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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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.

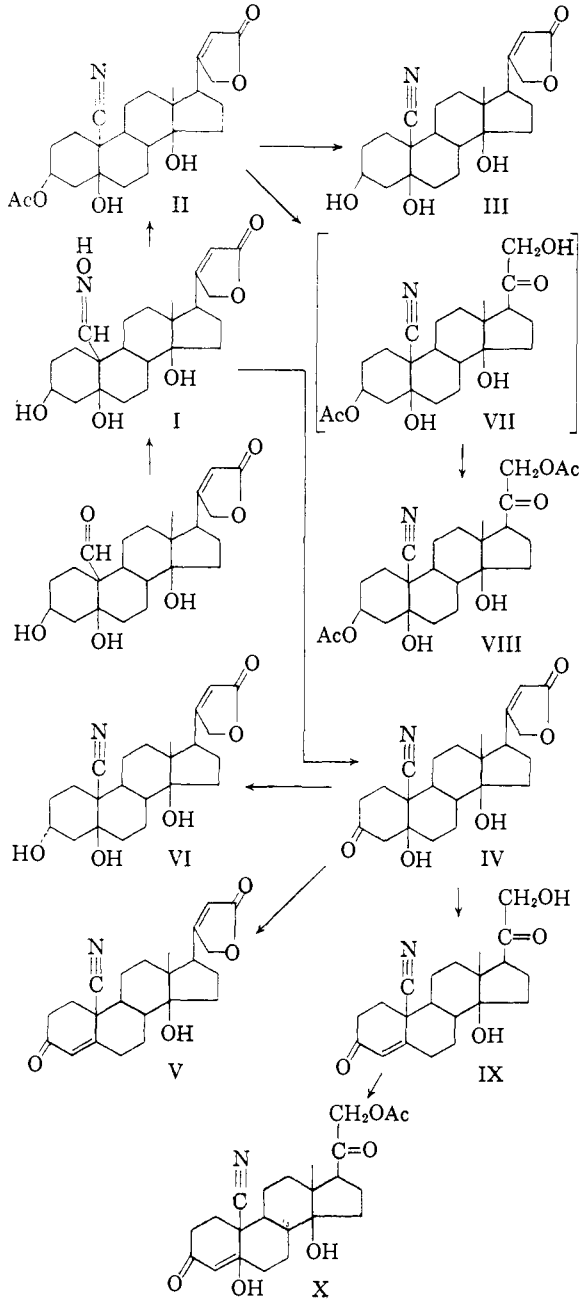
In order to prepare the 3-keto-$\Delta^4$-compound (V) the 10-cyano-3-acetoxy compound (II) first had to be hydrolyzed under non-alkaline conditions (because of the instability of the lactone side chain). This could be accomplished by treatment with *p*-toluenesulfonic acid in refluxing aqueous ethanol, 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 3$\alpha$-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 (5$\beta$) series produces the 3$\alpha$-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-3$\beta$,14$\beta$,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-5$\beta$,14$\beta$-dihydroxy-3-ketocardenolide (IV) in the same fashion gave 19-nor-10-cyano-14$\beta$-hydroxydesoxycorticosterone (IX) which was converted to the 21-acetate X with acetic anhydride and pyridine.

The presence of both the 3-keto-$\Delta^4$- and unsaturated lactone chromophores in the same molecule (as in V) again produced a single enhanced maximum at 226 m$\mu$, 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).

responding 10-acetoxymethyl steroid.[1] However, the 3-keto-$\Delta^4$-chromophore alone (as in IX or X) absorbed at 229–230 mμ with the cyano group a C-10, instead of at the expected 238–240 mμ. Thus, the cyano group has a definite hypsochromic effect. However the semicarbazone of compound V absorbed at the expected 219 and 272 mμ.

## Experimental[3]

**Strophanthidin Oxime** (I) was prepared from strophanthidin by the method of Jacobs.[4] Recrystallization from aqueous methanol gave m.p. 270–272° dec., $[\alpha]_D$ +65.0°, $\lambda_{max}^{MeOH}$ at 215 mμ (ε 18,100); infrared peaks at 2.81, 3.04, 5.46, 5.74, 5.86 and 6.20 μ; lit. m.p.[4] 270–275°, $[\alpha]_D$ +71.3° (pyridine); m.p.[5] 265–270°, m.p.[6] 256°, $[\alpha]_D$ +67° (pyr.).

