Hydrocyanation. Part IX.[1] Synthesis of β-Cyano-aldehydes by Conjugate Hydrocyanation of Allylideneamines Followed by Hydrolysis

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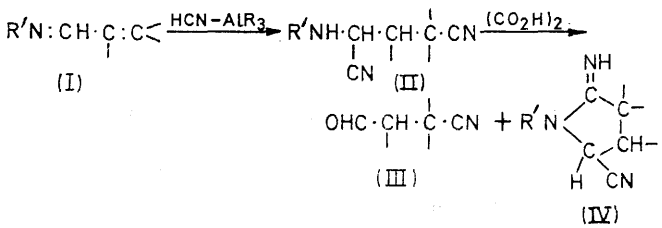
Conjugate hydrocyanation of αβ-unsaturated aldehydes with diethylaluminium cyanide or with hydrogen cyanide and an alkylaluminium was only successful with a substrate having a sterically hindered formyl group. Attempts to desulphurise β-cyano-thiocarboxylates to β-cyano-aldehydes failed. However, allylideneamines (I) carrying a bulky *N*-alkyl substituent reacted with hydrogen cyanide–alkylaluminium to give 1,3-dicyanopropylamines (II), which were hydrolysed to β-cyano-aldehydes (III) in good yield. 2-Iminopyrrolidines (IV) were formed as by-products.

HYDROCYANATION of αβ-unsaturated aldehydes by conventional methods leads to only 1,2-adducts (α-cyanohydrins);[2] β-cyano-aldehydes have not hitherto been synthesised by this route. These compounds could be useful as intermediates for the synthesis of complex natural products; we have therefore attempted to find a general, simple route for their preparation.

Conjugate hydrocyanation of αβ-unsaturated aldehydes with diethylaluminium cyanide[3a] and with hydrogen cyanide and an alkylaluminium[3b] did not give 1,4-adducts, except in the case of the steroidal Δ^{16}-17-carbaldehyde (Va). Attempted desulphurisation of a β-cyano-thiocarboxylate[1] was also unsuccessful. However, treatment of allylideneamines (I) with hydrogen cyanide–alkylaluminium followed by hydrolysis of the resulting 1,3-dicyanopropylamines (II) gave β-cyano-aldehydes (III) together with 2-iminopyrrolidines (IV) formed as by-products (Scheme 1).



R′ = cyclohexyl (C_6H_{11}) or Bu^t; R_3 = Et_3, Et_2Cl, or $EtCl_2$.

SCHEME 1

The αβ-unsaturated aldehydes used are known except for the Δ^5-6-formyl-B-nor-steroids (Xa) and (Xb) and the steroidal Δ^2-3-carbaldehydes (XVb), (XVc), and (XVd). The β-nor-aldehydes were prepared by dehydration of 3β-acetoxy-6β-formyl-5β-hydroxy-B-nor-5β-androstane-17-one[4] with methanolic potassium carbonate to give compound (Xa), followed by acetylation to give compound (Xb). The Δ^2-3-carbonitrile (XVa) derived from 17β-acetoxy-5α-androstan-3-one was reduced with di-isobutylaluminium hydride; treatment of the product with acid gave compound (XVb), which was acylated to give compounds (XVc) and (XVd). The preparation of the β-cyano-thiocarboxylate (VIIIa) is described in the preceding paper.[1] The 17β-thiocarboxylate (IXa) was prepared by thioesterification of the

[1] Part VIII, W. Nagata, T. Okumura, and M. Yoshioka, preceding paper.

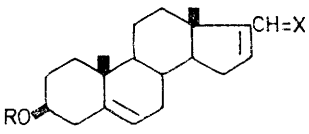
[2] P. Kurz, 'Methoden der Organischen Chemie,' vol. VIII, Thieme Verlag, Stuttgart, 1952, p. 265.

[3] (*a*) W. Nagata and M. Yoshioka, *Tetrahedron Letters*, 1966, 1913; (*b*) W. Nagata, M. Yoshioka, and S. Hirai, *ibid.*, 1962, 461; Part IV, *J. Amer. Chem. Soc.*, in the press. See also Parts V and VII. *J. Amer. Chem. Soc.*, in the press.

[4] R. Takasaki, *Chem. and Pharm. Bull.* (*Japan*), 1962, **10**, 439.

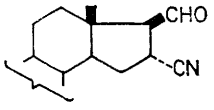
corresponding carboxylic acid. Allylideneamines were obtained by condensation of conjugated aldehydes with cyclohexylamine or t-butylamine, except for the cyclohexylidene-ethylideneamines (XVIIIb) and (XVIIIc). They were prepared by a Wadworth–Horner type reaction of cyclohexanone with diethyl alkylaminovinylphosphates developed recently [5] for a new formylolefination procedure.

pound whose i.r. spectrum was consistent with the formulation (Xc). When treated with methanolic potassium hydroxide, the compound was converted into the Δ^5-6-formyl-3-hydroxy-B-nor-steroid (Xa). Similarly, no β-cyano-aldehydes were obtained by treatment of the Δ^2-2-carbaldehyde (XIIb), the 3-isomer (XVc), and in cyclohexylideneacetaldehyde (XVIIIa) with diethylaluminium cyanide at room temperature in benzene for

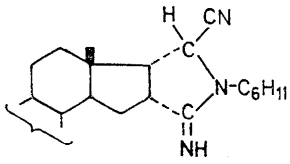


(V)

