1β,3β-Dihydroxy-16α,17α-oxido-Δ⁵-pregnen-20-one (VII).—1β,3β-Dihydroxy-Δ⁵,¹⁶-pregnadien-20-one (IV) (895 mg.) was dissolved in 68 ml. of methanol and cooled to 10°. At this temperature, 1.8 ml. of 4 *N* sodium hydroxide and 3.6 ml. of 30% hydrogen peroxide were added, and the resulting solution was allowed to stand at 5° overnight. It then was neutralized with acetic acid, 100 ml. of water was added, and the volume of the resulting suspension was reduced *in vacuo* to *ca.* 100 ml. Cooling and filtration gave 693 mg., m.p. 190–197°. Recrystallization from benzene gave the analytical sample, m.p. 200–202° (after drying for three hours at 100° *in vacuo*); $[\alpha]^{23}D$ −8.9°; λ^{Nujol} 2.88, 5.90 μ.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.80; H, 8.67.

16β-Bromo-1β,3β,17α-trihydroxy-Δ⁵-pregnen-20-one 1,3-Diacetate (VIII).—The foregoing epoxide (VII, 1.25 g.) was acetylated with pyridine–acetic anhydride and, upon the usual workup (recrystallization from isopropyl ether), gave 1.4 g. of a diacetate, m.p. 158–162. This was dissolved in 50 ml. of glacial acetic acid, 5 ml. of a solution of acetic acid saturated with hydrogen bromide was added, and the reaction was allowed to proceed for 1 hour at room temperature. The solution then was quenched in a large amount of water, the resulting solid was filtered off (1.53 g., dec. 190–195°) and used as such in the next step.

1β,3β,17α-Trihydroxy-Δ⁵-pregnen-20-one 1,3-Diacetate (IX).—Bromohydrin VIII (980 mg.) was dissolved in 25 ml. of tetrahydrofuran, 0.24 ml. of triethylamine was added, and the solution was hydrogenated over 400 mg. of 5% palladium-on-charcoal. After one mole of hydrogen had been absorbed, the catalyst was filtered off, amine hydrobromide was washed out in a separatory funnel, and the organic layer was dried and concentrated *in vacuo*. The residual oil was chromatographed over Florisil, and from the benzene–ether eluates 578 mg. of IX, m.p. 174–179°, was obtained. Recrystallization from isopropyl ether gave an analytical sample, m.p. 179–180°, $[\alpha]^{22}D$ −34.3; λ^{Nujol} at 2.90, 2.95, 5.77, 5.86, 8.10 μ.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.43; H, 8.28.

1β,3β,17α,21-Tetrahydroxy-Δ⁵-pregnen-20-one 1,3,21-Triacetate(X).—The foregoing diacetate IX (428 mg.) was dissolved in 7 ml. of chloroform, and 1.8 ml. of a solution of bromine in chloroform (3.68 g. in 40 ml.) was added. Upon the addition of a small amount of hydrogen bromide in chloroform, the reaction mixture decolorized. After standing for 25 minutes at room temperature, 2 g. of potassium acetate, 7.2 ml. of methanol and 850 mg. of sodium iodide were added, and the mixture stirred at 45° for 45 minutes. Ice-water (20 ml.) was added, and the color of the liberated iodine was discharged with a dilute solution of hydrazine. The aqueous phase was extracted with chloroform, the latter extract was washed with water, dried over potassium acetate, and concentrated to dryness *in vacuo*. Potassium acetate (2 g.), 2 ml. of water and 20 ml. of acetone were added, and the mixture was refluxed for 17 hours. It then was concentrated to a low volume, extracted with chloroform, the extract washed with water and dried over magnesium sulfate. Filtration and concentration *in vacuo* gave an oil which was chromatographed over Florisil (30 g.). Eluates with benzene–ether (1:1) gave 43.5 mg. of crystalline X, m.p. 169–177°, positive color reaction with red tetrazolium; λ^{Nujol} 2.86, 5.78 (broad) μ.

1β,17α,21-Trihydroxy-Δ⁴-pregnene-3,20-dione (XI).—The foregoing triacetate (X, 38 mg.) was subjected to the action of *Flavobacterium dehydrogenans*, as described for the preparation of V. The crude extract was chromatographed over silicic acid,[20] and with 1% methanol in chloroform, 19 mg. of the α,β-unsaturated ketone XI was eluted, m.p. 203–207° (soft. at 180). Its infrared spectrum was identical with XI obtained by a different route.[24]

BLOOMFIELD, N. J.

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

Steroids. CXXIV.[1] Studies in Cyano Steroids. Part I. The Synthesis of a Series of C-6-Cyano Steroid Hormones

BY A. BOWERS, E. DENOT, MARÍA BLANCA SÁNCHEZ, L. M. SÁNCHEZ-HIDALGO AND H. J. RINGOLD

RECEIVED APRIL 13, 1959

The fission of steroid 3β-acetoxy-5α,6α-epoxides and 3-cycloethylene-ketal-5α,6α-epoxides with potassium cyanide has been studied. Dependent upon the conditions the reaction was attended with or without concomitant elimination of the initially formed 5α-hydroxyl group to afford either the 5α-hydroxy-6-cyanide or the Δ⁵-6-cyanide. Under more vigorous conditions a double elimination at C-3 and C-5 occurred to form Δ³,⁵-6-cyanides. Manipulation of appropriate intermediates gave the 6-cyano-Δ⁴-3-ketones, which exist mainly in the enol form. Application of this general method led to the synthesis of the 6α-cyano derivatives of progesterone, 17α-acetoxyprogesterone, testosterone and cortisone.

In 1953, Fried and Sabo made a significant contribution to steroid hormone studies by disproving the then widely held view that structural modification of the adrenal hormones cortisone and hydrocortisone always led to a decrease in biological activity. They demonstrated that introduction of a chlorine[2] or a fluorine[3] atom at C-9(α) significantly enhanced the anti-inflammatory activity of the parent hormone. This finding stimulated considerable interest in modified steroid hormones and prodigious efforts have been made to introduce atoms or groups or further unsaturation at key positions throughout the steroid nucleus.

For both chemical and empirical reasons the position that has attracted the most attention has been C-6 and the earliest modification was the preparation of a series of 6-hydroxy (or acetoxy) and 6-keto steroid hormones. Amongst the more important may be mentioned the 6β-hydroxy analogs of testosterone,[4,5] progesterone,[4,6,7] desoxycorticosterone[4,5,8,9] Reichstein's Compound S[7,10,11] and cortisone.[11] The corresponding C-6 ketones of all the above compounds have also been pre-

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(2) J. Fried and E. F. Sabo, *ibid.*, **75**, 2273 (1953).

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(4) C. Amendolla, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.*, 1226 (1954).

(5) J. Romo, G. Rosenkranz, C. Djerassi and F. Sondheimer, *J. Org. Chem.*, **19**, 1509 (1954).

(6) M. Ehrenstein and T. O. Stevens, *ibid.*, **5**, 318 (1940).

(7) C. P. Balant and M. Ehrenstein, *ibid.*, **17**, 1587 (1952).

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(10) D. H. Peterson, S. H. Eppstein, P. D. Meister, B. J. Magerlein, H. C. Murray, H. M. Leigh, A. Weintraub and L. M. Reineke, *ibid.*, **75**, 412 (1953).

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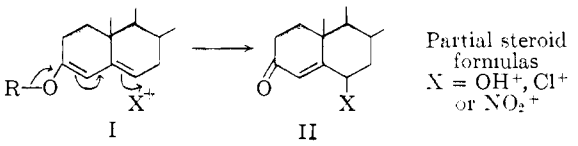
pared[4,11-14] and the 6α-hydroxy analogs of progesterone,[6] desoxycorticosterone[7,8] cortisone[15] and prednisone[15] are known.

However in every case the introduction of an oxygen function at C-6 led to a decrease in biological activity. Improved biological activity was first realized in a C-6 modified steroid hormone with the introduction of the C-6-methyl group[16-27] and very high biological activities have been reported for many 6α-fluoro[28-34] and 6α-chloro[35] steroid hormones.

Among the C-6-nitro steroid hormones reported recently[36,37] the high oral progestational activity of 6α-nitro-17α-acetoxyprogesterone[37] is worthy of note.

As a continuation of our studies relating to the synthesis of steroid hormones with electronegative substituents at C-6,[28,29,31-37] we now report the synthesis of a series of C-6 cyano steroid hormones.

Previous publications from these laboratories have demonstrated that 6β-hydroxy,[5] 6β-nitro[37] and 6β-chloro[35]-Δ^4-3-ketones are synthesized readily by electrophilic attack at C-6 of a $\Delta^{3,5}$-dienyl acetate or enol ether system (I→II).



Electrophilic cyanide (CN^+) is not readily available, but such compounds as cyanogen and the cyanogen halides can be considered as pseudo-electrophiles. Attempts were made to introduce a cyano group into C-6 by treatment of either $\Delta^{3,5}$-androstadien-3,17β-diol diacetate[38] or the 3-ethyl enol ether[39] of Reichstein's compound "S," both with cyanogen and cyanogen iodide under many varied conditions. However, under no circumstances could a 6-cyano compound be isolated. Either starting material was recovered or the corresponding Δ^4-3-ketone obtained. This approach was abandoned in favor of a route *via* a 5α,6α-epoxide.

The fission of unsymmetrical epoxides is complicated by many factors,[40] but it has been observed without exception that steroid 5α,6α-epoxides undergo nucleophilic attack at C-6 (β) to afford the diaxial 6β-substituted 5α-alcohol; examples include fission of such an epoxide with hydrochloric acid,[41] hydrofluoric acid,[30] boron trifluoride,[28, 29,31-34,42] nitric acid,[37] methylmagnesium halide,[16-27,43] lithium aluminum hydride[44] and acetic acid.[45] To the authors' knowledge the fission of epoxides with nucleophilic cyanide ion has not been recorded, but it appeared, nevertheless, to represent a plausible approach to 6-cyano steroids.

