Bis-semicarbazone, recrystallized from a large volume of methanol, as colorless, microcrystalline rhombs, m.p. 246°.

Anal. Calcd. for $C_{12}H_{20}O_2N_6$: C, 53.42; H, 6.85; N, 28.77. Found: C, 53.36; H. 6.66; N, 28.77.

γ-(6-Methyl-3-keto-cyclohexen-1-yl)-butyric Acid (VI).—Δ^4-9-Methyloctalin-3,8-dione, 500 mg., was shaken with 20 ml. of 2% aqueous sodium hydroxide solution whereupon it dissolved rapidly. The solution was allowed to stand at room temperature for 2 hours in an atmosphere of nitrogen. After an ether extraction the reaction mixture was acidified to congo red with 2.5 *N* hydrochloric acid, salted with sodium chloride and the product was isolated through ether extraction. The ether solution was washed with a saturated sodium chloride solution, dried over anhydrous sodium sulfate, and the solvent was removed *in vacuo* to yield 300 mg. of a pale yellow oil. This product was purified by chromatography on 15 g. of acid washed alumina, elution being effected with mixtures of ether and acetic acid. The crystalline fractions, were sublimed at 100° (0.05 mm.) and recrystallized from ether–petroleum ether to afford (VI) as lustrous needles, m.p. 78–79°, $\lambda_{max.}^{C_2H_5OH}$ 2380 Å., $E_{1\,cm.}^{1\%}$ 690.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.35; H, 8.11; C-methyl, 1.0. Found: C, 67.38; H, 8.25; C-methyl, 0.78.

The semicarbazone, recrystallized from methanol, was obtained as colorless needles, m.p. 197–197.5° (dec.).

Anal. Calcd. for $C_{12}H_{19}O_3N_3$: C, 57.14; H, 7.41; N, 16.67. Found: C, 57.10; H, 7.37; N, 16.63.

Dehydrogenation of Acid (IV) to 5,8-Dimethylcoumarin (VIII).—A mixture of 1.78 g. of acid (IV), m.p. 46–48°, and 830 mg. of 10% palladium-on-charcoal were heated at 250° for 1 hour in an open tube. After cooling, the product was dissolved in ether and filtered from the catalyst. The ether solution was given a Norite treatment, filtered and the ether evaporated to a tan colored solid. Two recrystallizations of this material from ether–petroleum ether afforded colorless needles, m.p. 121.5–122°, $\lambda_{max.}^{CH_3OH}$ 2900 Å., $E_{1\,cm.}^{1\%}$ 744.

Anal. Calcd. for $C_{11}H_{10}O_2$: C, 75.80; H, 5.75. Found: C, 75.75; H, 5.65.

The *infrared* spectrum of this substance demonstrated its aromatic character and showed further a band in the carbonyl region at 5.88 μ identical in position with the carbonyl band found in coumarin. This substance was found, moreover, to be insoluble in cold 10% aqueous alkali but dissolved on warming and was reprecipitated on back acidification.

Acknowledgment.—The authors are indebted to Mr. R. N. Boos for the microanalyses herein reported.

RAHWAY, NEW JERSEY RECEIVED MARCH 12, 1951

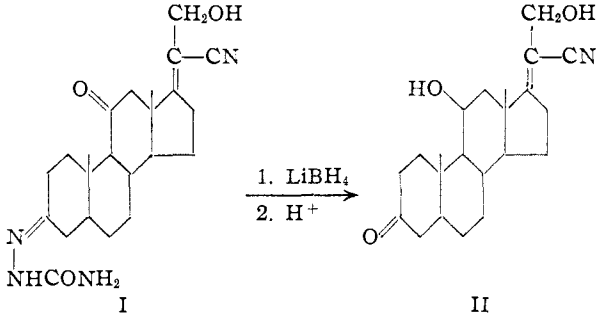
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Synthesis of 11-Hydroxylated Cortical Steroids. The Preferential Reduction of Carbonyl Systems in the Presence of Carbon–Nitrogen Multiple Bonds