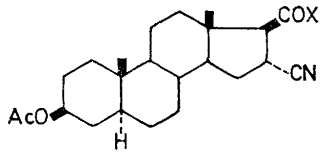
a; R = H, X = O
b; R = Ac, X = O
c; R = H, X = 
d; R = Ac, X = N·C_6H_{11}
e; R = Ac, X = N·Bu^t



(VI) R = Ac

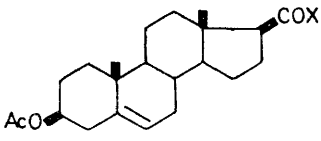


(VII) R = Ac



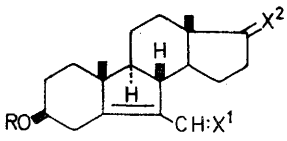
(VIII)

a; X = SPh
b; X = H



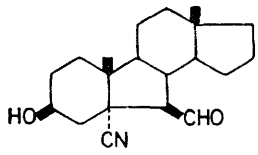
(IX)

a; X = SEt
b; X = H

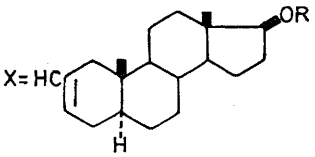


(X)

a; R = H, $X^1 = X^2 = O$
b; R = Ac, $X^1 = X^2 = O$
c; R = Ac, $X^1 = X^2$ = 
d; R = H, X^1 = N·C_6H_{11}, $X^2 = H_2$

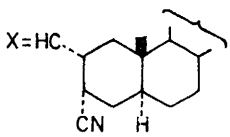


(XI)



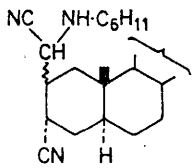
(XII)

a; R = H, X = O
b; R = Ac, X = O
c; R = H, X = N·C_6H_{11}
d; R = Bz, X = N·C_6H_{11}
e; R = Bz, X = 



(XIII)

a; R = H, X = O
b; R = Bz, X = O



(XIV)

a; R = H
a′; R = H
b; R = Bz

*Hydrocyanation of Conjugated Aldehydes.**—Treatment of the Δ^{16}-17-carbaldehyde (Va) [1] with diethylaluminium cyanide under mild conditions (in toluene at 0° for 30 min.) gave the 1,2-adduct (Vc) (84%); the 1,4-adduct (VI) was obtained in 58% yield from the conjugated aldehyde (Vb) [1] under more forcing conditions (at room temperature for 5 hr.).

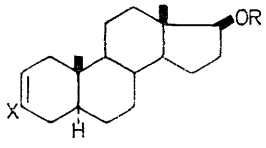
With other conjugated aldehydes, the reaction did not afford 1,4-adducts. Reaction of the Δ^5-6-formyl-B-nor-steroid (Xb) with diethylaluminium cyanide in toluene–benzene at room temperature for 2 days or at 50° for 1·5 hr. followed by treatment with acid gave a compound whose i.r. spectrum was consistent with the formulation (Xc). When treated with methanolic potassium hydroxide, the compound was converted into the Δ^5-6-formyl-3-hydroxy-B-nor-steroid (Xa). Similarly, no β-cyano-aldehydes were obtained by treatment of the Δ^2-2-carbaldehyde (XIIb), the 3-isomer (XVc), and in cyclohexylideneacetaldehyde (XVIIIa) with diethylaluminium cyanide at room temperature in benzene for 17 hr., in benzene–dichloromethane for 8·5 hr., and in toluene for 2·5 hr., respectively. Also, a combination of hydrogen cyanide and ethylaluminium dichloride, the hydrocyanating agent that converted cholest-4-en-3-one into its 1,4-adduct without prior formation of cholestenone α-cyanohydrin,[3b] was not effective for converting even the simple conjugated aldehyde (XVIIIa) into its 1,4-adduct (XIX).

Resistance of these αβ-unsaturated aldehydes to con-

* The elucidation of the structures of the products is described later.

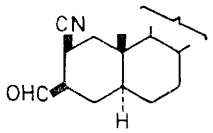
[5] W. Nagata and Y. Hayase, *J. Chem. Soc.* (*C*), 1969, 460.

jugate hydrocyanation may be ascribed to greater reactivity of the formyl carbon atom towards cyanide ion than of the β-carbon atom, combined with great stability of the 1,2-adduct formed. The exceptional



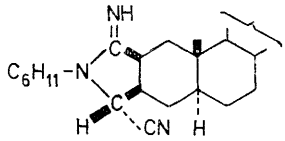
(XV)

a; R = Ac, X = CN
b; R = H, X = CHO
c; R = Ac, X = CHO
d; R = Bz, X = CHO
e; R = H, X = CH:N·C_6H_{11}
f; R = Bz, X = CH:N·C_6H_{11}
g; R = Bz, X = CH:N·Bu^t

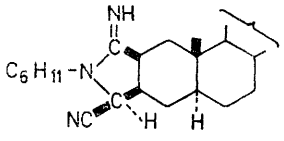


(XVI)

