[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT DIVISION OF THE SCHERING CORPORATION]

Transformation Products of Strophanthidin. I. The Preparation of 14β,19-Dihydroxydesoxycorticosterone 19,21-Diacetate

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RECEIVED NOVEMBER 26, 1958

Strophanthidol has been converted to its 19-monoacetate IV. Oxidation of IV at C-3 followed by ozonolysis of the lactone side chain, dehydration of the C-5 hydroxyl and acetylation at C-21 produced 14β,19-dihydroxydesoxycorticosterone 19,21-diacetate (VII).

Strophanthidin is an interesting and unique starting material for the preparation of other steroids: (a) it possesses hydroxyl groups at C-3 and C-5, easily converted to a 3-keto-Δ^4 system by oxidation at C-3 followed by dehydration; (b) the unsaturated lactone attached to C-17 gives the ketol side chain simply on ozonolysis; (c) the C-19 aldehyde is a ready source of 19-hydroxy steroids.

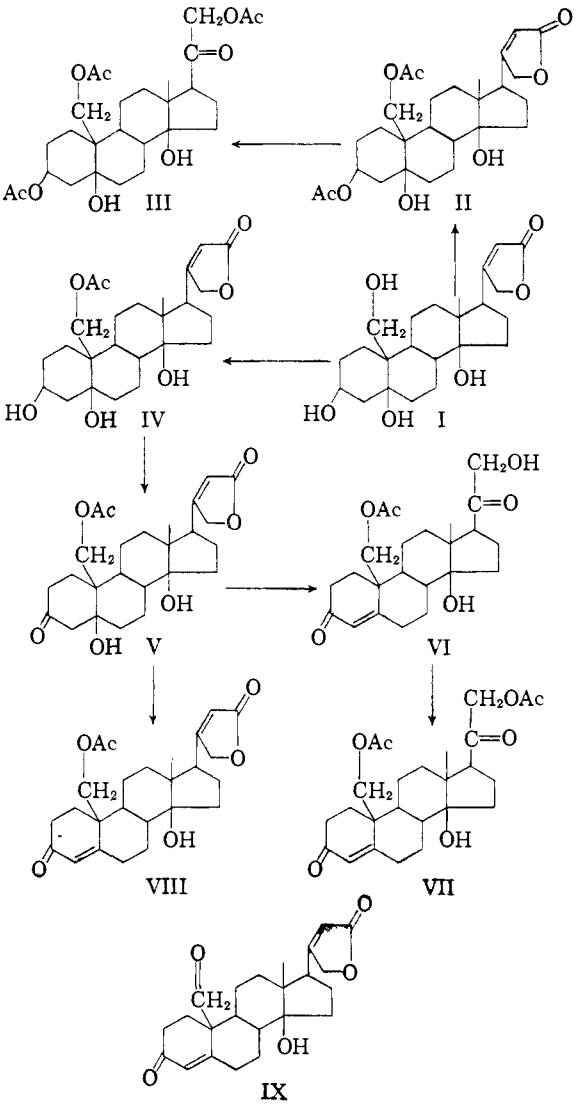
Oxidation of strophanthidin with pyridine–chromium trioxide, followed by dehydration in refluxing acetic acid, does give a small yield of a compound to which we assign the structure 3,19-dioxo-Δ^4-cardadienolide (IX). Obviously, either the C-19 aldehyde or the unsaturated lactone was not able to survive such treatment in good yield.

Strophanthidol (in which the C-19 aldehyde of strophanthidin has been reduced to the alcohol) was the next intermediate of choice. As might be expected, acetylation with one mole of acetic anhydride in pyridine produced the 19-monoacetate IV in reasonable yield. However, treatment with up to ten moles of acetic anhydride still gave appreciable quantities of the monoacetate, indicating perhaps some steric interference between the 3β- and 5β-hydroxy groups.

Oxidation of IV with chromium trioxide–pyridine produced the 3-ketone V, which we were unable to obtain crystalline. Treatment with refluxing acetic acid for a short period removed the 5-hydroxyl group as water and produced the 3-keto-Δ^4-compound VIII.

