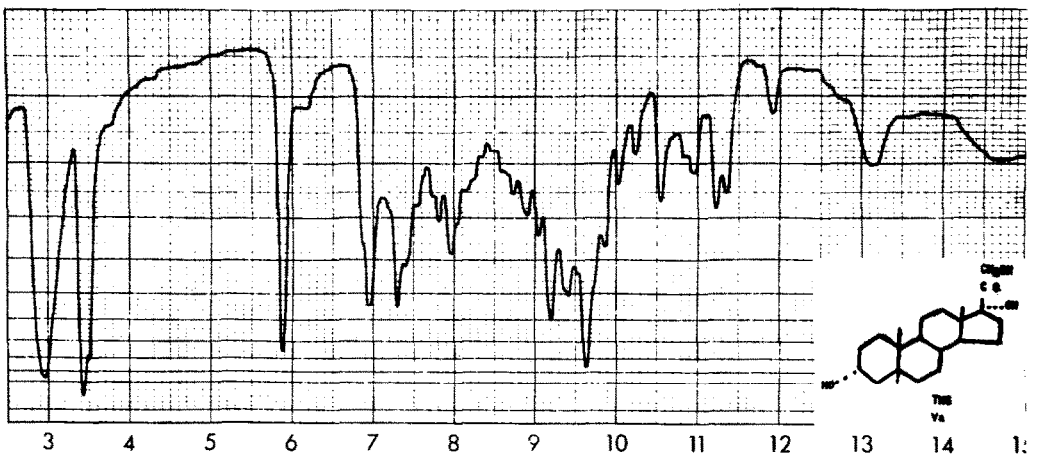
Table I

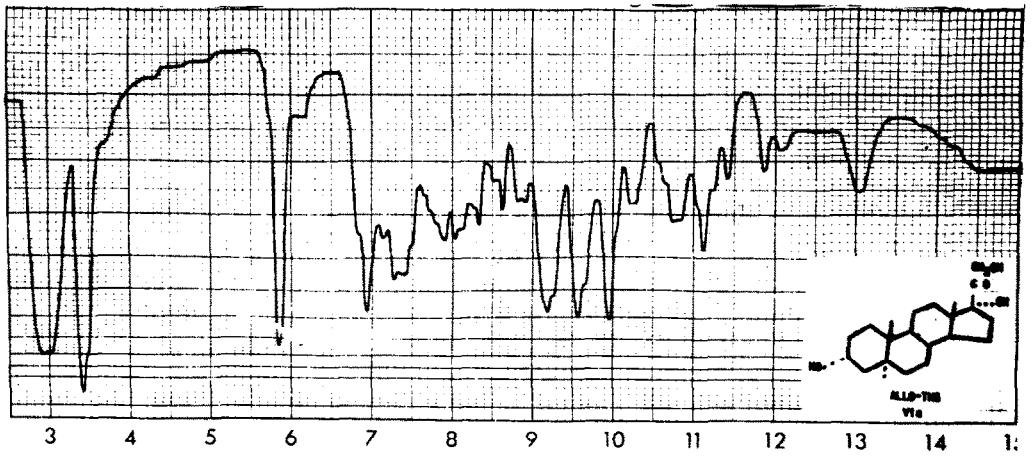
5β compound	ratio 3β:3α alcohol produced	reference
1. Dihydro-DOCA (XII)	7.6 : 1	this paper
2. Dihydro-Reichstein's S acetate (II)	4 : 10	" "
3. Dihydro-corticosterone acetate	high (amount of 3α insignificant)	3
4. Dihydro-hydrocortisone acetate	4 : 10	2
5. Dihydro-16α,17α-epoxy-DOCA (XVIII)	low (amount of 3β insignificant)	this paper

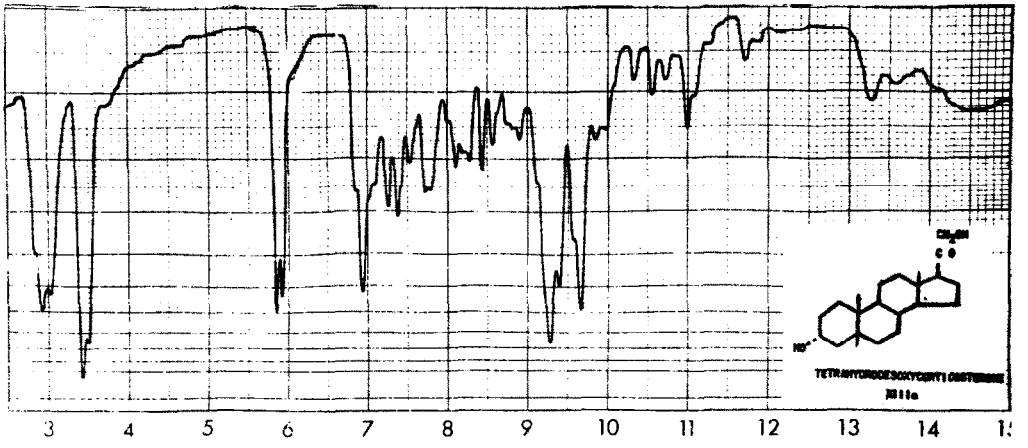
In order to estimate the influence of the 16α,17α-epoxy group on the stereochemistry of reduction of a 5β-3-keto compound, 16α,17α-epoxydesoxycorticosterone acetate (XVII) was hydrogenated in the presence of palladium to afford the 5β-dihydro derivative XVIII, in addition to a small amount of the 5α epimer XIX. The 5β compound XVIII was then catalytically reduced in the presence of Raney nickel to give the 3α isomer XX in 72% yield. Assignment of the 3α structure to compound XX was carried out by opening the epoxide with hydrogen bromide followed by treatment of the resulting bromo derivative with nickel. The acetylated product was identical with THS 3,21-diacetate (Vc). The conversion XVIII ⟶ XX indicates, then, that the influence of the epoxy group in XVIII parallels that of the 17α-hydroxyl in II: both cause predominant formation of 3α isomers on Raney nickel - dioxane hydrogenation of the 5β-3-keto moiety.