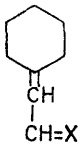
a; R = H
b; R = Bz



(XVIIa) R = Bz

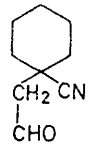


(XVIIb) R = Bz

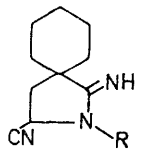


(XVIII)

a; X = O
b; X = N·C_6H_{11}
c; X = N·Bu^t



(XIX)



(XX)

a; R = C_6H_{11}
b; R = Bu^t

RCH:CH·CH:NBu

(XXI) R = Ph
(XXIII) R = Me

RCH(CN)·CH_2·CHO

(XXII) R = Ph
(XXIV) R = Me

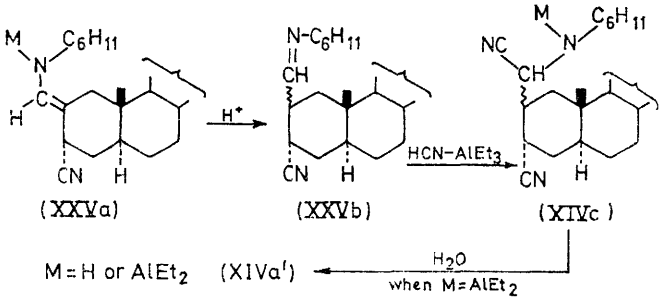
conjugate hydrocyanation of the Δ^{16}-17-carbaldehyde (Vb) could be attributed to steric interactions between the C-17 functionality and the C-18 methyl and C-12 methylene groups, which would reduce the reactivity of the formyl group and the stability of the initially formed 1,2-adduct.

Attempted Desulphurisation of a β-Cyano-thiocarboxylate.—Desulphurisation of the 16α-cyano-17β-thiocarboxylate (VIIIa) with deactivated Raney nickel [6] gave a small amount of the β-cyano-aldehyde (VIIIb). The use of non-deactivated Raney nickel (W-1—3) in the presence or in the absence of 1,2-dianilinoethane [7] resulted in poor recovery (<20%) of the product. The reduction probably led to further-reduced polar substances which would be adsorbed on the nickel. Since the thiocarboxylate (IXa) was smoothly desulphurised with Raney nickel to the 17-carbaldehyde (IXb) by the standard procedure,[6] the cyano-group must inhibit desulphurisation.

* The elucidation of the structure of the products is described later.

*Synthesis of β-Cyano-aldehydes via Hydrocyanation of Allylideneamines.**—We expected that the high reactivity of the formyl carbon atom would be reduced by replacing the formyl oxygen atom by the less electronegative nitrogen, and that the stability of the 1,2-adduct would be lessened by attaching a bulky group to the nitrogen. We therefore examined the hydrocyanation of *N*-cyclohexylallylideneamines. We also anticipated that the hydrocyanation products would be readily convertible into β-cyano-aldehydes.

The Δ^2-2-cyclohexyliminomethyl-17β-hydroxy-steroid (XIIc) was treated with diethylaluminium cyanide in tetrahydrofuran–benzene at room temperature for 35 min., and the hydrocyanation product was subjected to two-layer hydrolysis [5] with 5% aqueous oxalic acid, benzene, and tetrahydrofuran to give the 3α-cyano-2α-carbaldehyde (XIIIa) (67%) and the dicyano-amine (XIVa) (8·8%). However, similar treatment of the 17-benzoyloxy-analogue (XIId) gave largely the 1,2-adduct (XIIe) with little of the 1,4-adduct (XIIIb). This dependence of the products on the C-17 functionality suggests that the presence of a protic substance is essential for conjugate hydrocyanation of allylideneamines. In accord with this suggestion, treatment of the Δ^2-2-cyclohexyliminomethyl-17β-benzoyloxy-derivative (XIId) mixed with an equimolar amount of propan-2-ol with diethylaluminium cyanide at 25° for 30 min. followed by homogeneous hydrolysis afforded the β-cyano-aldehyde (XIIIb) in 69% yield. Replacement of the propan-2-ol by ethanol, t-butyl alcohol, cholesterol, or water gave similar results. The conjugate hydrocyanation would be expected to proceed better with a hydrogen cyanide–alkylaluminium reagent, which inherently contains a protic species. As expected, the reaction of compound (XIIc) with hydrogen cyanide–triethylaluminium in tetrahydrofuran was complete in 20 min. at room temperature, and the dicyano-amine (XIVa′) was obtained as its hydrate in 96% yield. This is thought to be formed by acid-catalysed conversion of the initially formed 1,4-adduct (XXVa) into the imino-form (XXVb), followed by 1,2-addition (Scheme 2).



SCHEME 2

When the dicyano-amine (XIVb) prepared from (XIId) in the same way was subjected to homogeneous hydrolysis without purification, the cyano-aldehyde (XIIIb) was

[6] A. V. McIntosh, A. M. Searcy, E. M. Meinzer, and R. H. Levin, *J. Amer. Chem. Soc.*, 1949, **71**, 3317.
[7] H. J. Bestmann and H. Schulz, *Chem. Ber.*, 1959, **92**, 530.

obtained in 67% overall yield. The homogeneous hydrolysis (heating the hydrocyanation product with 5% oxalic acid, tetrahydrofuran, and ethanol) was found necessary for converting the steroidal dicyano-compounds into the β-cyano-aldehydes. The relatively low yield (67%) of the cyano-aldehyde (XIIIb) as compared with that (96%) of the dicyano-amine (XIVa′) is probably due to the formation of a pyrrolidino-compound [*cf.* formula (IV) and later results] which was not isolated here.