The conversion of the unsaturated lactone group to the ketol side chain by means of ozone has been studied extensively by Reichstein and his collaborators.[1] The first product of the reaction is the glyoxylic ester of the 21-hydroxy group, which must then be hydrolyzed with bicarbonate. In order to avoid the danger of extensive isomerization at C-17,[2] we omitted a separate hydrolysis step, and relied on the mild acid conditions of the work-up to produce the desired 21-hydroxy compound.

Pilot experiments on the ozonolysis of the unsaturated lactone side chain were carried out on strophanthidol 3,19-diacetate; this was converted to pregnane-3β,5β,14β,19,21-pentol-20-one 3,19,21-triacetate in *ca.* 45% yield. Ehrenstein,[3] employing the conventional technique of alkaline hydrolysis after ozonolysis, obtained a somewhat higher yield of the same product, but with a lower m.p.



Next, ozonolysis was carried out on the 3-ketone V. The intermediate pregnanetriol was dehydrated by treatment with warm acetic acid, then acetylated at C-21 to produce 36% of 14β,19-dihydroxydesoxycorticosterone 19,21-diacetate(VII).

The assignment of the β-configuration to the ketol side chain in VII is supported by rotational data (Table I). The rotatory contribution for the

(1) *Cf.* K. Meyer and T. Reichstein, *Helv. Chim. Acta*, **30**, 1508 (1947).

(2) In steroids containing a 14-iso (14-β) configuration, the preferred conformation at C-17 is also iso (α) [*cf.* K. Meyer, *ibid.*, **30**, 1976 (1947); A. Lardon, *ibid.*, **32**, 1517 (1949)]. Bicarbonate hydrolysis of 3β,19-diacetoxy-21-glyoxyloxy-14-isopregnane-5β,14β-diol-20-one does produce some of the 17α-ketol [C. Balant and M. Ehrenstein, *J. Org. Chem.*, **17**, 1576 (1952)].

(3) C. Balant and M. Ehrenstein, *ibid.*, **17**, 1576 (1952).

TABLE I

MOLECULAR ROTATIONAL DATA[a]

	M_D	M_D
Desoxycorticosterone	+611 (chl.)	
19-Hydroxydesoxycorticosterone	+640 (chl.)	− 29
3β,5β,14β,19-Tetrahydroxy-14β,17α-etianic acid	+ 11 (EtOH)	
3β,5,19-Trihydroxy-14β,17α-etianic acid	+227 (chl.)	+216
14β,17α-Desoxycorticosterone acetate	+402 (chl.)	
14β-Hydroxy-17α-desoxycorticosterone acetate	~+200 (calcd.)	
14β-Hydroxydesoxycorticosterone acetate	+505 (chl.)	
14β,19-Dihydroxydesoxycorticosterone acetate	+522 (pyr.)	

[a] Values for the first six compounds are from tables in M. Ehrenstein and M. Dunnenberger, *J. Org. Chem.*, **21**, 783 (1956).

introduction of a 19-hydroxy group into a 3-keto-Δ^4-steroid is small, and for purposes of our calculations, may be neglected.[4] Introduction of a 14β-hydroxyl group into a 14-iso, 17-iso steroid results in a ΔM_D of +216° and, therefore by calculation, 14β-hydroxy-17-isodesoxycorticosterone acetate should have M_D +200°. Our compound, 14β,-19-dihydroxydesoxycorticosterone-19,21-diacetate (VII), has M_D +522°, which is in good agreement with the value of +505° reported[5] for 14β-hydroxydesoxycorticosterone acetate.

The unsaturated lactone side chain produces an ultraviolet maximum at *ca.* 218 mμ (*cf.* compound IV). A 19-acetoxy group apparently has little effect on the 3-keto-Δ^4-system, as evidenced by compound VII, which has a maximum at 239 mμ. However, when both chromophores are present in the same compound (VIII), only a single enhanced maximum is observed at 226 mμ. If an aldehyde group is attached to C-10 instead of the acetoxymethyl group (*e.g.*, compound IX) the single maximum is at 223 mμ.