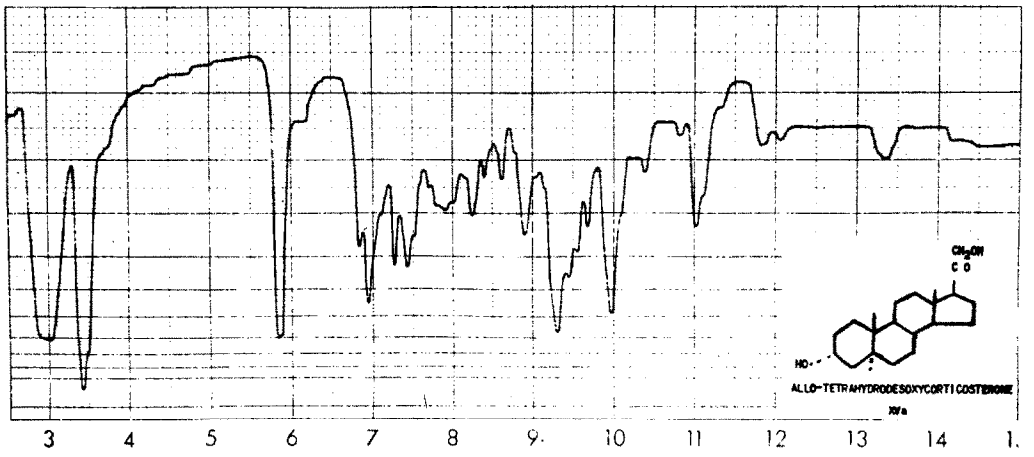


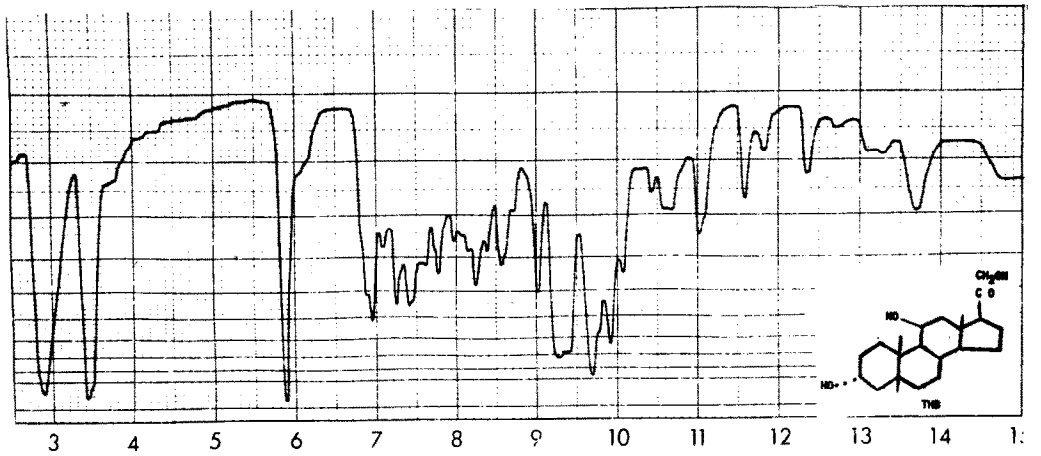
Shown below are infrared spectra (4% in KBr) of nine steroid metabolites, syntheses of which were reported in this and earlier articles.[2,3,27]