A suitable starting material for preliminary studies was pregnenolone acetate-α-epoxide[28] (IIIa), but prolonged heating of this epoxide in ethanol or 1-propanol solution with an excess of potassium cyanide led only to the hydrolysis of the acetate group to afford pregnenolone-α-epoxide (IIIb).[46,47] However, when the reaction was carried out in a sealed tube at 150° for 16 hours a product was obtained in 24% yield, λ_{max}^{EtOH} 260 mμ, ε 20,890, the infrared curve of which had strong absorption bands at 2190 (>C=C(CN)—)[48] and 1695 cm.$^{-1}$ (20-

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(45) Z. Hattori *J. Pharm. Soc. Japan*, **59**, 411 (1939), *C. A.*, **33**, 8622 (1939).
(46) This compound has not been adequately described in the literature, but its structure was proved readily when it smoothly afforded 5α,6α-oxidopregnan-3β-ol-20-one-3-acetate[28] upon acetylation.
(47) The use of potassium cyanide for the hydrolysis of steroid esters has been reported previously; *cf.* Q. R. Peterson, THIS JOURNAL, **77**, 1743 (1955).
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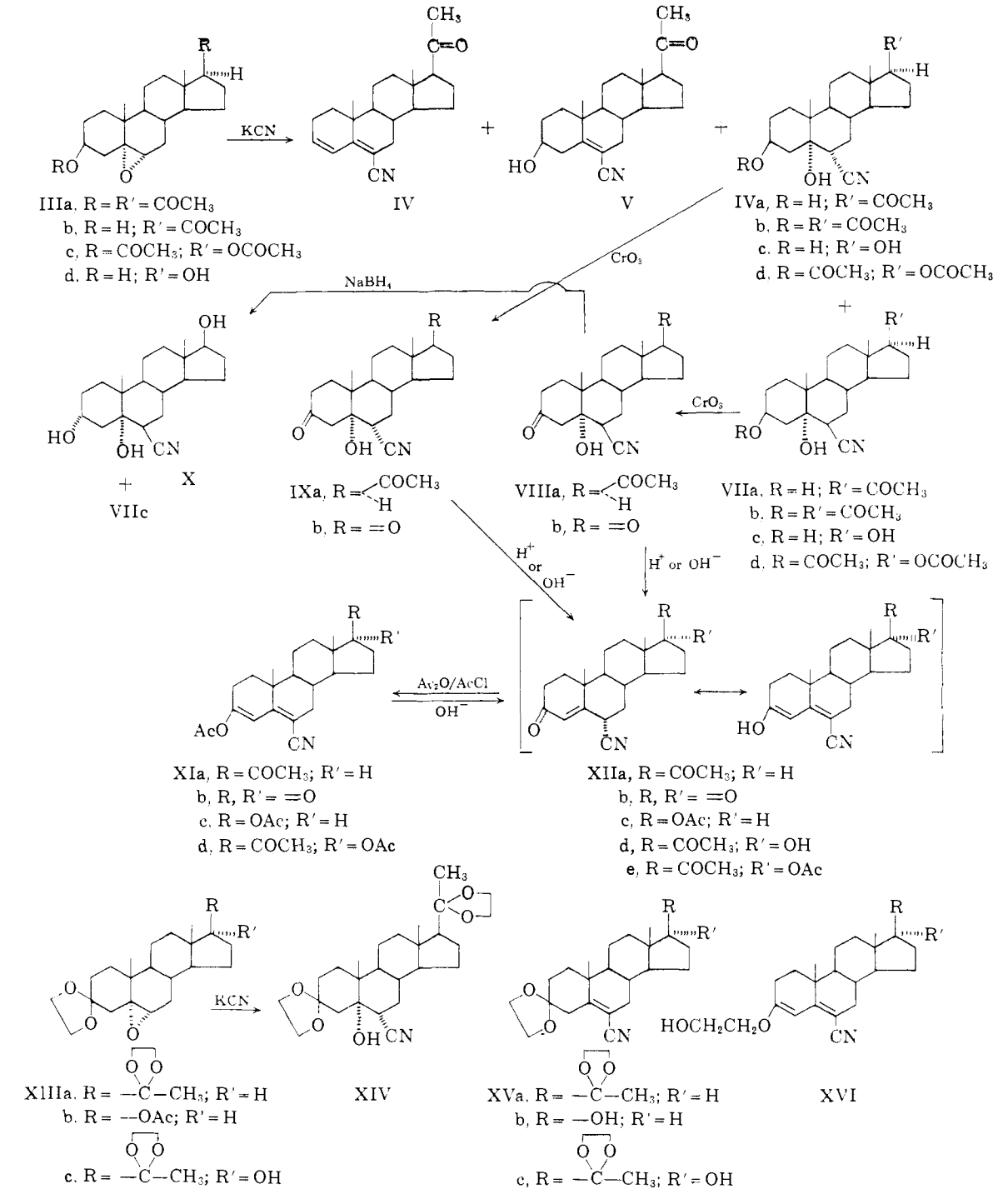


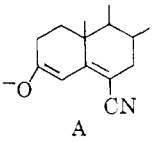
Fig. 1.

ketone) and showed no evidence of hydroxyl group bands. These spectral data taken in conjunction with the analytical results led to the formulation of this product as 6-cyano-$\Delta^{3,5}$-pregnadien-20-one (IV). After the rapid hydrolysis of the acetate group the initial reaction presumably was fission of the epoxide by cyanide ion to afford the 6β-cyano-3β,5α-diol VIIa which then underwent dehydration (β-hydroxyl elimination) to afford the 3β-hydroxy-vinyl cyanide V. The latter vinylogous β-hydroxynitrile, not unexpectedly, under the rather drastic reaction conditions underwent further dehydration to the 6-cyano-$\Delta^{3,5}$-diene IV. If this rationale was correct then it should be possible to isolate the intermediate mono- and dihydroxy nitriles by an appropriate choice of experimental conditions. Indeed, this was the case. The general inconvenience of sealed tube experiments prompted us to utilize ethylene glycol as a solvent and when pregnenolone acetate-α-epoxide (IIIa) was heated under reflux for 1 hour in this solvent with twice its weight of potassium cyanide the

major product (48% yield) was the 6-cyano-$\Delta^{3,5}$-diene IV identical in every respect with the product isolated from the sealed tube experiment. When the reaction temperature was reduced to 140° two new products were isolated and separated by chromatography over alumina. The less polar compound, isolated in low yield, exhibited maximum absorption in the ultraviolet at 220–222 mμ, ϵ 10,000, and bands in the infrared at 3550 (>C(OH)–), 2200 (>C(CN)–C=C–)[48] and 1695 cm.$^{-1}$ (20-ketone) On the basis of these spectral data and the elemental analytical results it was formulated as 6-cyano-Δ^5 pregnen-3β-ol-20-one (V).[49] The second product contained one more additional oxygen atom (elemental analysis) and did not exhibit selective absorption in the ultraviolet but had a band at 2220 cm.$^{-1}$ (>C(CN)–)[48] in the infrared. It formed a monoacetate after treatment with acetic anhydride and pyridine which still showed strong hydroxyl band absorption in the infrared. These data were clearly consistent with this product being either 6α- or 6β-cyanopregnan-3β,5α-diol-20-one[50] (VIa) or (VIIa).

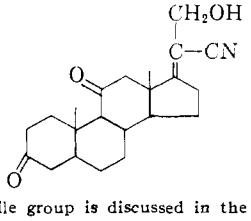
A further modification was to carry out the fission of the epoxide IIIa by heating in ethylene glycol with potassium cyanide for 3.5 hours at 90–95° when three products were obtained. The least polar toward alumina was 5α,6α-oxidopregnan-3β-ol-20-one (IIIb) and the second product was the same 6-cyano-3β,5α-diol (VIa) or (VIIa) which was isolated from the 140° experiment. The third product was a new compound which did not exhibit selective absorption in the ultraviolet, but showed a band in the infrared at 2225 cm.$^{-1}$ (–C≡N)[48] and formed a monoacetate under mild acetylation conditions which still displayed a strong hydroxyl band in the infrared. It was concluded therefore that these two compounds differed only in the stereochemistry of the nitrile group at C-6 and they were formulated as VIa and VIIa, respectively. Chemical evidence supporting this conclusion was forthcoming. Oxidation of both VIa and VIIa with 8 *N* chromic acid in acetone solution[51] led to the corresponding 6α- and 6β-cyano-5α-hydroxy-3,20-diones IXa and VIIIa. It is well known that C6-substituted 5α-hydroxy-3-ketones smoothly dehydrate under very mild alkaline[23–27] or acid conditions[25–34] to afford the corresponding 6α-substituted-Δ^4-3-ketones. However treatment of both VIIIa and IXa with 0.2% methanolic potassium hydroxide for 18 hours at room temperature led in each case to non-crystalline products both of which had maximal light absorption in the ultraviolet at 228–230 and 288–290 mμ, ϵ 4300, 11,300 and 5,050, 10,300, respectively. The infrared spectra of these two products were essentially identical and displayed bands at 3500, 2220, 1700, 1670. 1640 and 1580 cm.$^{-1}$.