The reaction of other *N*-cyclohexylallylideneamines with the hydrogen cyanide–alkylaluminium reagent in tetrahydrofuran was then examined. Conjugate hydrocyanation of the B-nor-Δ^5-6-methyleneamine (Xd) did not proceed well with hydrogen cyanide–triethylaluminium, resulting in predominant formation of the 1,2-adduct, but was successful with hydrogen cyanide–ethylaluminium dichloride (room temperature; 20 hr.) to give, after hydrolysis, the product of angular cyanation (XI), in 55% yield. The successful introduction of the angular cyano-group is significant in the light of the expected utility of the method in the synthesis of complex natural products.

Formation of pyrrolidino-compounds (IV) reduced the yields of β-cyano-aldehydes in the reactions of other *N*-cyclohexylallylideneamines. The 16α-cyano-17β-carbaldehyde (VI) was obtained in 25% yield along with the iminopyrrolidine (VII) (6·2%) on treatment of the Δ^{16}-17-methyleneamine (Vd) with hydrogen cyanide–triethylaluminium (25°; 30 min.) followed by homogeneous hydrolysis. Treatment of the Δ^2-3-cyclohexyliminomethyl-17-benzoate (XVf) with hydrogen cyanide–triethylaluminium at 25° for 1 hr. followed by homogeneous hydrolysis and chromatography on alumina gave the 2β-cyano-3β-carbaldehyde (XVIb) in only 11% yield, together with two iminopyrrolidine derivatives (XVIIa) (12%) and (XVIIb) (17%). With the 17β-hydroxy-analogue (XVe) the reaction led to a similar result, but the β-cyano-aldehyde (XVIa) was unstable and therefore difficult to purify. Conjugate hydrocyanation of the cyclohexylidene-ethylideneamine (XVIIIb) with hydrogen cyanide–triethylaluminium at −10° for 2·5 hr. gave, after two-layer hydrolysis, (1-cyanocyclohexyl)acetaldehyde (XIX) (39%) and the iminopyrrolidine (XXa) (24%).

Attempts were made to reduce the formation of the iminopyrrolidines (IV), which are apparently formed by cyclisation of the dicyano-amines (II) during acid hydrolysis. We hoped to inhibit the formation of the dicyano-amines (II) by replacing the hydrogen cyanide–triethylaluminium by diethylaluminium cyanide and propan-2-ol (1 mol.), so that the proton concentration might be kept low at a later stage of the reaction by the rapid transformation of the propanol into ethane and an isopropoxide (by interaction with diethylaluminium cyanide). However, preliminary experiments with substrates (XVe) and (XVIIIb) were discouraging: the product after hydrolysis consisted of the αβ-unsaturated aldehyde, the dicyano-amine, and a small amount of the β-cyano-aldehyde. A considerable improvement was produced only in the reaction of the Δ^{16}-17-methyleneamine (Vd), which gave the 16α-cyano-17β-carbaldehyde (VI) in 47% yield.

We then planned to reduce pyrrolidine formation during hydrolysis of the dicyano-amines (II) by use of the bulkier t-butyl group instead of the cyclohexyl *N*-substituent. This proved effective, though it considerably reduced the reactivity of allylideneamines to conjugate hydrocyanation. Thus, the 16α-cyano-17β-carbaldehyde (VI) and the 2β-cyano-3β-carbaldehyde (XVIb) were obtained in 55 and 64% yield, respectively, by treatment of the Δ^{16}-17-t-butyliminomethyl derivative (Ve) and the 3-*N*-t-butyliminomethyl-17-benzoate (XVg) with hydrogen cyanide–triethylaluminium, in the presence of a small amount of water as an accelerator,* at room temperature for 1·5 hr. and 2 hr., respectively, followed by hydrolysis. Conjugate hydrocyanation of the *N*-t-butylcyclohexylidene-ethylideneamine (XVIIIc) was effected by treatment with hydrogen cyanide–triethylaluminium at room temperature for 30 min. to give, after hydrolysis, the β-cyano-aldehyde (XIX) in 72% yield together with the imino-pyrrolidine (XXb) (11%). General applicability of this method was tested on *N*-(2-benzylidene-ethylidene)-t-butylamine (XXI), a simple but electrically deactivated, aromatic allylideneamine, and *N*-(but-2-enylidene)-t-butylamine (XXIII), a simple aliphatic derivative. Conjugate hydrocyanation of the former was successful with hydrogen cyanide–diethylaluminium chloride (room temperature; 25·5 hr.) to give, after two-layer hydrolysis, 2-phenylsuccinaldehydronitrile (XXII) in 54% yield. The 2-methyl analogue (XXIV) was obtained in 15% yield as its 2,4-dinitrophenylhydrazone by treatment of compound (XXIII) with hydrogen cyanide–triethylaluminium at 0° for 1 hr. followed by hydrolysis. The low yield of the cyano-aldehyde (XXIV) may be ascribed to a loss and/or decomposition of this low molecular weight aldehyde during work-up.

We are thus able to prepare a variety of β-cyano-aldehydes (III) as outlined in Scheme 1. The choice of cyclohexyl or t-butyl as the *N*-substituent of the allylideneamines (I) and the choice of hydrocyanation conditions depend on the reactivity of the substrate (I) and the tendency of the initial product (II) to cyclise. The requirement of the presence of a protic species could be explained in terms of an effective activation of the conjugated imine system causing acceleration of attack of cyanide at the β-carbon atom.