3 4 5 6 7 8 9 10 11 12 13 14
ALLO-TETRAHYDRODESOXYCORTICOSTERONE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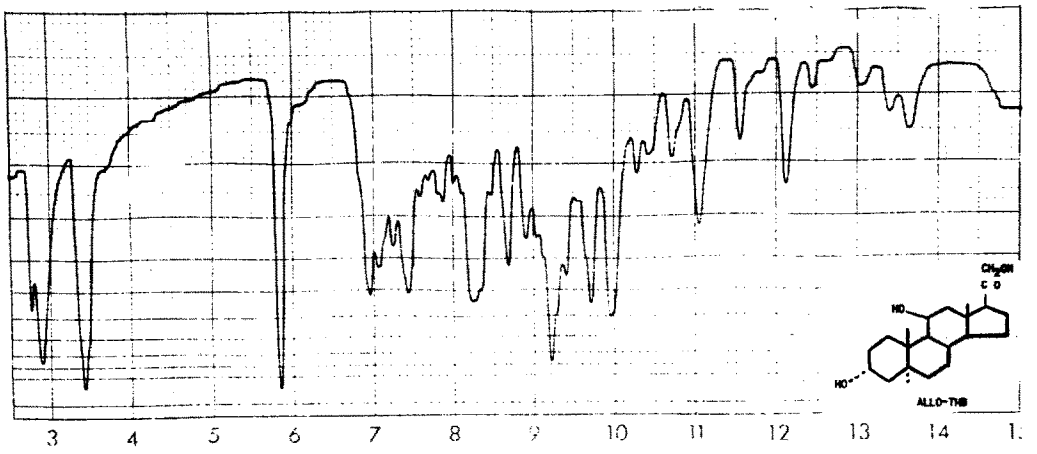
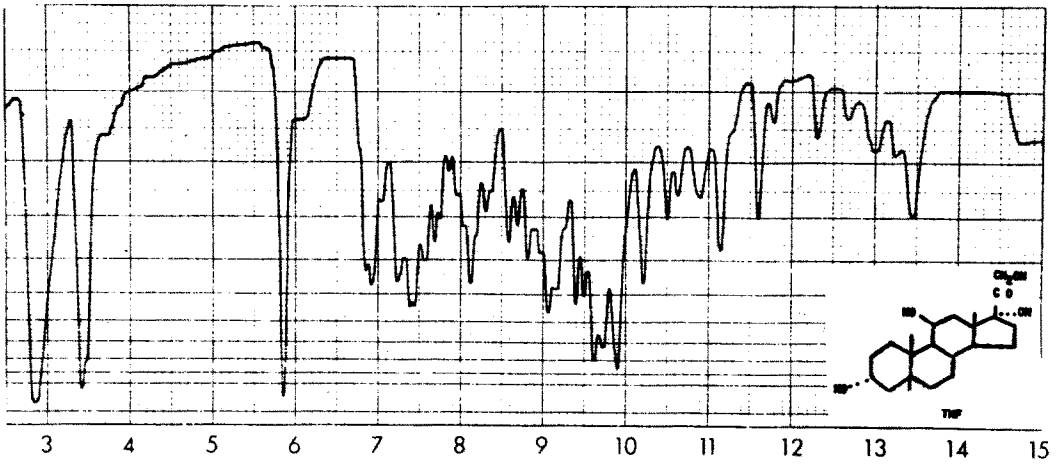
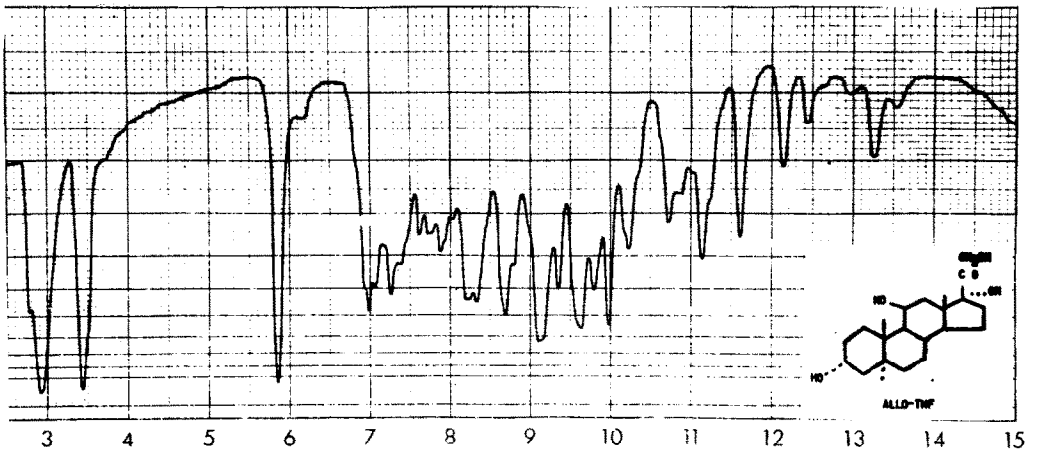
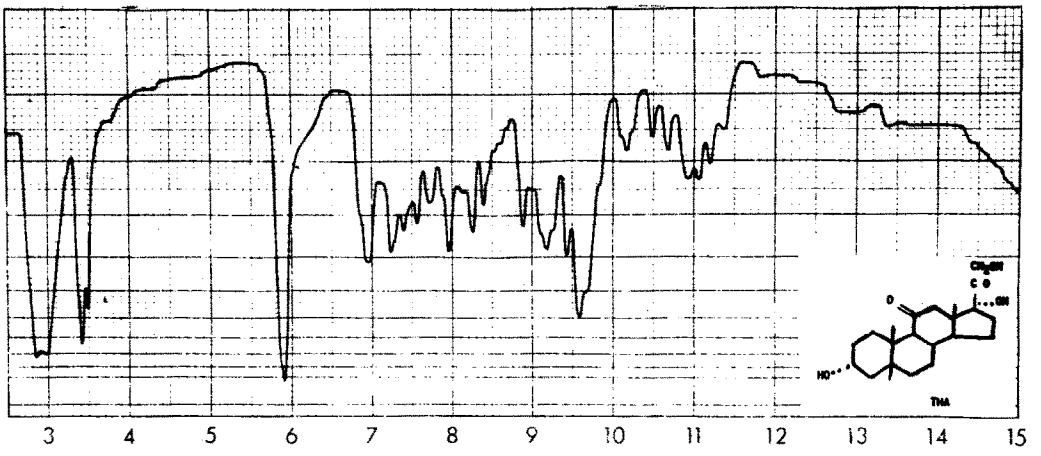