Chromatography failed to resolve this product into pure compounds and it was concluded that the product was a mixture of 6α-cyanoprogesterone and its enol form XIIa, the latter compound predominating. In the presence of a drop of 5% potassium hydroxide solution there was a shift of maximum absorption to 338–340 mμ, ϵ 18,700, consistent



A

with the enolate ion A.[52] Similarly treatment of VIIIa and IXa with anhydrous hydrogen chloride in acetic acid followed by precipitation with water afforded the same ketoenol mixture XIIa which was obtained by the alkaline dehydration; λ_{max} 230 and 288–290 mμ, ϵ 5130 and 10,250, respectively, changed by a trace of alkali to 338–340 mμ, ϵ 18,200. A satisfactory elemental analysis could not be obtained for this product and attempts to obtain a crystalline solid were abortive, but acetylation of both of the keto–enol mixtures derived from the ketones VIIIa and IXa with acetic anhydride and acetyl chloride led in each case to the same enol-acetate XIa, λ_{max} 264 mμ, ϵ 18,200. Mild alkaline hydrolysis of this enol-acetate XIa afforded the solid, non-crystalline keto–enol mixture of 6-cyanoprogesterone (XII) identical to that obtained previously, as evidenced by ultraviolet and infrared spectroscopy. Thus, the two isomeric ketones VIIIa and IXa clearly differed only in the stereochemistry of the nitrile group at C-6. The initial product from the diaxial epoxide cleavage would be the *trans*-5α-hydroxy-6β-nitrile VIIa which under the basic conditions of the reaction partly epimerized at C-6 to afford some of the 6α (equatorial) nitrile VIa. It was possible to deduce the stereochemistry at C-6 of the two products from a consideration of their molecular rotations. It is well known that 6α-substituted Δ^4-3-ketones are more dextrorotatory than their 6β-epimers[53] and it can be seen that this effect at C-6 is of a general nature and is not restricted only to C-6 substituted Δ^4-3-ketones since cholestan-3β,5α,6α-triol[54] (*MD* +88°) is more dextrorotatory than cholestan-3β,-5α,6β-triol[55] (*MD* +13°).

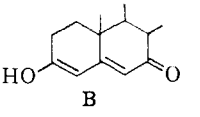


(49) R. E. Jones and F. W. Kocker, THIS JOURNAL, **76**, 3682 (1954), report λ_{max} 223 mμ, ϵ 13,680, for the vinyl nitrile.

(50) The stereochemistry of the nitrile group is discussed in the sequel and shown to be 6α.

(51) *Cf.* (a) K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); (b) A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *ibid.*, 2548 (1953).

(52) *Cf.* R. H. Lenhard and S. Bernstein, THIS JOURNAL, **78**, 989 (1956), report λ_{max} 320-321 and 391–392 mμ, ϵ 23,600 and 3,800, respectively, for the system B which changes to λ_{max} 390–391 mμ, ϵ 74,400, in ethanol containing 1% of potassium hydroxide.



B

(53) For a summary of the molecular rotation data from seven different pairs of epimeric C-6 substituted Δ^4-3-ketones *cf.* ref. 33.

(54) V. Prelog and E. Tagmann, *Helv. Chim. Acta*, **27**, 1867 (1944), report the preparation of this compound but its rotation has not been recorded. Consequently it was prepared by the osmium tetroxide oxidation of cholesterol and its constants are reported in the Experimental section.

(55) L. Ruzicka and V. Prelog, *ibid.*, **26**, 975 (1943).

The two epimeric 6-cyanopregnan-3β,5α-diol-20-ones VIa and VIIa had molecular rotations of +258 and +108. Accordingly the more dextrorotatory compound was assigned the 6α-cyano configuration (VIa) and its epimer VIIa the 6β-cyano structure.

Convincing chemical proof that these stereochemical assignments were correct was forthcoming when treatment of 6β-cyanopregnan-3β,5α-diol-20-one (VIIa) (axial cyano group) with potassium cyanide in ethylene glycol at 95° for 3 hours led to the formation of 6α-cyanopregnan-3β,5α-diol-20-one (VIa) (equatorial cyano group) in 25% yield. Also, in one instance the oxidation of VIIa led not to 6β - cyanopregnan - 5α - ol - 3,20 - dione (VIIIa) but to its 6α-epimer IXa.

An alternate approach to 6-cyano-Δ^4-3-ketones then was developed from 3-cycloethylene-ketal-5α,6α-epoxides. Progesterone-3,20-biscycloethylene-ketal-5α,6α-epoxide[56] (XIIIa), for example, was found to be superior to pregnenolone acetate-α-epoxide (IIIa) as a substrate for conversion into 6-cyanoprogesterone (XIIa) since even when a double elimination occurred at C-3 and C-5 the product was 6-cyano-3-(2'-hydroxyethyl)-$\Delta^{3,5}$-pregnadien-20-cycloethylene-ketal (XVIa), clearly a suitable compound for conversion into 6-cyanoprogesterone (XIIa). In a manner similar to the potassium cyanide fission of IIIa, the products obtained from XIIIa varied with the length of the reaction time. When XIIIa was heated under reflux with potassium cyanide in ethylene glycol for 35 minutes the product was 6α-cyanopregnan-5α-ol-3,20-biscycloethylene-ketal (XIV). It did not exhibit selective absorption in the ultraviolet and displayed bands at 3450 (—OH) and 2230 cm.$^{-1}$ (—C≡N).[48] The stereochemistry of the nitrile group was not proved but the 6α-(equatorial)-configuration was assigned on the basis of molecular rotation data.[57] When the reaction time was extended to 3.5 hours two different products were obtained. The less polar of the two toward alumina exhibited spectral data appropriate for a vinyl nitrile,[48,49] namely, maximum absorption in the ultraviolet at 222 mμ, ϵ 10,000, and a strong band in the infrared at 2200 cm.$^{-1}$. Analytical data substantiated the assigned structure as being 6-cyano-Δ^5-pregnen-3,20-biscycloethylene-ketal (XVa). The second product was isomeric with XVa and had maximum absorption in the ultraviolet at 282 mμ, ϵ 20,000. In the infrared it had bands at 3350 (—OH), 2200 (nitrile group attached to an unsaturated carbon atom),[48] 1620 and 1590 cm.$^{-1}$ ($\Delta^{3,5}$-diene-enol ether system).[58] These data could only be accommodated by structure XVIa. A double elimination took place at C-3 and C-5 analogous to the formation of IV from IIIa.[59] Perchloric acid in tetrahydrofuran hydrolysis of either XVa or XVIa led to the same non-crystalline mixture of 6α-cyanoprogesterone in equilibrium with its enol form XIIa as was obtained from VIIIa and IXa as described above.

Thus, two different approaches to 6-cyano-Δ^4-3-ketones had been established and application of these methods led to the synthesis of the 6-cyano analogs of Δ^4-androstene-3,17-dione, testosterone, 17α-acetoxyprogesterone and cortisone.

Potassium cyanide cleavage of 5α,6α-oxidoandrostan-3β,17β-diol diacetate[60] (IIIc) for 3.5 hours in ethylene glycol at 90–95° led to the isolation of three products which were separated by crystallization and chromatography over alumina. They were 5α,6α-oxidoandrostan-3β,17β-diol (IIId), 6α-cyano-androstan-3β,5α,17β-triol (VIc) and its 6β-epimer VIIc. By analogy with the structures assigned to the corresponding pregnane derivatives VIa and VIIa the most dextrorotatory of the two compounds ($M_D \pm 0$ compared to $M_D - 99$) was assigned the 6α-configuration. Attempts to chemically interrelate these two epimeric nitriles by acid treatment were unsuccessful. For example, treatment of both VIc and VIIc with anhydrous hydrogen chloride in acetic acid led smoothly to the corresponding diacetates VId and VIId. No inversion of the nitrile group in VIId could be detected.

Upon oxidation with 8 *N* chromic acid in acetone solution, VIc and VIIc[51] afforded the corresponding 3,17-diketones IXb and VIIIb, respectively. Sodium borohydride reduction of VIIIb led to a mixture of VIIc (52%) and the 3α-epimer X (28%). The unusually high yield of a 3α-alcohol from the borohydride reduction of a C-3-ketone was attributed to the increase in steric hindrance caused by the 5α-hydroxyl group to the approach of the borohydride ion from the α-face with a consequent decrease in the amount of the 3β-alcohol formed.

Both of the ketones VIIIb and IXb afforded a non-crystalline mixture of 6-cyano-Δ^4-androstene-3,17-dione and its enol form XIIb on acid treatment.

An extension to the androstane series of the method used to synthesize 6α-cyanoprogesterone from progesterone-bisketal-α-epoxide (XIIIa) led to the synthesis of 6α-cyanotestosterone (XIIc). Testosterone acetate 3-cycloethylene-ketal-5α,6α-epoxide (IIIb) after treatment with potassium cyanide in ethylene glycol under reflux for 4 hours afforded a mixture of 6-cyano-Δ^5-androsten-17β-ol-3-one-3-cycloethylene-ketal (XVb), λ_{max} 224 mμ, ϵ 13,000, and the 6-cyano-enol ether (XVIb), λ_{max} 284 mμ, ϵ 18,750. Acid hydrolysis of XVIb with hydrochloric acid in acetic acid led to a non-crystalline mixture of 6α-cyanotestosterone acetate and its enol form XIIc, acetylation of which with acetic anhydride and acetyl chloride afforded a homogeneous enol acetate (XIc).

In a like manner 6α-cyano-17α-acetoxyprogesterone (XIIe) was prepared. Treatment of 17α-hydroxyprogesterone-3,20-biscycloethylene-ketal-5α,6α-epoxide (XIIIc) with potassium cyanide in the usual way led to a mixture of 6-cyano-Δ^5-pregnen-17α-ol-3,20-biscycloethylene-ketal (XVc) and the $\Delta^{3,5}$-3-hydroxyethyl enol ether XVIc. Acid hydrolysis of either XVc or XVIc followed by

(56) G. Cooley, B. E. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 4112 (1957).

(57) M_D 5α,6α-epoxide IIIb − M_D 5α-ol-6β-nitrile VIIa = −78; M_D 5α,6α-epoxide IIIb − M_D 5α-ol-6α-nitrile VIa = −228; M_D XIII − M_D XIV = −209; more compatible with a 6α-configuration of the nitrile group than 6β for compound XIV.

(58) Strong doublets in this region have been observed in these laboratories for many $\Delta^{3,5}$-diene-3-ethyl-enol ethers.

(59) The fission of a Δ^4-3-cycloethylene ketal to afford a 3-(2',-hydroxy-ethyl)-$\Delta^{3,5}$-dienyl ether has been reported previously; *cf.* ref. 52.