**19-Nor-3β-acetoxy-10-cyano-5β,14β-dihydroxycardenolide (II).**—A solution of 9.51 g. of I in 80 ml. of pyridine and 40 ml. of acetic anhydride was allowed to stand at room temperature for 43 hours. The mixture was then poured into ice and hydrochloric acid, and extracted with methylene chloride. The organic extract was washed neutral with water, dried over $MgSO_4$, filtered and evaporated to a residue. Recrystallizations from ethyl acetate gave 6.34 g. of II, m.p. 289–291°, $[\alpha]_D$ +7.5°; infrared peaks at 2.89, 2.98, 4.48, 5.47, 5.84, 6.19, 7.86 and 8.00 μ.

*Anal.* Calcd. for $C_{25}H_{33}O_6N$: C, 67.70; H, 7.50; N, 3.16. Found: C, 67.55; H, 7.41; N, 2.92.

**19-Nor-10-Cyano-3β,5β,14β-trihydroxycardenolide (III).**—A solution of 2.0 g. of II in 80 ml. of 80% ethanol containing 200 mg. of *p*-toluenesulfonic acid was refluxed for 24 hours. The alcohol was removed by distillation and the oily residue extracted into chloroform, the organic extract washed with water, dried and evaporated to yield 1.54 g. This was chromatographed on Florisil, and the fractions eluted with methylene chloride containing 1–3% methanol were combined and crystallized from ethyl acetate to yield 670 mg. of III, m.p. 232–235°. The analytical sample, crystallized twice more from ethyl acetate, melted at 230.0–233.0°, $[\alpha]_D$ +26.2°; infrared peaks at 2.90, 2.99, 4.49, 5.56, 5.72 and 6.15 μ.

*Anal.* Calcd. for $C_{23}H_{31}O_5N$: C, 68.80; H, 7.78; H, 3.49. Found: C, 68.95; H, 7.55; N, 3.74.

**19-Nor-10-cyano-5β,14β-Dihydroxy-3-ketocardenolide (IV).**—A solution of 50 g. of I in 500 ml. of pyridine was oxidized for 18 hours at 30° with the pyridine–chromium trioxide complex (prepared by adding 50 g. of chromium trioxide in small portions to 500 ml. of pyridine at a temperature below 15°). A solution of 150 g. of sodium sulfite in water was added, the mixture stirred for 1.5 hours below 30°, then extracted with methylene chloride. The organic extracts were washed with water and evaporated to a residue (51 g.). This was extracted in a Soxhlet apparatus with ethyl acetate to remove dark inorganic material which was present. The ethyl acetate solution was then treated with Darco, filtered and concentrated to *ca.* 350 ml. to give 31.55 g. of IV, m.p. 274–278° dec., $[\alpha]_D$ +17.6°, $\lambda_{max}^{EtOH}$ at 216 mμ (ε 20,280); infrared peaks at 2.87, 4.49, 5.36, 5.68, 5.74, 5.79 and 6.15 μ.

*Anal.* Calcd. for $C_{23}H_{29}O_5N$: C, 69.15; H, 7.32; N, 3.51. Found: C, 69.39; H, 7.04; N, 3.26.

**19-Nor-10-cyano-14β-hydroxy-3-keto-$\Delta^4$-cardadienolide (V).**—A solution of 6.00 g. of IV in 60 ml. of glacial acetic acid was refluxed for one hour and poured into water. Sodium hydroxide solution was added to neutralize the acetic acid, and the solids were collected by filtration to yield 5.62 g., m.p. 275°. Crystallization from ethyl acetate gave 5.20 g. of V, m.p. 270.6–272.0°, $[\alpha]_D$ +124.0°, $\lambda_{max}^{MeOH}$ at 226 mμ (ε 27,600); infrared peaks at 2.96, 4.50, 5.52, 5.78, 5.95, 6.10 and 6.18 μ.

*Anal.* Calcd. for $C_{23}H_{27}O_4N$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.23; H, 7.13; N, 3.64.

The 3-monosemicarbazone of V, prepared in the usual fashion with semicarbazide acetate, melted at 280° dec., $[\alpha]_D$ +301.0°; $\lambda_{max}^{EtOH}$ at 219 mμ (ε 16,300), at 272 mμ (ε 30,900).