BY N. L. WENDLER, HUANG-MINLON AND M. TISHLER

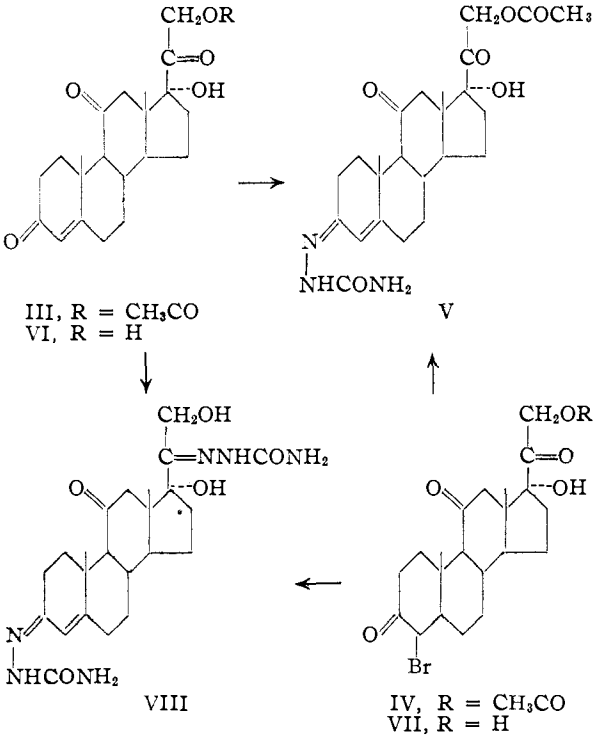
By employing the 3-mono- and 3,20-disemicarbazone derivatives of substituted pregnane-3,11,20-triones, it has been found possible to effect selective reduction of the carbonyl functions at positions 11 and 20 by means of lithium borohydride. This approach has enabled a partial synthesis of Reichstein's Substances E and U as well as the transformation of Cortisone to Compound F and 11-dehydrocorticosterone to corticosterone.

The synthesis of 17(α)-hydroxycorticosterone (Kendall's Compound F) in this Laboratory was reported recently.[1] In connection with that work it had been discovered that 20-cyano-17-pregnene-21-ol-3,11-dione 3-monosemicarbazone (I) on reduction with lithium borohydride and subsequent hydrolysis produced 20-cyano-17-pregnene-11(β), 21-diol-3-one (II).[2] The preferential reduction of the 11-carbonyl function in the presence of both



I II

cyano and semicarbazone groupings was thereby established. This ability to effect preferential reduction of carbonyl groups in the presence of carbon–nitrogen multiple bonds, and specifically in the presence of semicarbazone linkages has not only afforded a new route to otherwise difficultly accessible cortical steroids but has also provided a means for their direct interconversions. It should be added,

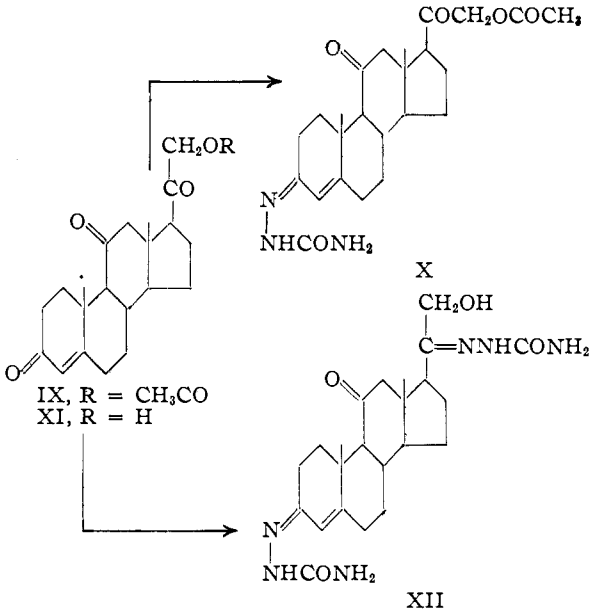


(1) Wendler, Graber, Jones and Tishler, THIS JOURNAL, **72**, 5793 (1950).

(2) To appear in a forthcoming publication.