(60) L. Ruzicka and A. C. Muhr, *Helv. Chim. Acta*, **27**, 503 (1944).

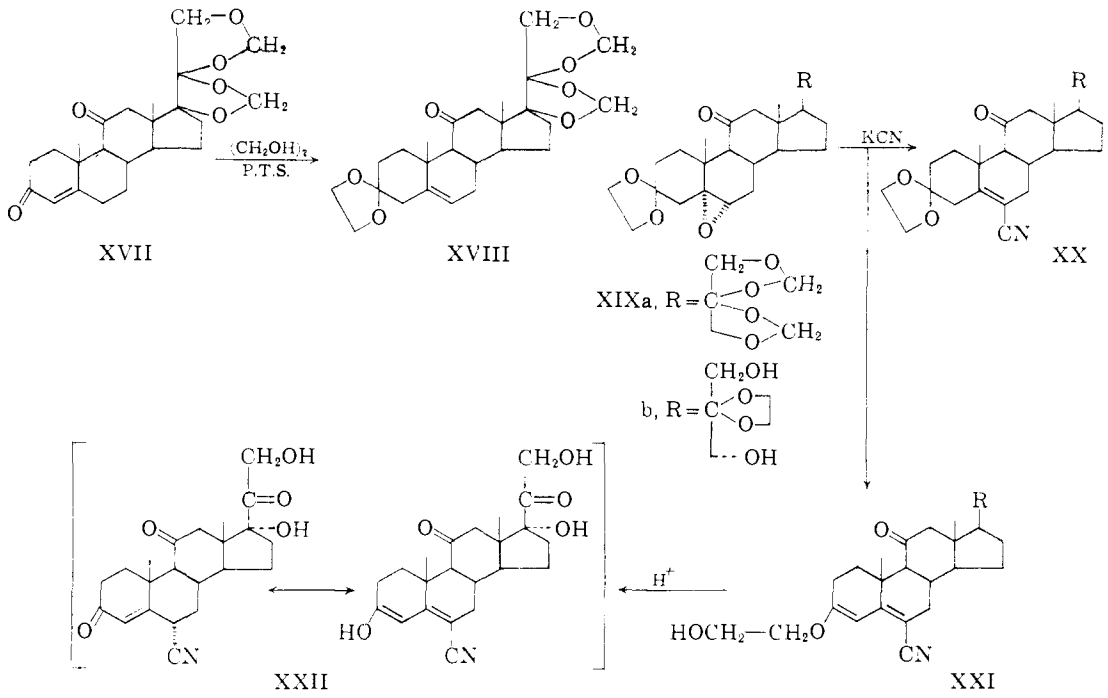


Fig. 2.

acetylation with acetic anhydride and acetyl chloride afforded 6-cyano-$\Delta^{3,5}$-pregnadien-3,17α-diol-20-one diacetate (XId), whence mild alkaline hydrolysis afforded a mixture of 6α-cyano-17α-acetoxyprogesterone and its enol form XIIe.

Thus the synthesis of a 6-cyano analog of an androgenic, a progestational and an oral progestational hormone had been accomplished. However, to complete our preliminary studies of the biological effect of a C-6 cyano group it was deemed necessary to synthesize a 6-cyano cortical hormone.

In view of the instability of the cortical side chain to potassium cyanide[61] it was necessary to suitably protect this grouping and a convenient starting material appeared to be the bismethylene dioxy derivative[62] of cortisone (XVII; Fig. 2). This compound readily formed the corresponding Δ^5-3-cycloethylene-ketal XVIII, whence epoxidation with permonophthalic acid afforded the corresponding 5α,6α-epoxide XIX. Following the usual procedure, cleavage of XIX with potassium cyanide in ethylene glycol led to a mixture of the vinyl nitrile XXa and the 6-cyano-$\Delta^{3,5}$-enol ether XXIa. However, all attempts to hydrolyze either XX or XXI with aqueous formic acid, acetic acid, hydrogen chloride in acetic acid (with or without water being present) failed to afford 6-cyanocortisone (XXII). It appeared that the 6-cyano-Δ^4-3-ketone system was destroyed by the rather vigorous acid conditions required to regenerate the cortical sidechain from the bismethylene dioxy protective grouping. An alternate, successful synthesis of 6-cyanocortisone then was carried out from cortisone-bisketal-5α,6α-epoxide[63] (XIXb). Cleavage of the latter epoxide with potassium cyanide led to both the vinyl cyanide XXb and the 6-cyano-enol ether XXIb. Hydrolysis of XXIb with perchloric acid in tetrahydrofuran gave a mixture of 6α-cyanocortisone and its enol from XXII characterized by the double maximum in the ultraviolet, λ_{max} 220–222 and 286–288 mμ, ϵ 4,270 and 10,750.

(61) Δ^5-Pregnen-17α,21-diol-20-one-3-cycloethylene-ketal (Compound "S" monoketal) could not be recovered after treatment with potassium cyanide in ethylene glycol under reflux for 1 hour.

(62) R. E. Beyler, R. M. Moriarty, F. Hoffman and L. H. Sarett, THIS JOURNAL, **80**, 1517 (1958).

Experimental[64]

Treatment of $\Delta^{3,5}$-Androstadiene-3,17β-diol Diacetate with Cyanogen and Cyanogen Iodide.—A solution of $\Delta^{3,5}$-androstadiene-3,17β-diol diacetate[38] (500 mg.) in dry ether at 0° was saturated with cyanogen and then kept at 0° for 24 hours. Addition of water and isolation with ether afforded unchanged enol acetate. This experiment was repeated using the following solvents instead of ether: dimethylformamide, nitromethane and chloroform containing 2% pyridine; in every case only starting material could be recovered. Similarly, abortive results were obtained when cyanogen iodide was substituted for cyanogen.

Treatment of the 3-Ethyl Enol Ether of Reichstein's Compound "S" Acetate with Cyanogen or Cyanogen Iodide.—The experiments described above with cyanogen and cyanogen iodide were repeated using the 3-ethyl enol ether of Reichstein's compound "S" acetate.[39] In every case only starting material or Reichstein's compound "S" acetate could be isolated.

Treatment of 5α,6α-Oxidopregnane-3β-ol-20-one Acetate (IIIa) with Potassium Cyanide.—(a) Potassium cyanide (2.0 g.) was added to a solution of the epoxide IIIa[28] (1.0 g.) in ethanol (50 cc.) and heated under reflux for 24 hours.

(63) J. A. Edwards and H. J. Ringold, forthcoming publication from these laboratories.

(64) Melting points are uncorrected. Rotations were measured in chloroform solution unless stated otherwise and the ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Dr. L. J. Throop and his staff for these measurements and for the infrared spectra which were obtained with a Perkin–Elmer model-21 spectrophotometer with a sodium chloride prism. The alumina used in this work had previously been suspended in boiling ethyl acetate for 6 hours, filtered and dried at 100°. The elemental analysis were carried out by Dr. A. Bernhardt, Mulheim, Ruhr, Germany.

Addition of water and extraction with ethyl acetate afforded 5α,6α-oxidopregnane-3β-ol-20-one (IIIb) (910 mg.), m.p. 177–184°, raised by one crystallization from acetone–hexane to 188–190°, $[\alpha]D$ +17°, raised by one crystallization from acetone–hexane to 188–290°, $[\alpha]$ +17°, lit.[65] reports m.p. 185–187°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.79; H, 9.82.

Acetylation of IIIb (acetic anhydride–pyridine) readily afforded IIIa identical with an authentic sample.[28]

Similar treatment of IIIa with potassium cyanide in 1-propanol led only to IIIb.

(b) Potassium cyanide (2.0 g.) was added to a solution of the epoxide IIIa (1.0 g.) in ethanol (50 cc.) and heated in a sealed tube at 150 ± 10° for 16 hours. Addition of water and extraction with ethyl acetate afforded a product which was adsorbed from benzene–hexane (80:20, 100 cc.) onto alumina (40 g.). Elution with benzene–hexane (80:20, 250 cc.) afforded 6-cyano-$\Delta^{3,5}$pregnadiene-20-one (IV) (240 mg.), m.p. 119–125°, raised by several crystallizations from acetone–hexane to 138–142°, $[\alpha]D$ −101°, λ_{max}^{EtOH} 260 mμ, ε 20,890; λ_{max}^{KBr} 2190, 1695, 1620 and 1585 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{29}ON$: C, 81.69; H, 9.04; O, 4.93; N, 4.33. Found: C, 81.33; H, 9.16; O, 5.42; N, 4.38.

(c) Potassium cyanide (4.0 g.) was added to a solution of the epoxide IIIa (2.0 g.) in ethylene glycol (120 cc.) and heated under reflux for 1 hour. Addition of water and isolation with ethyl acetate gave a product which was adsorbed from benzene (50 cc.) onto alumina (80 g.). Elution with benzene (900 cc.) and one crystallization of the product from acetone–hexane afforded 6-cyano-$\Delta^{3,5}$-pregnadiene-20-one (IV) (970 mg.), m.p. 133–136°, λ_{max}^{EtOH} 260–262 mμ, ε 19,050, undepressed on admixture with the product isolated in the preceding experiment (b).

(d) Potassium cyanide (2 g.) was added to a solution of the epoxide (1.0 g.) in ethylene glycol (60 cc.) and heated at 140° for 1 hour. After cooling, addition of water and isolation with ethyl acetate gave a product which was adsorbed from benzene (100 cc.) onto alumina (40 g.). Elution with benzene–ether (90:10, 400 cc.) afforded a semi-crystalline fraction (220 mg.), λ_{max}^{EtOH} 222 mμ, ε 10,230, which after further chromatography over alumina afforded 6-cyano-Δ^5-pregnene-3β-ol-20-one (V) (85 mg.), m.p. 132–137°, raised by several crystallizations from aqueous methanol to 149–152°, $[\alpha]D$ −23°, λ_{max}^{EtOH} 220–222 mμ, ε 10,000; λ_{max}^{KBr} 2200, 1695 and 1625 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{31}O_2N$: C, 77.37; H, 9.15; N, 4.10. Found: C, 77.62; H, 9.23; N, 3.98.