**19-Nor-10-cyano-3α,5β,14β-trihydroxycardenolide (VI).**—A mixture of 500 mg. of IV and 500 mg. of potassium borohydride in 50 ml. of purified tetrahydrofuran was refluxed for 2 hours. Acetic acid and water were added, and the solution evaporated to a residue under reduced pressure. Recrystallization from ethyl acetate gave 270 mg. of VI, m.p. 311–312° dec., $[\alpha]_D$ +27.0°, $\lambda_{max}^{MeOH}$ at 216 mμ (ε 16,900); infrared peaks at 2.84, 2.94, 4.49, 5.56, 5.69, 5.75 and 6.15 μ. Its infrared spectrum did not match that of III or IV.

*Anal.* Calcd. for $C_{23}H_{31}O_5N$: C, 68.80; H, 7.78; N, 3.49. Found: C, 68.55; H, 7.50; N, 3.68.

**19-Nor-10-cyano-3β,14β,21-trihydroxypregnan-20-one 3,-21-Diacetate (VIII).**—A solution of 3.0 g. of II in 225 ml. of pyridine and 450 ml. of ethyl acetate was cooled to −60°, and ozone was introduced until a deep blue color developed and persisted for 10 minutes. Excess ozone was blown out by a stream of oxygen, then 6 g. of zinc and 225 ml. of acetic acid were added and the mixture slowly warmed to 60° and filtered. Most of the solvent was removed under reduced pressure, water was added, then hydrochloric acid to an acid reaction. The mixture was extracted with methylene chloride, and the organic extracts washed with water, dilute sodium hydroxide and water, dried and evaporated to a residue: 570 mg., m.p. 202–213°. Acetylation with acetic anhydride–pyridine gave 540 mg., m.p. 196–200, and recrystallization from methanol yielded 180 mg. of VIII, m.p. 212.4–215°, $[\alpha]_D$ +27.0° (pyridine); infrared peaks at 2.93, 4.48, 5.72, 5.82, 5.94, 6.11, 8.06 and 8.17 μ.

*Anal.* Calcd. for $C_{25}H_{35}O_7N$: C, 65.05; H, 7.64; N, 3.04. Found: C, 65.04; H, 7.78; N, 3.06.

**19-Nor-10-cyano-14β-hydroxydesoxycorticosterone (IX).**—A solution of 8.0 g. of IV dissolved in 1 l. of pyridine and 500 ml. of ethyl acetate was treated with ozone at −50° in the usual fashion, then treated with 16 g. of zinc and 1 l. of acetic acid and warmed to 60°. The mixture was filtered, and the filtrate evaporated to a low volume under reduced pressure. Water and hydrochloric acid were added, the solution extracted with methylene chloride, and the organic extracts washed with water, dilute sodium hydroxide and water, dried and evaporated to a residue: 3.07 g., m.p. 221°. Crystallization from methanol gave 2.00 g. of IX, m.p. 223.0–225.0°, $[\alpha]_D$ +177.0° (pyridine), $\lambda_{max}^{MeOH}$ at 230 mμ (ε 17,300); infrared peaks at 2.90, 4.50, 5.80, 6.00 and 6.14 μ.

*Anal.* Calcd. for $C_{21}H_{27}O_4N$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.99; H, 8.16; N, 3.77.

**19-Nor-10-cyano-14β-hydroxydesoxycorticosterone 21-acetate (X).**—The residue obtained from the ozonolysis of 8.0 g. of IV was treated with acetic anhydride and pyridine overnight at room temperature. The solution was poured into ice and hydrochloric acid and the solids collected by filtration: 3.35 g., m.p. 188–191°. Crystallization from methanol gave 2.48 g. of X, m.p. 196.0–198.0°, $[\alpha]_D$ +162.0° (pyridine), $\lambda_{max}^{MeOH}$ at 229 mμ (ε 17,600); infrared peaks at 2.93, 4.48, 5.72, 5.82, 5.94, 6.11, 8.06 and 8.17 μ.

*Anal.* Calcd. for $C_{23}H_{29}O_5N$: C, 69.15; H, 7.32; N, 3.51. Found: C, 69.03; H, 7.57; N, 3.60.

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(3) All m.p.'s are corrected. All rotations were taken in pyridine 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.

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