Experimental[6]

Strophanthidol 19-Acetate (IV).—A solution of 3.00 g. of strophanthidol, 45 ml. of pyridine and 0.77 g. of acetic anhydride (1 mole plus 5%) was allowed to stand overnight at room temperature, then evaporated to a non-crystalline residue (3.19 g.) under reduced pressure. Ethyl acetate and acetone were added, and slow evaporation overnight gave a crystalline residue. Recrystallization from aqueous acetone gave 2.87 g., m.p. 134–138°. The analytical sample, crystallized once more, was obtained as the monohydrate and melted at 136–139°, $(\alpha)_D$ +34.8° (EtOH).

Anal. Calcd. for $C_{25}H_{36}O_7 \cdot H_2O$: C, 64.36; H, 8.21. Found: C, 64.37; H, 8.37.

Drying at 65° *in vacuo* removed the hydrate.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 66.51; H, 8.28.

Treatment of the 19-monoacetate with 10 moles of acetic anhydride in pyridine still did not convert it completely to 3,19-diacetate, and *ca.* 50% of the original monoacetate could be recovered.

Strophanthidone 19-Acetate (V).—A solution of 5.0 g. of IV in 50 ml. of pyridine was added to a previously prepared slurry of 5.0 g. of chromium trioxide in 50 ml. of pyridine, and the resulting mixture stirred at room temperature for 18 hours. Then 15 g. of sodium sulfite in water was added, stirring continued for 1.5 hours, and the mixture extracted into methylene chloride. The organic extracts were washed with water, dried and evaporated to a resinous residue: 4.86 g., λ_{max}^{MeOH} 218 mμ (ε 14,600). All attempts at crystallization failed, but the unpurified resin behaved satisfactorily in subsequent reactions.

19-Acetoxy-14β-hydroxy-3-keto-Δ^4-cardadienolide (VIII).—A solution of 630 mg. of V in 15 ml. of acetic acid was refluxed for 20 minutes, then poured into water, neutralized with 10% sodium hydroxide and extracted into methylene chloride. The organic extracts were washed with water, dried and evaporated. Crystallization from ethanol gave 470 mg. of III, m.p. 183–185°. The analytical sample, crystallized once more, melted at 185–187°, $(\alpha)_D$ +100.9° (dioxane), λ_{max}^{MeOH} 226 mμ (ε 22,300).

Anal. Calcd. for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found: C, 69.91; H, 7.67.

14β,19-Dihydroxydesoxycorticosterone 19,21-Diacetate (VII).—A solution of 4.0 g. of V in 400 ml. of pyridine and 400 ml. of ethyl acetate was cooled to −60°, and treated with a stream of ozone until a blue color persisted. Excess ozone was removed by a stream of oxygen, then 8 g. of zinc dust and 40 ml. of acetic acid were added while the mixture was warmed slowly to 0°, then on the steam-bath to 60°. The mixture was filtered and the filtrate concentrated to a low volume under reduced pressure, then poured into water. The pyridine was neutralized with dilute hydrochloric acid, the mixture extracted with methylene chloride, and the organic extracts washed with 5% dilute sodium hydroxide solution and water, dried and evaporated to give 2.47 g. This was acetylated with acetic anhydride and pyridine, then chromatographed on Florisil to yield, after crystallization from acetone–hexane, 1.45 g. (36%), m.p. 146.4–148.2°, $(\alpha)_D$ +116.7° (pyridine), λ_{max}^{MeOH} 239 mμ (ε 16,600).

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68. Found: C, 67.09; H, 7.65.

3,19-Dioxo-14β-hydroxy-Δ^4-cardadienolide (IX).—A solution of 2.0 g. of strophanthidin in 20 ml. of pyridine was added to a slurry of 2.0 g. of chromium trioxide in 20 ml. of pyridine and the mixture stirred at room temperature for 21 hours. A solution of 6 g. of sodium sulfite in water was added and stirring continued for 1.5 hours. The resulting solution was then continuously extracted with ether to give 0.73 g. of an oil. This was refluxed in 10 ml. of acetic acid for 25 minutes, then poured onto ice, neutralized with 15% sodium hydroxide and extracted into methylene chloride. The oily material obtained from the organic extracts (700 mg.) was chromatographed on Florisil. Material eluted with methylene chloride (99%)–methanol (1%) totaled 440 mg. Two crystallizations from ethyl acetate gave 90 mg. of IX, m.p. 252–253° dec. The analytical sample, crystallized once more, melted at 255.4–258.0° dec., λ_{max}^{EtOH} 223 mμ (ε 23,800), $[\alpha]_D$ + 72° (pyr.).[7]

Anal. Calcd. for $C_{23}H_{28}O_5$: C, 71.83; H, 7.36. Found: C, 71.60; H, 7.53.