Further elution with ether (500 cc.) gave 6α-cyanopregnane-3β,5α-diol-20-one (VIa) (160 mg.), m.p. 220–230°, raised by crystallizations from ethyl acetate to 258–259°, $[\alpha]D$ +72°; λ_{max}^{EtOH} 240–246 and 280–288 mμ, ε 21 and 34, respectively; λ_{max}^{KBr} 3400, 2220 and 1690 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{33}O_3N$: C, 73.50; H, 9.25; O, 13.35; N, 3.90. Found: C, 73.46; H, 9.01; O, 13.51; N, 4.12.

Acetylation of VIa with an excess of acetic anhydride in pyridine solution at room temperature for 18 hours smoothly afforded 6α-cyanopregnane-3β,5α-diol-20-one 3-acetate (VIb), m.p. 245–247°, $[\alpha]D$ +47°; λ_{max}^{KBr} 3300, 2205, 1720(sh), 1700 and 1260 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{35}O_4N$: C, 71.79; H, 8.79; N, 3.49; O, 15.93. Found: C, 71.67; H, 8.65; N, 3.19; O, 16.43.

(e) Potassium cyanide (20 g.) was added to a solution of pregnenolone acetate epoxide (IIIa) in ethylene glycol (600 cc.) and heated at 90° (steam-bath) for 3.5 hours. Addition of water and extraction with ethyl acetate afforded a product which was adsorbed from benzene (300 cc.) onto alumina (500 g.). Elution with benzene–ether (50:50, 1,500 cc.) gave a fraction which after one crystallization from acetone–hexane afforded pregnenolone-5α,6α-epoxide (IIIb), 1.3 g., m.p. 186–188° undepressed on admixture with the product obtained in experiment (a) above. Further elution with ether (1,300 cc.) gave 6α-cyanopregnane-3β,5α-diol-20-one (VIa) (1.95 g.), m.p. 252–255° raised by one crystallization from ethyl acetate to 257–259° undepressed on admixture with the same product obtained from the previous experiments, $[\alpha]D$ +74°.

Further elution with ether–acetone (90:10, 1,500 cc.) afforded 6β-cyanopregnane-3β,5α-diol-20-one (VIIa)[66] (1.19 g.), m.p. 206–212° raised by crystallizations from ethyl acetate to 223–225°, $[\alpha]D$ +30°. The m.p. was strongly depressed on admixture with VIa, λ_{max}^{EtOH} 284–286 mμ, ε λ_{max}^{KBr} 3500, 2240 and 1690 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{33}O_3N$: C, 73.50; H, 9.25; O, 13.35; N, 3.90. Found: C, 73.38; H, 9.09; O, 13.44; N, 4.02.

Acetylation of VIIa with an excess of acetic anhydride in pyridine solution at room temperature for 16 hours afforded 6β-cyanopregnane-3β,5α-diol-20-one 3-acetate (VIIb), m.p. 225–227°, $[\alpha]D$ +7°; λ_{max}^{KBr} 3400, 2200, 1720, 1685 and 1245 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{35}O_4N$: C, 71.79; H, 8.79; O, 15.94. Found: C, 71.69; H, 8.73; O, 16.26.

Cholestane-3β,5α,6α-triol.—Osmium tetroxide (280 mg.) was added to a solution of cholesterol (350 mg.) in pyridine–chloroform (1:1, 20 cc.). After 5 days at room temperature the solvent was removed *in vacuo* and the residue was treated with a suspension of lithium aluminum hydride (1.0 g.) in tetrahydrofuran (50 cc.) under reflux for 18 hours. After decomposition of the excess of reagent with ethyl acetate, dilute hydrochloric acid was added. Isolation with ethyl acetate then afforded a product which was adsorbed from benzene onto alumina (20 g.). Elution with benzene–ether (70:30, 500 cc.) afforded cholestane-3β,5α,6α-triol (210 mg.), m.p. 227–232 raised by crystallizations from acetone to 232–234°, $[\alpha]D$ +21°; lit.[54] reports m.p. 236–238°.

Epimerization of 6β-Cyanopregnane-3β,5α-diol-20-one (VIIa).—Potassium cyanide (400 mg.) was added to a solution of 6β-cyanopregnane-3β,5α-diol-20-one (VIIa) in ethylene glycol (10 cc.) and heated at approximately 90° (steam-bath) for 4 hours. Addition of water and isolation with ethyl acetate afforded a product which was adsorbed from benzene onto alumina 20 g. Elution with benzene–ether (70:30, 250 cc.) afforded 6α-cyanopregnane-3β,5α-diol-20-one (VIa), 51 mg., m.p. 251–256°, raised by one crystallization to 256–258°, undepressed on admixture with an authentic sample; $[\alpha]D$ +73°.

Oxidation of 6α-Cyanopregnane-3β,5α-diol-20-one (VIa).—The diol VIa (500 mg.), m.p. 256–259°, in acetone (15 cc.) was treated at 0° with an excess of 8 *N* chromic acid in the usual way.[51] Addition of water and filtration afforded 6α-cyanopregnane-5α-ol-3,20-dione (IXa) (420 mg.), m.p. 238–245°, raised by crystallizations from acetone–hexane to 242–244°, $[\alpha]D$ +51°; λ_{max}^{EtOH} 278–288 mμ, ε 53; λ_{max}^{KBr} 3320, 2230, 1720 and 1685 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{31}O_3N$: C, 73.91; H, 8.74; O, 13.43; N, 3.92. Found: C, 73.84; H, 8.54; O, 13.58; N, 3.82.

Oxidation of 6β-Cyanopregnane-3β,5α-diol-20-one (VIIa).—The diol VIIa (200 mg.), m.p. 222–224°, in acetone (20 cc.) was treated at 0° with an excess of 8 *N* chromic acid in the usual way.[51] Addition of water and filtration afforded 6β-cyanopregnane-5α-ol-3,20-dione (VIIIa) (165 mg.), m.p. 243–246°, raised by one crystallization from acetone–hexane to 246–248°, depressed (220–242°) on admixture with IXa; $[\alpha]D$ +35°; λ_{max}^{KBr} 3500, 1730 and 1690 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{31}O_3N$: C, 73.91; H, 8.74; O, 13.43; N, 3.92. Found: C, 73.75; H, 8.71; N, 3.99.

In another experiment apparently identical to the one described above the product was 6α-cyanopregnane-5α-ol-3,20-dione (IXa) (86% yield), m.p. 239–243°, raised by one crystallization from methanol–chloroform to 243–245°, $[\alpha]D$ +49°, undepressed on admixture with authentic IXa. The infrared spectra of the two compounds were identical.

6-Cyanoprogesterone (XIIa).—(a) Potassium hydroxide (100 mg.) in methanol (10 cc.) was added to a solution of 6α-cyanopregnan-5α-ol-3,20-dione (IXa) (400 mg.) in methanol

(65) Y. Urushibara, M. Chuman and S. Wada, *Bull. Chem. Soc. Japan*, **24**, 83 (1951); *C. A.*, **47**, 5956[i] (1953).

(66) The 6β (axial) nitrile VIIa might reasonably have been expected to have been eluted before the 6α (equatorial) nitrile VIa. Possibly hydrogen bonding between the 6α-cyano group and the 5α-hydroxyl group in VIa reduces the polarity of this compound toward alumina. However two recent publications discuss examples at C-6 and C-7 where the axially substituted compounds are more polar than the equatorial isomers; *cf.* O. Wintersteiner and M. Moore, THIS JOURNAL, **81**, 422 (1958), and W. J. McAleer, M. A. Kozlowski, T. H. Stoudt and J. M. Chemerda, *J. Org. Chem.*, **23**, 958 (1958).

(40 cc.). After 18 hours at room temperature the solution was diluted with water, neutralized with acetic acid and then extracted with ethyl acetate. After washing with water, the dried solution (Na_2SO_4) was evaporated to afford a non-crystalline mixture of 6α-cyanoprogesterone and its enol form XIIa, m.p. 91–98°, $[\alpha]D$ −88°; λEtOH 228–230 and 288–290 mμ, ε 4,300 and 11,300, respectively; $\lambda_{max}^{EtOH(KOH)}$ 338–340 mμ, ε 18,700; λ_{max}^{KBr} 3500, 2220, 1700, 1670, 1640 and 1580 cm.$^{-1}$. Similar alkaline treatment of 6β-cyanopregnan-5α-ol-3,20-dione (VIIIa) led to the same product; λ_{max}^{EtOH} 228–230 and 288–290 mμ, ε 5,050 and 10,300. The infrared spectra were essentially identical.

(b) Dry hydrogen chloride was bubbled through a solution of 6α-cyanopregnan-5α-ol-3,20-dione (IXa) (50 mg.) in acetic acid (5.0 cc.) for 10 minutes at 15° and then the flask was tightly stoppered. After a further 2.5 hours at 15° addition of water and filtration afforded XIIa (41 mg.), m.p. 97–112°; λ_{max}^{EtOH} 230 and 288–290 mμ, ε 5130 and 10,250, respectively; $\lambda_{max}^{EtOH(KOH)}$ 338–340 mμ, ε 18,200. The infrared spectrum was essentially identical with the product obtained from the two previous experiments.

Hydrogen chloride in acetic acid treatment of VIII also led to XIIa, m.p. 103–120°, λ_{max}^{EtOH} 230 and 288–290 mμ, ε 4,850 and 9,970, respectively.