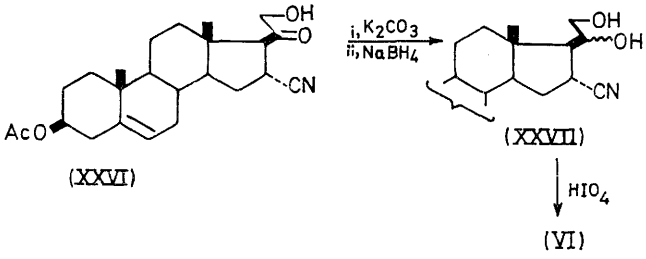
The stereochemical results of the conjugate hydrocyanations reported here are in accord with previous discussion of the similar reactions of αβ-unsaturated ketones [8] and carboxylic acid derivatives.[1]

Elucidation of Structures of Products.—The 16α-cyano-17β-carbaldehyde (VI) was identified by comparison

* For discussion of the acceleration of conjugate hydrocyanation by water, see Part V. W. Nagata, M. Yoshioka, and M. Murakami, *J. Amer. Chem. Soc.*, in the press.

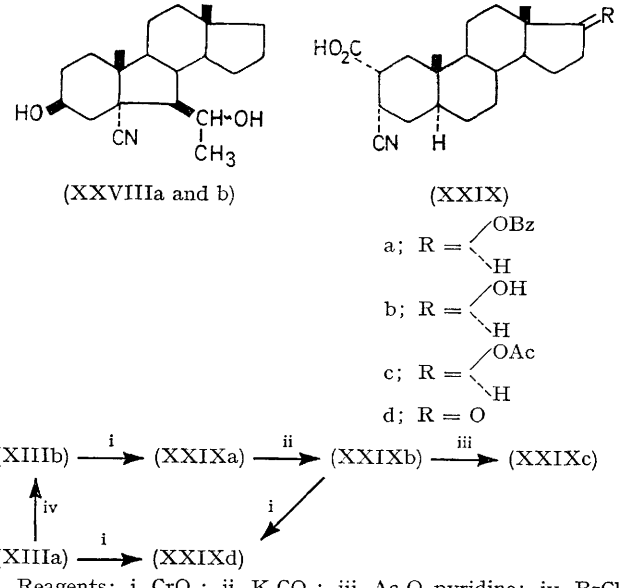
[8] Part VI, W. Nagata, M. Yoshioka, and T. Terasawa, *J. Amer. Chem. Soc.*, in the press.

with an authentic sample prepared by reduction of the 21-hydroxy-20-oxo-16α-carbonitrile (XXVI) [1] with sodium borohydride followed by oxidation with periodic acid (Scheme 3).



SCHEME 3

The 5α-cyano-6β-formyl formulation assigned to the B-nor-nitrile (XI) is based on its conversion into the known epimeric secondary alcohols (XXVIIIa and b) [3b] on treatment with methylmagnesium iodide. The structure of the 3α-cyano-2α-formyl-17-benzoate (XIIIb) follows from its oxidation to the carboxylic acid (XXIXa), which was converted into the known 17-acetate (XXIXc) [1] *via* the 17β-ol (XXIXb). The fact that no epimerisation at C-2 occurred in hydrolysis of (XXIXa) to (XXIXb) was shown by oxidation of the latter to the same 17-ketone (XXIXd) as obtained by oxidation of the 3α-cyano-2α-formyl-17β-ol (XIIIa), which was convertible into the 17-benzoate (XIIIb) (Scheme 4). The



Reagents: i, CrO_3; ii, K_2CO_3; iii, Ac_2O–pyridine; iv, BzCl–pyridine.

SCHEME 4

structure of (XIIIb) is supported by its n.m.r. spectrum which shows a triplet of doublets (J_t 4, J_d 13 Hz) at δ 2·542 p.p.m. (2β-proton) and a multiplet of a small half-bandwidth (8 Hz) at δ 3·250 p.p.m. (3β-proton). The structures of the dicyano-amines (XIVa) and (XIVa'), whose configurations at the 2-position have not been established, are based on analysis and i.r. spectra, which show the absence of a formyl group. Compound (XIVa'), obtained as a hydrate, is either epimeric to (XIVa) or a mixture of the 2α- and 2β-epimers.

The 2β-cyano-3β-formyl configuration assigned to (XVIb) is deduced from n.m.r. data. Its spectrum shows the signal of the C-19 protons at low field (δ 1·134 p.p.m.) and a multiplet due to the C-2 proton at δ 3·267 p.p.m. which collapsed to a triplet ($J = 5$ Hz) on irradiation (100 MHz spectrum) at the frequency of the C-3 proton, as expected for the axial 2β-cyano-configuration. A quartet at δ 2·220 p.p.m. ascribable to the C-3 proton collapsed to a doublet (J 14 Hz) on irradiation at the frequency of the C-2 proton, in agreement with the 3β-formyl structure.

The β-cyano-aldehyde structures of compounds (XIX), (XXII), and (XXIVa) are based on analysis and i.r. spectra, which show the presence of a cyano-group and a non-conjugated formyl group.