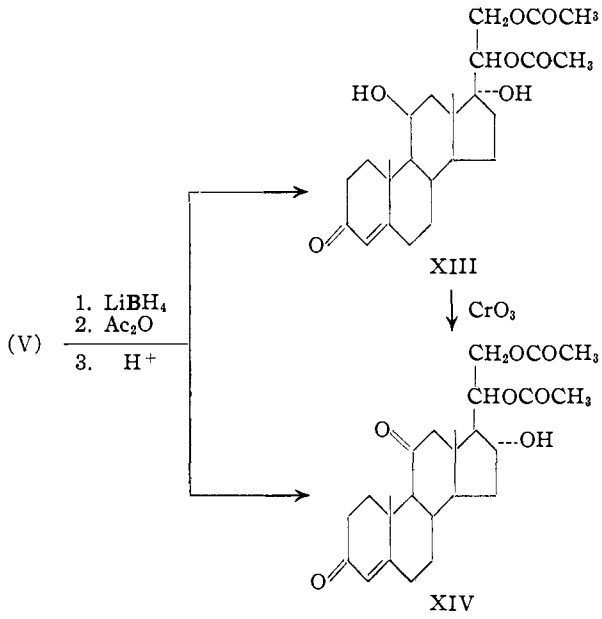
however, that the yields of these transformations *via* semicarbazones are low.

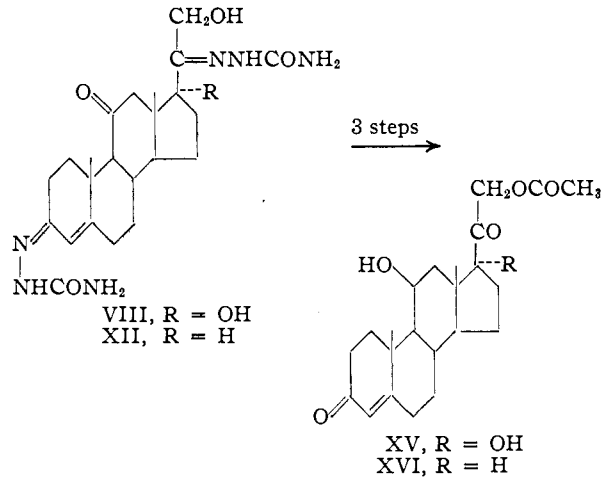
Cortisone acetate (III) and 4-bromopregnane-17(α),21-diol-3,11,20-trione 21-acetate (IV) were found to yield exclusively the 3-monosemicarbazone (V), even under forcing conditions in the presence of an excess of reagent. On the other hand, both cortisone (VI) and 4-bromopregnane-17(α),21-diol-3,11,20-trione (VII) gave the 3,20-bis-semicarbazone (VIII) under similar conditions. This demonstrates the relatively hindered character of the 20-carbonyl group in virtue of a neighboring ester function at position 21. This fact is further substantiated by the exclusive formation of the 3-monosemicarbazone (X) from 11-dehydrocorticosterone acetate (IX) whereas the bis-semicarbazone (XII) is produced from 11-dehydrocorticosterone (XI) itself. Similar observations were made recently with pregnenolone and its 21-acetate.[3]



The reduction of cortisone acetate monosemicarbazone (V) with lithium borohydride followed by acetylation and removal of the semicarbazone grouping, produced a mixture of substances. Chromatography of this mixture afforded Reichstein's Substances E and U as their diacetates, (XIII) and (XIV), respectively, in small yield. Substance E thus obtained was found to be identical on mixed melting point comparison with a sample prepared by Sarett *via* another route.[4] It was further related to Substance U by conversion to the latter through mild chromic acid oxidation according to Reichstein and von Euw.[5] The incomplete reduction of the 11-carbonyl group, as evidenced by the formation of Substance U, is in all probability associated with a solubility factor, since partial separation of material was invariably observed during these reductions.

By a similar reaction sequence, cortisone-3,20-bis-semicarbazone (VIII) was converted to 17(α)-hydroxycorticosterone 21-acetate (XV) and 11-dehydrocorticosterone-3,20-bis-semicarbazone (XII) was similarly transformed in very small yield to corticosterone 21-acetate (XVI). The latter substance has already been partially synthesized by von Euw and Reichstein by a different reaction series.[6]





Experimental

Cortisone Acetate 3-Monosemicarbazone (V).—Prepared from either (III) or (IV) with excess semicarbazide acetate in acetic acid solution at 70–75° for two or three hours. Obtained as colorless plates from methanol, m.p. 218–220°.

Anal. Calcd. for $C_{24}H_{33}N_3O_6$: N, 9.12. Found: N, 8.99.

The yield of the pure monosemicarbazone prepared from (III) was *ca.* 80%, whereas this substance was obtained in only 30–40% yield from (IV).

Cortisone-3,20-bis-semicarbazone (VIII).—Prepared from (VI) in 70% yield essentially according to Wintersteiner and Pfiffner.[7] This substance was obtained from (VII) in only *ca.* 30% yield. It formed micro needles from dimethylformamide–methanol, m.p. over 340° (dec.).