3 4 5 6 7 8 10 11 12 13 14
ALLO-THB


3 4 5 6 7 8 9 10 11 12 13 14 15
THF


3 4 5 6 7 8 9 10 11 12 13 14 15
ALLO-THF


3 4 5 6 7 8 9 10 11 12 13 14 15
THA

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were measured in chloroform unless stated otherwise. Ethyl acetate was neutralized with bicarbonate before use in hydrogenations. Raney nickel (No. 28, Raney Catalyst Co., Chattanooga, Tenn.) was thoroughly washed with water before use. Hydrolysis of 21-acetoxy compounds was carried out by mixing a 1% solution of the steroid in methanol with a 5% aqueous solution containing an equal weight of potassium bicarbonate. After storing for 20 to 44 hrs at room temperature the solution was concentrated *in vacuo* at room temperature and the precipitated solid was either filtered and water-washed, or taken up in an organic solvent.

Palladium Hydrogenation of Reichstein's Compound S 21-acetate. A mixture of 30 g of Reichstein's Compound S 21-acetate, 10 g of 5% palladium on charcoal and 3 l of ethyl acetate was vigorously stirred for 6 hrs in an atmosphere of hydrogen. The filtered solution was concentrated to 1.5 l, set aside overnight at room temperature and the precipitated 5α-pregnane-17α,21-diol-3,20-dione 21-acetate (I) collected; 9.0 g, m.p. 248-250°, $(\alpha)_D^{25}$ +59°(dioxane) (reported[17] 249-251°, $(\alpha)_D^{20}$ +61°(dioxane)). Concentration of the filtrate to 900 ml and storage at room temperature for 2 days afforded additional 2 - 2.5 g of the same compound, m.p. 240-5°.

Further concentration to 200 ml and then to 70 ml gave 18 g of 5β-pregnane-17α,21-diol-3,20-dione 21-acetate (II), m.p. 187-192°, which on recrystallization from ethyl acetate melted at 192-4°, $(\alpha)_D^{25}$ +78°(ethanol) (reported 195-7°, $(\alpha)_D^{32}$ +81°(ethanol)[18]; 188-190°[19]; 192.5-4°, $(\alpha)_D^{20}$ +76° (ethanol)[20]; 198-200°, $(\alpha)_D^{28}$ +81°[21]).

Raney Nickel Hydrogenation of I. A solution of 6.0 g of the 5α isomer I in 700 ml of dioxane was stirred with 5 teaspoonfuls of Raney nickel for 4 hrs in an atmosphere of hydrogen. Filtration, distillation to dryness and recrystallization of the solid from 300 ml of methanol furnished 3.8 g of 5α-pregnane-3β,17α,21-triol-20-one (Reichstein's Compound P) 21-acetate (IIIa), m.p. 230-8°. Further concentration gave 0.5 g of comparable material. Recrystallization from methanol gave material melting at 234-6°, $(\alpha)_D^{28}$ +48°

(dioxane) (reported[17] 235-6°, $(\alpha)_D^{20}$+44°(dioxane)).

Raney Nickel Hydrogenation of II. A mixture of 15.05 g of the 5β isomer II, 750 ml of dioxane and 7 teaspoonfuls of Raney nickel was hydrogenated for 4 hrs. After filtration and distillation in vacuo the solid residue was dissolved in benzene and chromatographed over 350 g of Florisil. 5β-Pregnane-3β,17α,21-triol-20-one 21-acetate (IVb) was eluted with 10% ether in benzene; after recrystallization from acetone - ether the material weighed 3.6 g and melted at 219-220° (reported[22] 217-9°). Hydrolysis of a sample with potassium bicarbonate in aqueous methanol at room temperature, followed by filtration and recrystallization from acetone, gave 5β-pregnane-3β,17α,21-triol-20-one (IVa), m.p. 232-4°, $(\alpha)_D^{30}$+50°(ethanol) (reported[11] 224-6°, $(\alpha)_D$+54°(ethanol)). Sodium borohydride - sodium periodate degradation of IVa gave 5β-pregnane-3β-ol-17-one. The diacetate IVc was prepared from the monoacetate IVb and after recrystallization from methanol melted at 152-4°, $(\alpha)_D^{31}$+51°(dioxane) (reported 149-151°, $(\alpha)_D^{28}$+49°(dioxane)[19]; 154-7°, $(\alpha)_D^{28}$+51°(ethanol)[21]).