The structures of the iminopyrrolidines (VII), (XVIIa), (XVIIb), and (XXa), are based on analysis and i.r. data, which indicate the presence of a cyano-group and an imino-group in each. The pyrrolidine ring is expected to be *cis*-fused to the steroid nucleus in (VII), (XVIIa), and (XVIIb). The *cis*-fusion in compounds (XVIIa) and (XVIIb) is supported by the n.m.r. spectra, which show the C-19 proton signals at higher field (δ 0·77 and 0·767 p.p.m., respectively) as expected if these protons lie within the conical shielding region of the imino-group. The configuration of the cyano-group in compound (VII) was not determined. The cyano-groups in compounds (XVIIa and b) are assigned the α and β-configurations, respectively, on the basis of n.m.r. spectra; the C*H*·CN proton gives a singlet (δ 3·834 p.p.m.) in the spectrum of (XVIIa) and a doublet (δ 4·333 p.p.m., J 6 Hz) in that of (XVIIb), consistent with the dihedral angles between the C(3α)–H and NC·C–H bonds.

EXPERIMENTAL

For general directions see the preceding paper.[1] The dichloromethane used for extraction and purification of β-cyano-aldehydes was freed from methanol by washing with water, in order to avoid possible acetalisation.

3β-Hydroxy-17-oxo-B-norandrost-5-ene-6-carbaldehyde (Xa) *and its 3-Acetate* (Xb).—To 3β-acetoxy-5β-hydroxy-20-oxo-B-nor-5β-androstane-6β-carbaldehyde [4] (2·196 g.) in methanol (176 ml.) was added 2N-potassium carbonate (44 ml.) at 20°. After 5 hr. at 20°, the mixture was concentrated *in vacuo* below 40° to remove the bulk of the methanol, poured into water, and extracted with dichloromethane. Recrystallisation of the product from dichloromethane–methanol gave the *3β-hydroxy-B-nor-Δ⁵-6-carbaldehyde* (Xa) (1·401 g., 76%), m.p. 193—196°, $[\alpha]_D^{25}$ +11° (*c* 1·09); $\lambda_{max.}$ 255 nm. (ε 13,300); $\nu_{max.}$ 3600, 3446 (OH), 2764, 1675 (CHO), 1735 [C(17)=O], and 1607 (C=C) cm.$^{-1}$ (Found: C, 75·65; H, 8·6. $C_{19}H_{26}O_3$ requires C, 75·45; H, 8·65%).

Acetylation of (Xa) (0·448 g.) with acetic anhydride in pyridine afforded the *3-acetate* (Xb) (0·403, 77%), m.p. 163—165°, $[\alpha]_D^{25}$ −10° (*c* 1·3); $\lambda_{max.}$ 253 nm. (ε 12,900); $\nu_{max.}$ 2765, 1675 (CHO), 1733 (OAc), and 1608 (C=C) cm.$^{-1}$ (Found: C, 72·95; H, 8·2. $C_{21}H_{28}O_4$ requires C, 73·22; H, 8·2%).

17β-*Hydroxy*-5α-*androst*-2-*ene*-3-*carbaldehyde* (XVb), *its* 17-*Acetate* (XVc), *and its* 17-*Benzoate* (XVd).—To 17β-acetoxy-5α-androstan-3-one (32·23 g.) in ethanol (750 ml.) and acetic acid (300 ml.) cooled in ice was added potassium cyanide (100 g.) in water (170 ml.), and the mixture was stirred at room temperature for 3 hr. The crystals were filtered off, washed with water, and dried to give the cyanohydrin (37·5 g.), m.p. 155—158°, which was refluxed with dry pyridine (300 ml.) and phosphoryl chloride (75 ml.) for 11 hr. The mixture was concentrated to about one-third of the original volume, gradually mixed with ice-cold 2N-hydrochloric acid, and extracted with ether. Crystallisation of the product yielded 17β-acetoxy-5α-androst-2-ene-3-carbonitrile (XVa) (19·51 g., 55%), m.p. 134—135°. To this (19·5 g.) in dry benzene cooled in ice was added di-isobutylaluminium hydride (42 ml.) in dry benzene (100 ml.). After 1 hr. at 0°, the mixture was poured into 4N-sulphuric acid (1 l.), left overnight, and then extracted with ethyl acetate–methanol (4 : 1). The product (16·13 g.) was chromatographed. Gradient elution with benzene–dichloromethane (1 : 0 to 1 : 1) gave the 17β-*hydroxy*-Δ²-3-*carbaldehyde* (XVb) (6·331 g.), m.p. 128—130° (from acetone), $[\alpha]_D^{23}$ +105° (*c* 0·98); $\lambda_{max.}$ 233 nm. (ε 16,800); $\nu_{max.}$ 3626, 3442 (OH), 2730, 1678 (CHO), and 1645 (C=C) cm.$^{-1}$ (Found: C, 79·55; H, 9·95. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%). Additional (XVb) (2·5 g., m.p. 113—115°; 1·0 g., m.p. 108—110°) was obtained from the mother liquor.

Acetylation afforded the 17β-*acetoxy*-Δ²-3-*carbaldehyde* (XVc), m.p. 123—125° (from ether), $[\alpha]_D^{22}$ +82° (*c* 1·12); $\nu_{max.}$ 2743, 1678 (CHO), 1725 (OAc), and 1646 (C=C) cm.$^{-1}$ (Found: C, 76·85; H, 9·4. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·35%).