3β,5β,14β,19,21-Pentahydroxypregnane-20-one 3,19,21, Triacetate (III).—A solution of 8.0 g. of strophanthidol 3,19-diacetate (II) in 800 ml. of pyridine and 800 ml. of ethyl acetate was cooled to −60° and treated with ozone of the usual fashion. Excess ozone was removed by a stream of oxygen and zinc dust and acetic acid added to destroy ozonides. After filtering, the solution was concentrated under reduced pressure to a low volume, then poured into water, the water made slightly acid with dilute hydrochloric acid, then extracted with methylene chloride. The organic extracts were washed with water, dried and evaporated to a residue. This was acetylated with acetic anhydride and pyridine at room temperature for 22 hours to give 6.0 g., m.p. 191–196°. Crystallization from methanol yielded 3.55

(4) *Cf.* A. Meyer, *Experientia*, **11**, 99 (1955).

(5) K. Meyer and T. Reichstein, *Helv. Chim. Acta*, **30**, 1508 (1947).

(6) All m.p.'s are corrected. All rotations were taken in a one-dm. tube at 25° and at a concentration of *ca.* 1%. Analyses and optical data were obtained by the Microanalytical and Physical Chemistry Departments of these laboratories.

(7) NOTE ADDED IN PROOF.—After completion of this work, compound (IX) was described by other investigators. A. Katz [*Helv. Chim. Acta*, **40**, 831 (1957)] reported m.p. 212–225°, $[\alpha]_D$ + 170° (ChfMeOH, 95:5); C. Tamm and A. Gubler [*ibid.*, **42**, 239 (1959)] reported m.p. 199–210°, $[\alpha]_D$ + 147° (Chf.).

g., m.p. 203.0–204.5°, and 0.42 g., m.p. 201.0–203.0 (total 48%), $(\alpha)_D$ +33.8° (pyridine), no ultraviolet absorption; lit.[3] m.p. 188.5–189.5°, $(\alpha)_D$ +71.7° ($CHCl_3$).

Anal. Calcd. for $C_{27}H_{40}O_9$: C, 63.76; H, 7.93. Found: C, 63.33; H, 8.19.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT DIVISION, SCHERING CORP.]

Transformation Products of Strophanthidin. II. Some 10-Cyano Derivatives[1]

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RECEIVED NOVEMBER 26, 1958

Strophanthidin oxime (I) can be dehydrated to the 10-cyano derivative either by treatment with acetic anhydride and pyridine (to give II) or by treatment with the chromium trioxide–pyridine complex (to give IV). Subsequent ozonolysis of the unsaturated lactone side chain produces 10-cyano derivatives (VII, IX, X) related to desoxycorticosterone.

Strophanthidin, possessing a relatively unhindered aldehyde group at C-10, is readily converted to the corresponding oxime. Treatment of this with acetic anhydride and pyridine not only acetylated the secondary hydroxyl at C-3, but also dehydrated the oxime to a nitrile (I → II). This reaction makes possible the preparation of 10-cyano steroids related to desoxycorticosterone by transformation of the proper strophanthidin intermediates.