Further elution with benzene - ether mixtures and with ether gave 5β-pregnane-3α,17α,21-triol-20-one (THS) 21-acetate (Vb), which after recrystallization from ethyl acetate weighed 9.03 g, m.p. 221-4°. Hydrolysis of Vb with potassium bicarbonate in aqueous methanol at room temperature gave 5β-pregnane-3α,17α,21-triol-20-one (THS) (Va), which after recrystallization from ethyl acetate melted at 212-6°, $(\alpha)_D^{30}$+64°(ethanol) (reported[11] 214-6°, $(\alpha)_D^{27}$+60°(ethanol)).

5α-Pregnane-3β,17α,21-triol-20-one 3-tosylate 21-acetate (IIIb). A suspension of 3.3 g of the 3β-ol IIIa in 15 ml of pyridine was stirred for 16 hrs at 0° with 5 g of p-toluenesulfonyl chloride, then allowed to stand at 0° overnight. Ice-water was added, the solid filtered, washed

with water and recrystallized from methanol. In three crops there was obtained a total of 3.81 g of the tosylate IIIb, m.p. 95°(dec), sometimes solidifying and remelting at 137-140°, $(\alpha)_D^{18}$+31.5°.

Anal. Calcd. for $C_{30}H_{42}O_7S$: C, 65.91; H, 7.74. Found: C, 65.88; H, 7.96.

Epimerization of Tosylate IIIb. A solution of 3.51 g of IIIb in 140 ml of dimethylformamide[5] was heated at 80° for 70 hrs. The solvent was distilled in vacuo, the residue treated with water and the solid filtered. Recrystallization from 40 ml of methanol gave 1.16 g of 5α-pregnane-3α,17α,21-triol-20-one 3-formate 21-acetate (VIc), m.p. 208-212°. The analytical sample (acetone) melted at 214-5°, $(\alpha)_D^{18}$+62°.

Anal. Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.69; H, 8.90.

The filtrate was evaporated and the residue chromatographed over 50 g of Florisil. With 5% ether in benzene there was obtained 5α-pregn-2-ene-17α,21-diol-20-one 21-acetate (VIIa) which after recrystallization from acetone weighed 350 mg and melted at 214-220°. The pure sample melted at 219-222°, $(\alpha)_D^{17}$+88°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.32; H, 8.91.

Further elution with 5% ether in benzene and recrystallization of the product from acetone gave additional 480 mg of the formate VIc, m.p. 212-5°.

Elution with 50% ether in benzene afforded 5α-pregnane-3α,17α,21-triol-20-one 21-acetate (VIb), which after recrystallization from acetone melted at 223-232° and weighed 150 mg. The pure sample had the m.p. 231-4°.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.58; H, 9.20.

Hydrolysis of VIb or VIc with potassium bicarbonate in aqueous methanol at room temperature, followed by extraction with ethyl acetate, furnished 5α-pregnane-3α,17α,21-triol-20-one (allo-THS; 3-epi-Reichstein's

Compound P) (VIa), which was recrystallized from ethyl acetate; m.p. 224-6°, $(\alpha)_D^{18}$ +54°(methanol) (reported[6] 223-4°, $(\alpha)_D^{26}$ +51.6°(methanol)).

5β-Pregnane-3α,17α,21-triol-20-one 3-tosylate 21-acetate (Ve) was obtained when a solution of 12 g of the acetate Vb and of 15 g of p-toluenesulfonyl chloride in 35 ml of pyridine was stored overnight at 0°. The product was isolated as described for IIIb and recrystallized from methanol to give 13 g, m.p. 160-2°(dec). The pure compound melted at 148-150°, sometimes at 160-2°.

Anal. Calcd. for $C_{30}H_{42}O_7S$: C, 65.91; H, 7.74. Found: C, 66.20; H, 7.50.

Epimerization of Tosylate Ve. A solution of 8.2 g of Ve in 350 ml of dimethylformamide was heated at 80° for 70 hrs. Distillation of the solvent in vacuo, addition of water, filtration and recrystallization of the solid from methanol gave 3.5 g of 5β-pregnane-3β,17α,21-triol-20-one 3-formate 21-acetate (IVd), m.p. 150-5°. The analytical sample (from methanol or heptane) melted at 154-6°, $(\alpha)_D^{18}$ +54°.