Anal. Calcd. for $C_{23}H_{34}O_5N_6$: N, 17.71. Found: N, 17.84.

11-Dehydrocorticosterone Acetate 3-Monosemicarbazone (X).—Prepared in the same manner as described for the preparation of (V). Obtained as needles from chloroform–methanol, m.p. 228.5–229° (gas evolution).

(3) Mancera, THIS JOURNAL, **72**, 5752 (1950).

(4) Sarett, Abstracts of the 118th Meeting of the American Chemical Society, Chicago, Ill., Sept. 3–8, 1950, p. 19-C.

(5) Reichstein and von Euw, *Helv. Chim. Acta*, **24**, 247-E (1941).

(6) von Euw and Reichstein, *Helv. Chim. Acta*, **27**, 1287 (1944).

(7) Wintersteiner and Pfiffner, *J. Biol. Chem.*, **116**, 291 (1936).

Anal. Calcd. for $C_{24}H_{33}N_3O_5$: N, 9.50. Found: N, 9.57.

11-Dehydrocorticosterone-3,20-bis-semicarbazone (XII).—Prepared in the same manner as described for the preparation of (VIII). Obtained as a micro-crystalline solid, m.p. over 300° (dec.).

Anal. Calcd. for $C_{23}H_{34}N_6O_4$: N, 18.03. Found: N, 18.02.

Reichstein's Substances E and U Diacetate (XIII) and (XIV).—A solution of 4.2 g. of (V) in 600 cc. of dry tetrahydrofuran was added with stirring at 25° to a solution of 2.4 g. of lithium borohydride in 120 cc. of tetrahydrofuran. Some separation of material was observed at this point. The mixture was stirred for one hour after complete addition and then the excess lithium borohydride was decomposed under cooling with 10% aqueous acetic acid. Concentration of the resulting clear solution and trituration of the residue with water afforded, on filtration and drying at 90°, 3.3 g. of crude, reduced product. The latter was acetylated with 19 cc. of pyridine and 18 cc. of acetic anhydride at 90° for ten minutes. The solvents were removed *in vacuo* and the residue washed with water and dried at room temperature. This crude reacetylated material was treated with 35 cc. of acetic acid, 11 cc. of water, 5.95 g. of sodium acetate and 5.6 cc. of 90% pyruvic acid and heated for four hours at 75°. At the end of this period the solvents were removed *in vacuo* and the residue dissolved in chloroform. The chloroform solution was washed with 5% aqueous sodium bicarbonate solution and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the residue chromatographed on acid-washed alumina. Fractional elution with benzene–chloroform afforded Reichstein's Substance E diacetate, obtained as needles from ethyl acetate–ether, m.p. 229–231°.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 67.08; H, 7.98.

A mixed melting point of this material with an authentic specimen[4] was not depressed.

Further fractions from the chromatography yielded Reichstein's Substance U diacetate obtained as thick prisms from ethyl acetate, m.p. 252–253°.

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67. Found: C, 67.46; H, 7.24.

A mixed melting point of this material with an authentic sample prepared by chromic acid oxidation[5] of Reichstein's Substance E diacetate showed no depression.

17(α)-Hydroxycorticosterone (XV).—A solution of 0.8 g. of the disemicarbazone (VIII) in 5 cc. of dimethylformamide and 10 cc. of tetrahydrofuran was added dropwise to a stirred solution of 0.5 g. of lithium borohydride in 25 cc. of tetrahydrofuran. The temperature was maintained at 25° and stirring was continued for two hours after addition was complete. At the end of this period the excess lithium borohydride was decomposed with 50 cc. of 10% aqueous acetic acid and the resulting clear solution was concentrated *in vacuo* nearly to dryness. Trituration of the residue with water gave a colorless solid which was filtered, washed with water and dried first at room temperature and finally at 70° for two hours. This crude reduction product (m.p. over 340°) was reacetylated as described above, with 10 cc. of pyridine and 10 cc. of acetic anhydride at 90° for ten minutes. The solvents were evaporated *in vacuo*, replaced by methanol and the methanol solution treated with Norite. The colorless filtrate from this treatment gave an evaporation of the solvent 0.59 g. of material. To this reacetylated reduction product were added 7.5 cc. of glacial acetic acid, 2.5 cc. of water, 1.28 g. of anhydrous sodium acetate and 1.2 cc. of 90% aqueous pyruvic acid. The mixture was heated in a nitrogen atmosphere at 75° for four hours. At the end of this period of heating the mixture was concentrated *in vacuo* at 50° nearly to dryness. Water was added and the organic material was extracted with ethyl acetate. The ethyl acetate solution was washed with water, 5% aqueous sodium bicarbonate, treated with anhydrous sodium sulfate and Norite and filtered. The colorless filtrate was concentrated to a small volume and seeded. In this way there was obtained 75 mg. of colorless sandy crystals, m.p. 211–216°. Recrystallization first from ethyl acetate and finally from acetone gave pure material, m.p. 219–220°, which was not depressed on admixture with authentic 17-(α)-hydroxycorticosterone acetate[1] $\lambda_{max.}^{C_2H_5OH}$ 2425 Å., $E_{1\,cm.}^{1\%}$ 380.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.98. Found: C, 68.56; H, 8.17.