6-Cyano-$\Delta^{3,5}$-pregnadiene-3-ol-20-one Acetate (XIa).—A solution of 6-cyanoprogesterone (XIIa) (400 mg.) (prepared as in method a above) in acetic anhydride–acetyl chloride (1:1, 15 cc.) was heated under reflux for 2 hours in a nitrogen atmosphere. The solvent then was removed at 95° *in vacuo* and the residue crystallized from methanol to afford 6-cyano-$\Delta^{3,5}$-pregnadiene-3-ol-20-one acetate (XIa) (225 mg.), m.p. 147–160°, raised by crystallizations from methanol to 168–170°, $[\alpha]D$ −35°, λ_{max}^{EtOH} 264 mμ, ε 18,200; λ_{max}^{KBr} 2200, 1770, 1700 and 1670 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{31}O_3N$: C, 75.56; H, 8.19; O, 12.58. N, 3.67. Found: C, 75.27; H, 8.36; O, 12.54; N, 3.75.

Similarly enol acetylation of 6-cyanoprogesterone (XIIa) derived from experiments b, c and d above led to the same enol acetate XIa.

Potassium Cyanide Cleavage of 5α,6α-Oxidopregnane-3,20-bis-cycloethylene-ketal (XIIIa).—(a) Potassium cyanide (6.0 g.) was added to a solution of 5α,6α-oxidopregnane-3,20-biscycloethylene ketal[56] (XII) (3.0 g.) in ethylene glycol (100 cc.) and heated under reflux for 35 min. After immediate cooling, water was added and the product isolated with ethyl acetate and then adsorbed from benzene onto alumina (150 g.). Elution with benzene (3.5 l.) afforded 6-cyanopregnane-5α-ol-3,20-biscycloethylene-ketal (XIV) (2.17 g.), m.p. 218–221°, raised by several crystallizations from acetone–hexane to 227–228°, $[\alpha]D$ ±0°; λ_{max}^{EtOH} 222–228 mμ, ε, 99; λ_{max}^{KBr} 3450 and 2230 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{39}O_5N$: C, 70.08; H, 8.82; N, 3.14. Found: C, 70.15; H, 8.68; N, 3.27.

(b) Potassium cyanide (2.0 g.) was added to a solution of the bis-ketal epoxide XIIIa (1.0 g.) in ethylene glycol (40 cc.) and heated under reflux for 1.25 hours. Water was added to the cooled solution and the product isolated with ethyl acetate and then adsorbed from benzene–hexane (50:50, 100 cc.) onto alumina (40 g.). Elution with benzene–hexane (50:50, 300 cc.) and benzene (100 cc.) afforded 6-cyano-Δ^5-pregnene-3,20-biscycloethylene-ketal (XVa) (200 mg.), m.p. 175–181°, raised by several crystallizations from acetone–hexane to 182–184°, $[\alpha]D$ −74°, λ_{max}^{EtOH} 224 mμ, ε 9,590; λ_{max}^{KBr} 2,200 and 1,640 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{37}O_4N$: C, 73.02; H, 8.72; N, 3.28; O, 14.97. Found: C, 72.69; H, 8.87; N, 3.31; O, 15.05.

Further elution with benzene–ether (90:10, 600 cc.) afforded 3-(2'-hydroxyethyl)-6-cyano-$\Delta^{3,5}$-pregnadiene-20-cycloethylene-ketal (XVIa) (460 mg.), m.p. 167–170°, raised by crystallizations from acetone–hexane to 175–177°, $[\alpha]D$ −96°, λ_{max}^{EtOH} 282–284 mμ, ε 23,990; λ_{max}^{KBr} 3550, 2200, 1620 and 1590 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{37}O_4N$: C, 73.02; H, 8.72; O, 14.97. Found: C, 73.00; H, 8.63; O, 15.18.

Perchloric Acid Hydrolysis of 6-Cyano-Δ^5-pregnen-3,20-bis-cycloethylene-ketal (XVa).—Perchloric acid (8.4 cc., 70%) was added to a solution of 6-cyano-Δ^5-pregnene-3,20-biscycloethylene ketal (XVa) (500 mg.) in tetrahydrofuran (8.4 cc.). After 3 hours at room temperature water (100 cc.) was added and the product was extracted with ethyl acetate. The combined extracts were washed with sodium bicarbonate solution (5%), water and then dried over sodium sulfate. Removal of the solvent afforded 6-cyanoprogesterone (XIIa), λ_{max} 228–230 and 288–299 mμ, ε 4,250 and 10,075, respectively. This product was dissolved in acetic anhydride (10 cc.) and acetyl chloride (10 cc.) and heated under reflux in a nitrogen atmosphere for 2 hours. Removal of the solvent at 95° in *in vacuo* and crystallization of the residue from methanol afforded 6-cyano-$\Delta^{3,5}$-pregnadiene-3-ol-20-one acetate (XIa) (285 mg.), m.p. 144–151°, raised by crystallizations from methanol to 168–170°, undepressed on admixture with an authentic sample; λ_{max}^{EtOH} 264 mμ, ε, 18,500.

Potassium Cyanide Cleavage of 5α,6α-Oxidoandrostane-3β,17β-diol Diacetate (IIIc).—Potassium cyanide (14 g.) was added to a solution of 5α,6α-oxidoandrostane-3β,17β-diol diacetate (IIIc) (7.2 g.) in ethylene glycol (420 cc.) and heated on the steam-bath for 3.5 hours. Addition of water and isolation with ethyl acetate afforded a product which was heated under reflux for 10 minutes with benzene (400 cc.) (a portion did not dissolve). After cooling to room temperature filtration afforded 6β-cyanoandrostane-3β,5α,17β-triol (VIIc) (2.15 g.), m.p. 299–303°, raised by crystallizations from aqueous methanol to 309–311°, $[\alpha]D$ −31° (dioxane); λ_{max}^{KBr} 3350, 3450 and 2220 cm.$^{-1}$; VIIc did not exhibit selective absorption in the ultraviolet.

Anal. Calcd. for $C_{20}H_{31}O_3N$: C, 72.03; H, 9.37; N, 4.20. Found: C, 71.65; H, 9.22; N, 3.92.

The filtrate from the benzene treatment of the product then was adsorbed onto alumina (200 g.). Elution with benzene–ether (50:50, 2 l.) afforded 5α,6α-oxidoandrostane-3β,17β-diol (IIId) (1.31 g.), m.p. 190–195°, raised by crystallizations from ethyl acetate to 203–204°, $[\alpha]D$ −75°. This product was identical in every respect to the product obtained by an alkaline hydrolysis (3% KOH–MeOH, 45 min. reflux) of IIIc.

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87; C, 15.66. Found: C, 74.32; H, 9.96; O, 15.25.

Further elution with ether–acetone (90:10, 1 l.) afforded 6α-cyanoandrostane-3β,5α,17β-triol (VIc) (760 mg.), m.p. 228–250°, raised by one crystallization from methanol to 246–250°. The analytical sample from methanol had m.p. 254–256°, $[\alpha]D$ +8°; λ_{max}^{KBr} 3350 and 2220 cm.$^{-1}$; VIc did not exhibit selective absorption in the ultraviolet.

Anal. Calcd. for $C_{20}H_{31}O_3N$: C, 72.03; H, 9.37; N, 4.20. Found: C, 71.68; H, 9.40; N, 3.90.

6β-Cyanoandrostane-3β,5α,17β-triol 3,17-Diacetate (VIId).—Acetic anhydride (1 cc.) was added to a solution of 6β-cyanoandrostane-3β,5α,17β-triol (VIIc) (200 mg.) in pyridine (10 cc.) and heated at 95° for 90 min. Addition of ice-water and isolation with ethyl acetate afforded the diacetate VIId, m.p. 195–197° raised by crystallizations from acetone–hexane to 202–204°, $[\alpha]D$ −68°; λ_{max}^{KBr} 3500, 2250, 1740 and 1715 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}O_5N$: C, 69.03; H, 8.45; O, 19.16. Found: C, 69.13; H, 8.31; O, 19.64.

Treatment of 6β-Cyanoandrostane-3β,5α,17β-triol (VIIc) with Hydrogen Chloride in Acetic Acid.—A solution of 6β-cyanoandrostane-3β,5α,17β-triol (VIIc) (200 mg.) in acetic acid (15 cc.) at room temperature was saturated with dry hydrogen chloride and then kept at room temperature for 3 hours. Addition of water and filtration afforded 6β-cyanoandrostane-3β,5α,17β-triol 3,17-diacetate (VIId), m.p. 189–194°, raised by one crystallization from acetone–hexane to 200–202°, undepressed on admixture with a sample prepared as in the preceding experiment; $[\alpha]D$ −68°. The infrared spectra of the two products were identical.

Treatment of 6α-Cyanoandrostane-3β,5α,17β-triol (VIc) with Hydrogen Chloride in Acetic Acid.—Repetition of the previous experiment with VIc led smoothly to 6α-cyanoandrostane-3β,5α,17β-triol 3,17-diacetate (VId), m.p. 230–232° (from acetone–hexane), $[\alpha]D$ ±0°.

Anal. Calcd. for $C_{24}H_{35}O_5N$: C, 69.03; H, 8.45; O, 19.16. Found: C, 68.94; H, 8.31; O, 18.69.

6α-Cyanoandrostane-5α-ol-3,17-dione (IXb).—A solution of 6α-cyanoandrostane-3β,5α,17β-triol (VIc) (200 mg.) in acetone (20 cc.) at 0° was oxidized for 1–2 minutes with an excess of 8 *N* chromic acid.[51] Addition of water and isolation with ether afforded 6α-cyanoandrostane-5α-ol-3,17-dione (IXb) (185 mg.), m.p. 276–280°, raised by crystalliza-

tions from acetone–hexane to 284–286°, $[\alpha]_D$ +82°; λ_{max}^{EtOH} 286–292 mμ, ε 54; λ_{max}^{KBr} 3,450, 2220, 1747 and 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{27}O_3N$: C, 72.92; H, 8.26; N, 4.25. Found: C, 73.39; H, 8.47; N, 4.57.