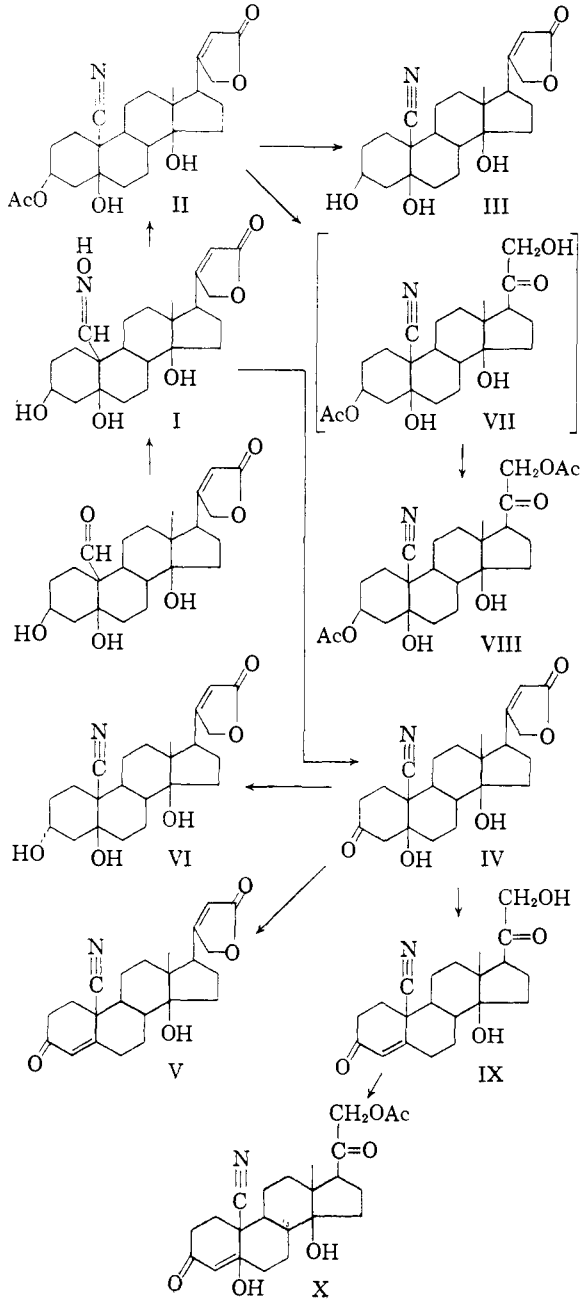
In order to prepare the 3-keto-Δ^4-compound (V) the 10-cyano-3-acetoxy compound (II) first had to be hydrolyzed under non-alkaline conditions (because of the instability of the lactone side chain). This could be accomplished by treatment with *p*-toluenesulfonic acid in refluxing aqueous ethanol, but the reaction mixture had to be purified by chromatography and the yield was less than 50%.

It was found, however, that oxidation of the oxime I with the pyridine–chromium trioxide complex oxidized the 3-hydroxyl to a ketone and simultaneously dehydrated the oxime group to the nitrile to produce compound IV in *ca.* 65% yield. This was readily dehydrated in refluxing acetic acid to give V in excellent yield.

Treatment of IV with potassium borohydride in refluxing tetrahydrofuran produced a triol (VI) which was not identical with the triol III prepared by hydrolysis of the 3-acetate II. The 3α-configuration was therefore assigned to the new hydroxyl group. This is also in keeping with the known observations[2] that sodium borohydride reduction of a 3-ketosteroid of the normal (5β) series produces the 3α-ol as the major product.

Ozonolysis of the 3-acetoxy-10-cyano compound II in the manner previously described[1] produced 19-nor-10-cyano-3β,14β,21-trihydroxypregnan-20-one 3,21-diacetate (VIII). However, the yield was lower than from the corresponding 10-acetoxymethyl compound,[1] suggesting perhaps some attack on the nitrile group by ozone. Ozonolysis of 19-nor-10-cyano-5β,14β-dihydroxy-3-ketocardenolide (IV) in the same fashion gave 19-nor-10-cyano-14β-hydroxydesoxycorticosterone (IX) which was converted to the 21-acetate X with acetic anhydride and pyridine.

The presence of both the 3-keto-Δ^4- and unsaturated lactone chromophores in the same molecule (as in V) again produced a single enhanced maximum at 226 mμ, as previously observed for the cor-



(1) For the previous paper see E. P. Oliveto, L. Weber, C. G. Finckenor, M. M. Pechet and E. B. Hershberg, THIS JOURNAL, **81**, 2831 (1959).

(2) R. B. Woodward, F. Sondheimer, D. Taub, K. Hensler and W. McLamore, *ibid.*, **74**, 4332 (1952); R. B. Woodward, F. Sondheimer and D. Taub, *ibid.*, **73**, 4057 (1951).