Benzoyl chloride (0·422 g.) was added to the 17-hydroxy-Δ²-3-carbaldehyde (XVb) (0·605 mg.) in dry pyridine (4 ml.). The mixture was kept at room temperature for 1 hr., mixed with a small amount of water to decompose the excess of reagent, poured into ice–water, and extracted with dichloromethane. Crystallisation of the product afforded material (0·59 g.) which gave the pure *benzoate* (XVd), m.p. 144·5—147° (from dichloromethane–methanol), $[\alpha]_D^{23}$ +103° (*c* 0·961); $\lambda_{max.}$ 231 nm. (ε 30,000); $\nu_{max.}$ 2724, 1682 (CHO), 1645 (C=C), 1714, 1603, and 1586 (OBz) cm.$^{-1}$ (Found: C, 79·7; H, 8·45. $C_{27}H_{34}O_3$ requires C, 79·75; H, 8·45%).

Ethyl 3β-*Acetoxyandrost*-5-*ene*-17β-*thiocarboxylate* (IXa).—3β-Acetoxyandrost-5-ene-17β-carboxylic acid (2·02 g.) was treated with thionyl chloride (20 ml.) for 20 min. at room temperature, and the mixture was concentrated to dryness. A mixture of the resulting acid chloride, toluene (20 ml.), ethanethiol (5 ml.), and pyridine (0·3 ml.) was kept at room temperature for 18·5 hr., then evaporated. The residue was chromatographed. Elution with dichloromethane afforded the *thioester* (IXa) (1·0 g., 45%), m.p. 149—150° (from dichloromethane–methanol), $[\alpha]_D^{24}$ +3·3° (*c* 0·90); $\lambda_{max.}$ 236 nm. (ε 4180); $\nu_{max.}$ 1730 (OAc) and 1679 (thio-ester) cm.$^{-1}$ (Found: C, 71·2; H, 8·95; S, 7·65. $C_{24}H_{36}O_3S$ requires C, 71·25; H, 8·95; S, 7·9%).

17-*Cyclohexyliminomethylandrosta*-5,16-*dien*-3β-*ol* 3-*Acetate* (Vd) *and the* N-*t*-*Butyl Analogue* (Ve).—A mixture of the Δ¹⁶-17-formyl derivative (Vb) [1] (0·425 g.), dry methanol (10 ml.), and cyclohexylamine (0·184 g.) was refluxed under nitrogen for 30 min., concentrated, cooled, and filtered. The crystals were washed with methanol and dried to give the Δ¹⁶-17-*cyclohexyliminomethyl derivative* (Vd) (0·446 g., 85%), m.p. 158—160°, $[\alpha]_D^{23}$ −42° (*c* 0·99); $\lambda_{max.}$ 238 nm. (ε 16,100); $\nu_{max.}$ 1728 (OAc) and 1635 (αβ-unsaturated imine) cm.$^{-1}$ (Found: C, 79·55; H, 9·75; N, 3·3. $C_{28}H_{41}NO_2$ requires C, 79·4; H, 9·75; N, 3·3%).

A mixture of the enal (Vb) [1] (0·182 g.), dry methanol (4 ml.), and t-butylamine (0·19 g.) was refluxed for 10 min. under nitrogen, cooled, and filtered. The crystals were washed with methanol and dried to yield 17-*t*-*butylimino-methylandrosta*-5,16-*dien*-3β-*ol* 3-*acetate* (Ve) (0·099 g., 47%), m.p. 145—146°, $\lambda_{max.}$ 235 nm. (ε 13,900); $\nu_{max.}$ 1730 (OAc) and 1639 (αβ-unsaturated imine) cm.$^{-1}$ (Found: C, 78·45; H, 9·85; N, 3·4. $C_{26}H_{29}NO_2$ requires C, 78·55; H, 9·9; N, 3·5%).

6-*Cyclohexyliminomethyl*-B-*norandrost*-5-*en*-3β-*ol* (Xd).—A mixture of 3β-hydroxy-B-norandrost-5-ene-6-carbaldehyde [3b] (0·439 g.), dry methanol (4 ml.), and cyclohexylamine (0·226 mg.) was refluxed for 1 hr. under nitrogen, then evaporated. The residue afforded the B-*nor-imine* (Xd) (0·453, 81%), m.p. 144—146° (from ether), $[\alpha]_D^{21}$ −152° (*c* 0·25); $\nu_{max.}$ 3615 (OH) and 1636 (αβ-unsaturated imine) cm.$^{-1}$ (Found: C, 81·25; H, 10·5; N, 3·65. $C_{25}H_{39}NO$ requires C, 81·25; H, 10·65; N, 3·8%).

2-*Cyclohexyliminomethyl*-5α-*androst*-2-*en*-17β-*ol* (XIIc) *and its* 17-*Benzoate* (XIId).—A mixture of the Δ²-2-formyl steroid (XIIa) [9] (1·435 g.), dry methanol (10 ml.), cyclohexylamine (0·71 g.), and acetic acid (1 drop) was refluxed for 30 min. under nitrogen, concentrated a little, cooled, and filtered. The crystals were washed with methanol and dried to give the Δ²-2-*cyclohexyliminomethyl derivative* (XIIc) (1·812 g., 99%), m.p. 190—192°, $[\alpha]_D^{23}$ +78° (*c* 0·94); $\lambda_{max.}$ 232 nm. (ε 19,800); $\nu_{max.}$ 3621 (OH), 1647 (C=N), and 1626 (C=C) cm.$^{-1}$ (Found: C, 81·2; H, 10·55; N, 3·55. $C_{26}H_{41}NO$ requires C, 81·4; H, 10·75; N, 3·65%).