6β-Cyanoandrostane-5α-ol-3,17-dione (VIIIb).—A solution of 6β-cyanoandrostane-5α,3β,17β-triol (VIIc) (1.0 g.) in acetone (200 cc.) at 0° was oxidized for 1–2 minutes with an excess of 8 *N* chromic acid.[51] Addition of water and extraction with ether afforded 6β-cyanoandrostane-5α-ol-3,-17-dione (VIIIb) (990 mg.), m.p. 283–287°, unchanged after crystallizations from acetone–hexane, $[\alpha]_D$ +43°. A mixture of IXb and VIIIb had m.p. 258–276°; λ_{max}^{KBr} 3500, 2215, 1735 and 1715 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{27}O_3N$: C, 72.92; H, 8.26; N, 4.25; O, 14.57. Found: C, 73.02; H, 8.29; N, 4.25; O, 14.78.

6-Cyano-Δ^4-androstene-3,17-dione (XIIb).—Dry hydrogen chloride was bubbled for 10 minutes through a solution of 6β-cyanoandrostane-5α-ol-3,20-dione (VIIIb) (50 mg.) in acetic acid. The solution was then kept at room temperature for 18 hours. Addition of ice-water and filtration afforded 6-cyano-Δ^4-androstene-3,17-dione (XIIb) as an amorphous solid (38 mg.), m.p. 107–112°, $[\alpha]_D$ −32°; λ_{max}^{EtOH} 228–230 and 288–290 mμ, ε 5,120 and 11,750; $\lambda_{max}^{EtOH/KOH}$ 338–340 mμ, ε 19,950; λ_{max}^{KBr} 2220, 3550, 1750, 1670, 1640 and 1600(sh) cm.$^{-1}$.

Sodium Borohydride Reduction of 6β-Cyanoandrostane-3,17-dione (VIIIb).—Sodium borohydride (300 mg.) in dioxane–water (5:1, 6 cc.) was added to a solution of the diketone VIIIb (550 mg.) in dioxane (15 cc.). After 3 hours at room temperature the solution was neutralized with acetic acid, poured onto ice-water and the product extracted with ethyl acetate. It was then suspended in benzene (75 cc.) and heated under reflux for 10 minutes when it was cooled to 20°. Filtration then afforded 6β-cyanoandrostane-3β,17β-diol (VIIc) (180 mg.), m.p. 295–303°, raised by one crystallization from aqueous methanol to 305–308°, undepressed on admixture with an authentic sample; $[\alpha]_D$ −28° (dioxane). The benzene filtrate was then adsorbed onto alumina (25 g.). Elution with benzene–ether (70:30, 350 cc.) afforded 6β-cyanoandrostane-3α,17β-diol (X) (150 (mg.) (28%)), m.p. 220–225°, raised by crystallizations from acetone–hexane to 223–225°, $[\alpha]_D$ −27°.

Anal. Calcd. for $C_{20}H_{31}O_3N$: C, 72.03; H, 9.37; O, 14.39; N, 4.20. Found: C, 71.76; H, 9.04; O, 14.18; N, 4.66.

Further elution with ether (150 cc.) afforded an additional 60 mg. of the 3β-alcohol VIIc, m.p. 298–303° (total yield (52%).

Potassium Cyanide Cleavage of Testosterone Ketal α-Epoxide Acetate (XIIIb).—Potassium cyanide (2.0 g.) was added to a solution of testosterone ketal α-epoxide acetate[31] (XIIIb) (1.0 g.) in ethylene glycol (40 cc.) and heated under reflux for 90 minutes. Addition of water and isolation with ethyl acetate afforded a product which was adsorbed from benzene onto alumina 70 g. Elution with benzene–ether (90:10, 600 cc.) gave 6-cyano-Δ^5-androstene-17β-ol-3-cycloethylene ketal (XVb) (320 mg.), λ_{max}^{EtOH} 224 mμ, ε 10,470, m.p. 173–186°, raised by several crystallizations from acetone–hexane to 213–214°, $[\alpha]_{D1}$ −107°; λ_{max}^{EtOH} 224 mμ, ε 13,180; λ_{max}^{KBr} 3,600, 2220 and 1100 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{31}O_3N$: C, 73.91; H, 8.74; O, 13.43; N, 3.92. Found: C, 74.36; H, 8.58; O, 13.31; N, 3.81.

Further elution with benzene–ether (50:50) and ether afforded 3-(2′-hydroxyethyl)-6-cyano-Δ^{3,5}-androstadiene-17β-ol (XVIb) (450 mg.), λ_{max}^{EtOH} 282–284 mμ, ε 16,000, m.p. 143–147°, raised by crystallizations from acetone–hexane to 154–156°, $[\alpha]_D$ −119°; λ_{max}^{EtOH} 284 mμ, ε 18,620; λ_{max}^{KBr} 3500, 2180, 1710 (acetone of crystallization) 1630 and 1580-(sh) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{31}O_3N \cdot CH_3COCH_3$: C, 72.25; H, 8.98; O, 15.40; N, 3.37. Found: C, 72.58; H, 8.63; O, 14.99; N, 3.58.

6α-Cyanotestosterone Acetate (XIIc).—Concentrated hydrochloric acid (0.2 cc.) was added to a solution of 3-(2′-hydroxyethyl)-6-cyano-Δ^{3,5}-androstadiene-17β-ol (XVIb) (100 mg.) in acetic acid (5.0 cc.). After 3 hours at room temperature addition of water and filtration afforded 6α-cyanotestosterone acetate (85 mg.) as an ill-defined non-crystalline solid, m.p. 115–127°, which resisted crystallization; λ_{max}^{EtOH} 230 and 288–290 mμ, ε 4,900 and 11,500, respectively; $\lambda_{max}^{EtOH-KOH}$ 340–342 mμ, ε 18,200.

6-Cyano-Δ^{3,5}-androstadiene-3,17β-diol Diacetate (XIc).—Crude 6α-cyanotestosterone acetate (XIIc) (1.0 g.), prepared as in the preceding experiment, was dissolved in acetyl chloride–acetic anhydride (1:1, 20 cc.) and heated under reflux in an atmosphere of nitrogen for 2 hours. Removal of the solvent *in vacuo* and crystallization of the residue from methanol afforded 6-cyano-Δ^{3,5}-androstadiene-3,17β-diol diacetate (XIc) (320 mg.), m.p. 200–202°, raised by several crystallizations from methanol to 216–217°, $[\alpha]_D$ −125°; λ_{max}^{EtOH} 262–264 mμ, ε 17,400; λ_{max}^{KBr} 2200, 1770, 1730 and 1660 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{31}O_4N$: C, 72.51; H, 7.86; O, 16.10; N, 3.52. Found: C, 72.31; H, 8.10; O, 15.87; N, 3.76.

Potassium Cyanide Cleavage of 5α,6α-Epoxidopregnane-17α-ol 3,10-Biscycloethylene-ketal (XIIIc).—Potassium cyanide (1.0 g.) was added to a solution of 5α,6α-epoxidopregnane-17α-ol-3,20-bis-cycloethylene-ketal (XIIIc) (500 g.) in ethylene glycol (20 cc.) and heated under reflux for 1.25 hours. Addition of water and isolation with ethyl acetate gave a product which was adsorbed from benzene (40 cc.) onto alumina (30 g.). Elution with benzene–ether (90:10, 300 cc.) afforded 6-cyano-Δ^5-pregnene-17α-ol-3,20-biscycloethylene-ketal (XVc) (130 mg.), m.p. 250–255°, raised by several crystallizations from acetone-ether to 255–256°, $[\alpha]_D$ −96°; λ_{max}^{EtOH} 224 mμ, ε 10,200; λ_{max}^{KBr} 3500, 2210 and 1105 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{37}O_5N$: C, 70.40; H, 8.41; N, 3.16. Found: C, 70.36; H, 8.54; N, 3.27.

Further elution with benzene–ether (70:30, 400 cc.) gave 6-cyano-3-(2′-hydroxyethyl)-Δ^{3,5}-pregnadiene-17α-ol-20-cycloethylene-ketal (XVIc) (210 mg.), m.p. 165–170°, raised by several crystallizations from acetone–ether to 178–179°, $[\alpha]_D$ −103°; λ_{max}^{EtOH} 282–284 mμ, ε 19,500; λ_{max}^{KBr} 3500, 3400, 2200, 1627 and 1588 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{37}O_5N$: C, 70.40; H, 8.41; N, 3.16. Found: C, 70.02; H, 8.2; N, 3.39.

6-Cyano-Δ^{3,5}-pregnadiene-3,17α-diol-20-one 3,17-Diacetate (XId).—(a) Perchloric acid (10 cc., 3 *N*) was added to a solution of 6-cyano-Δ^5-pregnene-17α-ol-3,20-biscycloethylene-ketal (XVc) (500 mg.) in tetrahydrofuran (15 cc.). After 3 hours at room temperature, addition of water and isolation with ethyl acetate afforded 6α-cyano-17α-hydroxyprogesterone (XIId) (non-crystalline), λ_{max}^{EtOH} 230 and 288 mμ, ε 4,680 and 9,775. The total crude product in acetic anhydride (5.0 cc.) and acetyl chloride (5.0 cc.) was heated under reflux for 2 hours in an atmosphere of nitrogen. The reaction mixture then was evaporated to dryness in high vacuum and the product crystallized from methanol to afford 6-cyano-Δ^{3,5}-pregnadiene-3,17α-diol-20-one-3,17-diacetate (XId) (220 mg.), m.p. 185–187°, raised by several crystallizations from methanol to 202–203°, $[\alpha]_D$ −112°, λ_{max}^{EtOH} 262–264 mμ, ε 18,620; λ_{max}^{KBr} 2200, 1770, 1740, 1700 and 1655 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{33}O_5N$: C, 71.04; H, 7.57; N, 3.19. Found: C, 70.75; H, 7.60; N, 3.00.