Anal. Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.80; H, 8.45.

The filtrate was evaporated and the residue chromatographed over 150 g of Florisil. With 5% ether in benzene there was obtained an additional amount of the formate IVd. Recrystallization from heptane gave 750 mg, m.p. 152-5°.

Hydrolysis of IVd, under conditions described for IVb, afforded the triolone IVa.

Elution with 20% ether in benzene afforded the 3β alcohol IVb which after recrystallization from acetone - ether melted at 216-9° (320 mg) and was identical with a sample of IVb described above.

Elution with ether - benzene (1:1) furnished the 3α alcohol Vb which was recrystallized from acetone. The product melted at 220-4° and weighed 300 mg.

5α-Pregnane-3β,17α-diol-20-one 3-tosylate (VIIIb). A solution of 22.8 g of 5α-pregnane-3α,17α-diol-20-one (VIIIa) (prepared by hydrogenation of a 0.75% solution of the 3β-formoxy compound VIIIc[23] in methanol for 10 hrs at atmospheric pressure in the presence of 5% palladium on charcoal. Distillation of the filtered solution at atmospheric pressure directly gave the dihydroxy-ketone VIIIa) in 100 ml of pyridine was magnetically stirred with 45 g of p-toluenesulfonyl chloride. The mixture was treated with water after 20 hrs at 0°, the solid filtered, water-washed and recrystallized from acetone. The product melted at 90-2° and weighed 24.5 g. The analytical sample partially resolidified at about 120° and melted again at approximately 130°.

Anal. Calcd. for $C_{28}H_{40}O_5S$: C, 68.82; H, 8.25. Found: C, 69.27; H, 8.61.

5α-Pregnane-3α,17α-diol-20-one (IXa). A solution of 19.2 g of the tosylate VIIIb in 600 ml of dimethylformamide was epimerized as described for Ve. The solid was washed with water and refluxed for 1 hr with 400 ml of 5% methanolic potassium hydroxide. The solution was concentrated, water added and the solid collected. Several fractional crystallizations from acetone afforded 4.7 g of IXa, m.p. 204-8° (reported[9] 215-6.5°), suitable for reduction with sodium borohydride[9]. The filtrates from IXa were evaporated and the residue was chromatographed over 270 g of Florisil. With 5% ether in benzene there was obtained 1.8 g of 5α-pregn-2-ene-17α-ol-20-one which after recrystallization from acetone melted at 195° and weighed 1.1 g. The analytical sample had m.p. 201-2°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.49; H, 10.40.

Several of the fractions eluted with 20% and 50% ether in benzene proved to contain the crude diolone IXa. Most of the impurity, insoluble in hot benzene, was removed by filtration. From the benzene filtrate there was obtained in several crops 1.3 g of IXa, m.p. 203-8°, bringing the total

amount of IXa isolated to 6.0 g. Acetylation of IXa gave the known[8,6] 3-acetate IXb.

5α-Pregnane-3β,21-diol-20-one 21-acetate (XIa). A solution of 6.54 g of 5α-pregnane-21-ol-3,20-dione acetate (X)[24,4] in 600 ml of dioxane was hydrogenated for 3 hrs at room temperature and atmospheric pressure in the presence of 6 teaspoonfuls of Raney nickel. The filtered solution was distilled and the solid recrystallized from methanol to afford 3.56 g of XIa, m.p. 204-5°, and 1.22 g, m.p. 197-9° (reported[24] 202-4°).

Raney Nickel Hydrogenation of 5β-Pregnane-21-ol-3,20-dione acetate (XII). A solution of 11 g of the 5β compound XII in 1 liter of dioxane was hydrogenated as described above. The product was chromatographed over 300 g of Florisil. The fractions eluted with 5% ether in benzene were recrystallized from ether - petroleum ether and gave a total of 6.09 g of 5β-pregnane-3β,21-diol-20-one 21-acetate (XIVb), m.p. 136-8° (reported 136-8°[13]; 119-123°[13]; 121-3°[14]), identical with an authentic sample[25].

Elution with 20% ether in benzene gave 5β-pregnane-3α,21-diol-20-one 21-acetate (XIIIb) which after recrystallization from acetone - ether weighed 800 mg, melted at 178-180°, $(\alpha)_D^{25}$ +105°, and was identical with an authentic sample[25] (reported[13] 179.5-181°, $(\alpha)_D^{18}$ +109°(chloroform)).

In actual practice, due to the tediousness of purification of the starting material XII, obtained by palladium on charcoal hydrogenation of DOCA[4], it was found convenient to employ samples of XII containing small amounts of its 5α epimer X. In such cases elution with ether - benzene (1:1) furnished corresponding amounts of the 5α-diolone XIa.