Corticosterone Acetate (XVI).—11-Dehydrocorticosterone 3,20-bis-semicarbazone (XII) was transformed to corticosterone acetate (XVI) in the same manner described above for the conversion of (VIII) to (XV). After chromatography of the final reaction product a very small amount of (XVI) was obtained as colorless crystals from acetone–ether, m.p. 147–152°.[8] A mixed melting point of this material with a sample prepared by acetylation of authentic corticosterone[9] showed no depression.

(8) Reichstein (*Helv. Chim. Acta*, **20**, 953 (1937)), observed that this compound gave a double melting point at 145–146.5° and 152.5–153°.

(9) We are indebted to the Worcester Foundation for Experimental Biology, Shrewsbury, Mass., for an authentic sample of corticosterone.

RAHWAY, NEW JERSEY RECEIVED MARCH 19, 1951

[JOINT CONTRIBUTION FROM THE INSTITUTO DE QUÍMICA DE LA UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO AND THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroidal Sapogenins. IX.[1] Oxidation of $\Delta^{5,16,20(22)}$-Furostatriene-3β,26-diol[2]

BY A. SANDOVAL, J. ROMO, G. ROSENKRANZ, ST. KAUFMANN AND CARL DJERASSI

$\Delta^{5,16,20(22)}$-Furostatriene-3β,26-diol diacetate (ψ-kryptogenin diacetate) (IIb) is oxidized with chromium trioxide to $\Delta^{5,17(20)}$-cholestadiene-3β,26-diol-16,22-dione diacetate (IV), which on saponification leads to 22,26-oxido-$\Delta^{5,17(20)}$-cholestadiene-3β,22-diol-16-one (VIIa). Both IV and VIIa yield the pyridazine derivative V of Δ^5-cholestene-3β,26-diol-16,22-dione (kryptogenin) when refluxed with hydrazine. Lithium aluminum hydride reduction of VII gives $\Delta^{5,17(20)}$-22-isospirostadien-3β-ol (Xa).

As pointed out in an earlier article,[3] Δ^5-cholestene-3β,26-diol-16,22-dione (kryptogenin) (I) occurs in a number of species of Mexican *Dioscoreae* and is obtained in appreciable amounts as a by-product in the commercial extraction of such plants. The conversion of I, by reductive methods,[3] to $\Delta^{5,20(22)}$-furostadiene-3β,26-diol (ψ-diosgenin) (III) affords one path for utilizing Δ^5-cholestene-3β,26-diol-16,22-dione (I) for the production of steroid hormones. Since this sapogenin is readily transformed[4] into $\Delta^{5,16,20(22)}$-furostatriene-3β,26-diol (ψ-kryptogenin) (II), it was of interest to study the behavior of this substance toward oxidizing agents and compare it with that of its 16,17-dihydro derivative III (ψ-diosgenin). As has been discovered by Marker,[5] the latter substance (III)

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

(2) For nomenclature of steroidal sapogenins see G. Rosenkranz and C. Djerassi, *Nature*, **166**, 104 (1950).

(3) St. Kaufmann and G. Rosenkranz, THIS JOURNAL, **70**, 3502 (1948).

(4) (a) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. M. Ruof, *ibid.*, **69**, 2200 (1947); (b) St. Kaufmann and G. Rosenkranz, U. S. Patent 2,535,073.

(5) R. E. Marker, THIS JOURNAL, **62**, 3350 (1940).