(b) Perchloric acid hydrolysis of 6-cyano-3-(2′-hydroxyethyl)-Δ^{3,5}-pregnadiene-17α-ol-20-one (XVIc) (1.55 g.) followed by enol acetylation was carried out exactly as described for XVc in the preceding experiment and afforded XId (800 mg.), m.p. 186–191°, raised by one crystallization from methanol to 197–200°, undepressed on admixture with a sample prepared as in method (a); λ_{max}^{EtOH} 264 mμ, ε 18,620.

6α-Cyano-17α-acetoxyprogesterone (XIIe).—A solution of 6-cyano-Δ^{3,5}-pregnadiene-3,17α-diol-20-one-3,17-diacetate (XId) (200 mg.) in methanol (6 cc.) containing potassium hydroxide (60 mg.) was kept at room temperature for 45 minutes when the solution was acidified with acetic acid. Addition of water and filtration afforded 6α-cyano-17α-acetoxyprogesterone (XIIe) (145 mg.) (mainly in the enol form) as an amorphous solid, m.p. 126–128°, $[\alpha]_D$ −120°; λ_{max}^{EtOH} 288–290 mμ, ε 14,790, plateau 220–230 mμ, ε 2,700.

Anal. Calcd. for $C_{24}H_{31}O_4N$: C, 72.51; H, 7.86; N, 3.52. Found: C, 72.01; H, 7.94; N, 3.67.

An attempt to crystallize the above product (m.p. 126–128°) from acetone–hexane afforded a semi-solid product, $[\alpha]_D$ −73°, λ_{max}^{EtOH} 230 and 288 mμ, ε 4,365 and 10,000; λ_{max}^{KBr} 2175, 1725 and 1630 cm.$^{-1}$.

3-Cycloethylene Ketal of Cortisone B.M.D. (XVIII).—Ethylene glycol (40 cc.) was added to a solution of cortisone B.M.D. (XVII) (3.0 g.) in benzene (400 cc.) containing *p*-toluenesulfonic acid monohydrate (200 mg.) and heated under reflux with a water separator for 8 hours. Sodium bicarbonate solution (20 cc., 5%) and water (250 cc.) were added and the product isolated with benzene. Removal of the solvent and crystallization of the product from benzene–hexane afforded the 3-cycloethylene ketal of cortisone B.M.D. (XVIII) (1.75 g.), m.p. 188–192°, raised by several crystallizations from benzene–hexane to 200–202°, $[\alpha]_D$ −88°; XVIII exhibited no selective absorption in the ultraviolet.

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67; O, 25.09. Found: C, 66.79; H, 7.73; O, 25.26.

Permonophthalic Acid Oxidation of the 3-Cycloethylene Ketal of Cortisone B.M.D. (XVIII).—Permonophthalic acid (3.8 g.) in ether (50 cc.) was added dropwise over 15 minutes to a solution of the cycloethylene ketal of cortisone B.M.D. (XVIII) (4.75 g.) in chloroform (50 cc.) at −10°. After keeping at 0° for 16 hours the solution was washed with cold 5% sodium bicarbonate solution until it was acid free and then with water to neutrality. Removal of the solvent after drying over sodium sulfate afforded a product which was adsorbed from benzene onto alumina (200 g.). Elution with benzene–ether (80:20, 1.5 l.) afforded the 3-cycloethylene ketal of cortisone B.M.D.-5α,6α-epoxide (XIXa) (2.55 g.), m.p. 293–297°. The analytical sample from ethyl acetate–hexane had m.p. >300°, $[\alpha]_D$ −90°.

Anal. Calcd. for $C_{25}H_{34}O_8$: C, 64.92; H, 7.41; O, 27.67. Found: C, 64.76; H, 7.63; O, 27.88.

Potassium Cyanide Cleavage of the 3-Cycloethylene Ketal of Cortisone B.M.D.-5α,6α-epoxide (XIXa).—Potassium cyanide (2.5 g.) was added to a solution of the epoxide XIXa (1.23 g.) in ethylene glycol (50 cc.) and heated under reflux for 45 minutes. Addition of water and isolation with ethyl acetate afforded a product which was adsorbed from benzene onto alumina (50 g.). Elution with benzene (750 cc.) afforded the Δ⁵-6-cyano-3-cycloethylene ketal (XXa) (250 mg.), m.p. 262–264°, raised by several crystallizations from benzene–hexane to 267–269°, $[\alpha]_D$ −138°, λ_{max}^{EtOH} 224 mμ, ε 10,075.

Anal. Calcd. for $C_{26}H_{33}O_7N$: C, 66.22; H, 7.05; N, 2.97. Found: C, 66.59; H, 7.15; N, 3.34.

Further elution with benzene–ether (90:10, 750 cc.) afforded by the 6-cyano enol ether XXIa (420 mg.), m.p. 192–197°, raised by several crystallizations from benzene–hexane to 209–211°, $[\alpha]_D$ −139°, λ_{max}^{EtOH} 284–286 mμ, ε 18,200.

Anal. Calcd. for $C_{26}H_{33}O_7N$: C, 66.22; H, 7.05; N, 2.97. Found: C, 66.76; H, 7.02; N, 3.14.

Potassium Cyanide Cleavage of Cortisone Bis-ketal-5α,6α-epoxide (XIXb).—Potassium cyanide (4.0 g.) was added to a solution of cortisone bis-ketal-5α,6α-epoxide[63] (XIXb) (2.0 g.) in ethylene glycol (80 cc.) and heated under reflux for 1 hour. Addition of water to the cooled solution and extraction with ethyl acetate gave a product which was adsorbed from methylene dichloride–benzene (1:30, 500 cc.) onto alumina (80 g.). Elution with ether–acetone (90:10, 1 l.) afforded after one crystallization from acetone–hexane 6-cyano-Δ⁵-pregnene-17α,21-diol-11-one-3,20-bis-cycloethylene ketal acetate (XXb) (440 mg.), m.p. 273–275°, raised by several crystallizations from acetone–hexane to 277–279°, $[\alpha]_D$ −56°; λ_{max}^{EtOH} 224 mμ, ε 11,000; λ_{max}^{KBr} 3450, 2200 and 1705 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{35}O_7N$: C, 65.94; H, 7.45; N, 2.96. Found: C, 65.64; H, 7.66; N, 3.07.

Further elution with ether–acetone (70:30, 800 cc.) afforded 6-cyano-3-(2′-hydroxyethyl)-Δ³,⁵-pregnadiene-17α,21-diol-11-one-20-cycloethylene ketal (XXIb) (370 mg.), m.p. 247–249°, raised by several crystallizations from ethyl acetate–hexane to 248–250°, $[\alpha]_D$ −59°; λ_{max}^{EtOH} 284–286 mμ, ε 17,800; λ_{max}^{KBr} 3450, 2200, 1690 and 1625 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{35}O_7N$: C, 65.94; H, 7.45; N, N, 2.96. Found: C, 65.64; H, 7.66; N, 3.06.

6α-Cyanocortisone (XXII).—Perchloric acid (3.7 cc., 35%) was added to a solution of 6-cyano-3-(2′-hydroxyethyl)-Δ³,⁵-pregnadiene-17α,21-diol-11,20-dione-20-cycloethylene ketal (XXIb) (220 mg.) in tetrahydrofuran (7.4 cc.). After 3 hours at room temperature water was added and the product extracted with ethyl acetate. The combined extracts were washed with sodium bicarbonate solution (5%), water and then dried over sodium sulfate. Removal of the solvent afforded 6α-cyanocortisone (XXII) as an amorphous solid, m.p. 152–162°, which resisted crystallization; $[\alpha]_D$ −22° (dioxane); λ_{max}^{EtOH} 220–222 and 286–288 mμ, ε 4,300 and 10,800, respectively; λ_{max}^{KBr} 3500, 2200, 1720(sh), 1700, 1670 and 1625 cm.$^{-1}$. The analysis for XXII was unsatisfactory.

Anal. Calcd. for $C_{22}H_{27}O_5N$: C, 68.55; H, 7.06; N, 3.63. Found: C, 67.56; H, 7.31; N, 2.95.

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[CONTRIBUTION FROM THE DIVISION OF PURE CHEMISTRY OF THE NATIONAL RESEARCH COUNCIL OF CANADA AND THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH[1]]

The Infrared Spectra of Steroid Lactones

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RECEIVED FEBRUARY 20, 1959

Characteristic features of the infrared spectra of twenty-six types of steroid lactones are summarized and discussed. For saturated γ- and δ-lactones it is observed that, in the absence of direct perturbing influences such as the inductive effects of vicinal substituents, the C=O stretching frequency in solution is negligibly influenced by the location of the lactone group with respect to the steroid ring system. The ranges previously assigned to the positions of the C=O stretching bands of saturated γ- and δ-lactone systems are confirmed, and other absorption specific to different types of steroid lactones is noted between 1450 and 1350 cm.$^{-1}$. The unsaturated lactone systems of $\Delta^{20(22)}$-cardenolides and $\Delta^{20,22}$-bufadienolides exhibit two bands in the C=O stretching region of the spectrum; the relative intensities of the two bands show large solvent effects, but they are not significantly influenced by the formal extension of the conjugated system into ring D.

Numerous publications during the past few years have served to focus attention on the prevalence of lactone groups in naturally occurring compounds; typical examples are the bitter principles, such as pictrotoxin and limonin, the santonins, nepetalactone, and gibberellic acid. Lactones are also encountered in steroids; unsaturated γ- and δ-lactone ring systems characterize the cardiac, squill and bufalin aglycones while various types of saturated steroid lactones have been obtained in the course of synthetic and degradative studies.

Infrared spectrometry has been used extensively to distinguish between γ- and δ-lactone ring systems in natural products; a range of 1780–1760 cm.$^{-1}$ is commonly reported for the C=O stretching frequency in saturated γ-lactones and 1750–1735 cm.$^{-1}$

(1) Published as Contribution No. 5303 from the Laboratories of the National Research Council of Canada, and No. XXXII in the series "Studies in Steroid Metabolism."