Hydrolysis of the 21-acetate XIIIb with potassium bicarbonate in aqueous methanol, followed by concentration in vacuo and filtration, or extraction with ether and concentration of the extract, gave 5β-pregnane-

3α,21-diol-20-one (XIIIa), m.p. 144-9°. A sample, twice recrystallized from acetone, melted at 142-3°, $(\alpha)_D^{18}$ +94° (reported[16] 152-3°). The infrared spectrum of the recrystallized sample showed a doublet at 5.85 and 5.91 μ, while the spectrum of the material before recrystallization had a single carbonyl peak at 5.84 μ. Thin layer chromatography[26] established the purity of the compound.

5β-Pregnane-3β,21-diol-20-one 3-tosylate 21-acetate (XIVe) was prepared by storing 5.28 g of compound XIVb and 6 g of p-toluenesulfonyl chloride in 18 ml of pyridine for 40 hrs at 0°. The product was precipitated with water and recrystallized from ethyl acetate to furnish a total of 6.72 g, m.p. 142-4°(dec), unchanged on further recrystallization.

Anal. Calcd. for $C_{30}H_{42}O_6S$: C, 67.89; H, 7.98. Found: C, 67.92; H, 7.72.

Epimerization of Tosylate XIVe. A solution of 6.04 g of XIVe in 250 ml of dimethylformamide was heated at 80° for 70 hrs. The solvent was distilled *in vacuo*, the gummy residue treated with water, the mixture thoroughly extracted with benzene and the extract chromatographed over 180 g of Florisil. Elution with benzene provided 5β-pregn-2-ene-21-ol-20-one acetate (XVI) which was recrystallized from petroleum ether, 1.40g, m.p. 97-9°. The pure sample melted at 102-4°, $(\alpha)_D^{18}$ +102°.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.69; H, 9.63.

Elution with 5% ether in benzene gave 5β-pregnane-3α,21-diol-20-one 3-formate 21-acetate (XIIId). Recrystallization from ether - petroleum ether gave a total of 0.92 g, m.p. 117-9°. The analytical sample melted at 117-8°, $(\alpha)_D^{18}$ +120°.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 77.25; H, 8.97. Found: C, 71.22; H, 8.92.

Hydrolysis of XIIId with potassium bicarbonate in aqueous methanol at room temperature for 40 hrs afforded the diolone XIIIa.

Elution with 20% ether in benzene gave 5β-pregnane-3α,21-diol-20-one 21-acetate (XIIIb) which was recrystallized from acetone - ether. The product weighed 0.52 g, melted at 177-181° and was identical with a sample of XIIIb described above.

5α-Pregnane-3β,21-diol-20-one 3-tosylate 21-acetate (XIb). A solution of 3.41 g of the 3β-hydroxy compound XIa (obtained as described above or by hydrogenation of 21-acetoxypregnenolone in methanol in the presence of palladium on charcoal) and of 5 g of p-toluenesulfonyl chloride in 18 ml of pyridine was stored overnight at 0°. After addition of water, filtration and recrystallization of the solid from acetone there was obtained a total of 4.14 g of the tosylate XIb, m.p. 162-4°.

Anal. Calcd. for $C_{30}H_{42}O_6S$: C, 67.89; H, 7.98. Found: C, 68.23; H, 7.80.

Epimerization of Tosylate XIb. A solution of 3.20 g of XIb in 150 ml of dimethylformamide was epimerized as described for Ve. The crude solid was recrystallized from ethyl acetate and gave 1.30 g of somewhat impure 5α-pregnane-3α,21-diol-20-one 3-formate 21-acetate (XVc), m.p. 204-210°. The filtrate was evaporated and the residue was chromatographed on 50 g of Florisil. Elution with benzene at first gave 5α-pregn-2-ene-21-ol-20-one acetate (VIIb) which was recrystallized from acetone to afford 370 mg, m.p. 178-181°. The analytical sample melted at 181-3°, $(\alpha)_D^{18}$ +138°.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.78; H, 9.32.

Continued elution with benzene furnished additional amounts of the formate XVc which after recrystallization from ethyl acetate melted at 217-9° and weighed 300 mg. The pure sample melted at 220-2°, $(\alpha)_D^{18}$ +104°.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.26; H, 8.91.

Elution with 20% ether in benzene afforded 5α-pregnane-3α,21-diol-20-one 21-acetate (XVb) which was recrystallized from a small amount of acetone to give 150 mg of material, m.p. 214-7°. The pure sample melted at 216-8°.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.48; H, 9,48.

Hydrolysis of a 1% solution of XVb or of a 0.1% solution of XVc in methanol with aqueous potassium bicarbonate afforded 5α-pregnane-3α,21-diol-20-one (XVa) which was isolated by filtration, dried and recrystallized from acetone; m.p. 161-5°. The analytical sample melted at 163-6°, $(\alpha)_D^{18}$ +84°(methanol).

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.21; H, 9.99.

Acetylation of XVa afforded the diacetate XVd, m.p. 164-5° (methanol) (reported 164-5°[12a]; 165°[12b]).

Palladium Hydrogenation of 16α,17α-Epoxydesoxycorticosterone acetate (XVII). A solution of 5 g of XVII in 500 ml of ethyl acetate was hydrogenated for 5 hrs in the presence of 5 g of 5% palladium on charcoal. The filtered solution was distilled in vacuo to dryness and the residual solid subjected to a series of laborious fractional recrystallizations from ether. There was obtained a total of 0.24 g of material, m.p. 170-190°, which was recrystallized twice from ethyl acetate to give 95 mg, m.p. 191-4°. The analytical sample of 16α,17α-epoxy-5α-pregnane-21-ol-3,20-dione acetate (XIX) melted at 194-6°.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.24; H, 8.12.

From the ether filtrates there was obtained a total of 3.01 g of the crude 5β isomer, m.p. 120-135°. The pure sample of 16α,17α-epoxy-5β-pregnane-21-ol-3,20-dione acetate (XVIII) melted at 137-8° (ether).

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.16; H, 8.49.

16α,17α-Epoxy-5α-pregnane-3β,21-diol-20-one 21-acetate (XXI). A solution of 1.0 g of the 5α compound XIX in 100 ml of dioxane was hydrogenated for 2 hrs in the presence of 2 teaspoonfuls of Raney nickel. Distillation of the solvent and recrystallization of the residue from methanol gave a total of 610 mg of the 3β-ol XXI, m.p. 195-202°. The pure sample melted at 199-201°.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.51; H, 9.00.

Raney Nickel Hydrogenation of XVIII. A 1% solution of 13.0 g of the 5β isomer XX in dioxane was hydrogenated for 3 hrs in the presence of 10 teaspoonfuls of Raney nickel. Distillation of the filtered solution gave a gum which was chromatographed over 400 g of Florisil. With 5% and 20% ether in benzene there was obtained 16α,17α-epoxy-5β-pregnane-3α,21-diol-20-one 21-acetate (XX) which after recrystallization from acetone - petroleum ether weighed 9.4 g, m.p. 141-5°. The analytical sample melted at 146°.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.63; H, 8.90.

Conversion of XX to Vc. A 200 mg sample of XX was dissolved in 1 ml of acetic acid, cooled in ice and treated with 1 ml of a saturated solution of hydrogen bromide in acetic acid. After 5 minutes the ice-bath was removed and after additional 15 minutes the resulting slurry was treated with cold water. The crude bromohydrin, m.p. 196-7°(dec), was filtered, washed with water and without further purification dissolved in 50 ml of dioxane. One teaspoonful of Raney nickel and 1 g of potassium acetate was added and the mixture hydrogenated for 3 hrs. Evaporation of solvent in vacuo was followed by addition of water. The solid was filtered, air-dried and acetylated with acetic anhydride-pyridine. The product, obtained by addition of water, filtration and

recrystallization from methanol, weighed 135 mg, melted at 200-4° and was identical with an authentic sample of THS 3,21-diacetate (Vc)[10,11].

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Nomenclature Appendix

Corticosterone -	11β,21-Dihydroxypregn-4-ene-3,20--dione
Cortisone -	17α,21-Dihydroxypregn-4-ene-3,11,20--trione
Desoxycorticosterone -	21-Hydroxy-pregn-4-ene-3,20-dione
DOC -	See desoxycorticosterone
DOCA -	21-Acetoxy of desoxycorticosterone
Hydrocortisone -	11β,17α,21-Trihydroxypregn-4-ene--3,20-dione
Reichstein's Compound P acetate -	3β,17α-Dihydroxy-21-acetoxy-5α--pregnan-20-one
Reichstein's Compound S acetate -	17α-Hydroxy-21-acetoxypregn-4-ene--3,20-dione
Tetrahydrodesoxy-corticosterone	3α,21-Dihydroxy-5β-pregnan-20-one
allo-tetrahydrodesoxy-corticosterone	5α Epimer of above
THA -	3α,17α,21-Trihydroxy-5β-pregnane--11,20-dione
THB -	3α,11β,21-Trihydroxy-5β-pregnan-20--one
THS -	3α,17α,21-Trihydroxy-5β-pregnan-20--one
allo-THS -	5α Epimer of above

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25. We thank Prof. Reichstein, University of Basel, who has kindly performed the mixed melting point determinations.
26. Kindly carried out by Dr. G. Rumney, Beilinson Hospital, Petah Tiqvah.
27. The infrared spectrum of allo-THS was previously reported (reference 6). Our spectrum differs in several small details, undoubtedly due to a different crystalline form.
28. Personal communication from Prof. Finkelstein. The compound was obtained after hydrolysis with β-glucuronidase and the quantity was 600 μg/24 hr urine. The excretion of THS was 2 mg/24 hr urine. The isolated allo-THS was identical with our synthetic compound in two chromatographic systems (1. benzene-formamide; 2. chloroform-formamide) and developed identical colors with blue tetrazolium and with 70% phosphoric acid. The sensitivity of both reactions was 20 $\mu g/cm^2$. The quantitative estimation was done by the Porter-Silber reaction.
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30. Trivial names in this paper are explained in the appendix.