The hydroxy-enal (XIIa) [9] was treated with benzoyl chloride in pyridine to afford 17β-benzoyloxy-5α-androst-2-ene-2-carbaldehyde, m.p. 198—201°, $[\alpha]_D^{23}$ +123° (*c* 1·05). A mixture of this benzoate (2·138 g.), dry methanol (15 ml.), and cyclohexylamine (0·782 g.) was refluxed for 20 min. under nitrogen, cooled, and filtered. The crystals were washed with methanol and dried to afford the 17β-*benzoyl-oxy*-Δ²-2-*cyclohexyliminomethyl steroid* (XIId) (2·307 g., 90%), m.p. 134—135°, $[\alpha]_D^{23}$ +112° (*c* 1·04), $\nu_{max.}$ 1646 (C=N), 1625 (C=C), 1714, 1604, and 1587 (OBz) cm.$^{-1}$ (Found: C, 81·0; H, 9·35; N, 2·8. $C_{33}H_{45}NO_2$ requires C, 81·25; H, 9·3; N, 2·85%).

3-*Cyclohexyliminomethyl*-5α-*androst*-2-*en*-17β-*ol* (XVe), *its Benzoate* (XVf), *and the* N-*t*-*Butyl Analogue* (XVg).—A mixture of the 17β-hydroxy-Δ²-3-carbaldehyde (XVb) (2·416 g.), dry methanol (10 ml.), and cyclohexylamine (1·21 g.) was refluxed for 15 min. under nitrogen, cooled, and filtered to give 3-*cyclohexyliminomethyl*-5α-*androst*-2-*en*-17β-*ol* (XVe) (2·928 g., 95%), m.p. 208—210°, $[\alpha]_D^{23}$ +87° (*c* 0·56); $\nu_{max.}$ 3618 (OH), 1648 (C=N), and 1625 (C=C) cm.$^{-1}$ (Found: C, 81·3; H, 10·9; N, 3·65. $C_{26}H_{41}ON$ requires C, 81·4; H, 10·75; N, 3·05%).

Condensation of the 17β-benzoyloxy-Δ²-3-formyl derivative (XVd) with cyclohexylamine as already described afforded the 17β-*benzoyl-imine* (XVf) (94%), m.p. 191—193°, $[\alpha]_D^{23}$ +90° (*c* 0·47); $\nu_{max.}$ 1648 (C=N), 1624 (C=C), 1713,

[9] J. C. Orr, O. Halpern, P. G. Holton, F. Alvares, L. Delfin, A. de la Roz, A. M. Ruiz, and A. Bowers, *J. Medicin. Chem.*, 1963, **6**, 166.

1605, and 1586 (OBz) cm.$^{-1}$ (Found: C, 81·3; H, 9·3; N, 3·05. $C_{33}H_{45}NO_2$ requires C, 81·25; H, 9·3; N, 2·85%).

A suspension of the enal (XVd) (0·528 g.), dry methanol (8 ml.), and t-butylamine (0·475 g.) was heated at reflux under nitrogen for 15 min., cooled, and filtered to yield *3-t-butyliminomethyl-5α-androst-2-en-17β-ol 17-benzoate* (XVg) (0·481 g., 80%), m.p. 150·5—151·5°, $[\alpha]_D^{23}$ +93° (*c* 1·02); $\lambda_{max.}$ 231 nm. (ε 33,600); $\nu_{max.}$ 1647 (C=N), 1625 (C=C), 1714, 1609, and 1589 (OBz) cm.$^{-1}$ (Found: C, 79·95; H, 9·4; N, 2·75. $C_{31}H_{43}NO_2$ requires C, 80·65; H, 9·4; N, 3·05%).

N-(*2-Cyclohexylidene-ethylidene*)*cyclohexylamine* (XVIIIb) *and the N-t-Butyl Analogue* (XVIIIc).—The *N*-cyclohexylallylideneamine (XVIIIb), b.p. 99—102°/0·05 mm., was prepared according to the method reported previously,[5] and purified by distillation.

In the same way, cyclohexanone was condensed with *diethyl β-(t-butylimino)ethylphosphonate* to give N-(*2-cyclohexylidene-ethylidene*)-*t-butylamine* (XVIIIc) (68%), b.p. 46—47°/0·007 mm., $\lambda_{max.}$ 240 nm. (ε 21,300); $\nu_{max.}$ (CCl_4) 1649 (C=N) and 1614 (C=C) cm.$^{-1}$. The *phosphonate*, m.p. 60·5—62·0° (from ether–pentane), $\nu_{max.}$ (CCl_4) 3413, 3280, 3232 (enamino-NH), and 1627 (C=N and enamino-C=C) cm.$^{-1}$ (Found: C, 50·85; H, 9·65; N, 6·4; P, 13·75. $C_{10}H_{22}NO_3P$ requires C, 51·05; H, 9·45; N, 5·95; P, 13·15%), was prepared in 54% yield from diethyl formylmethylphosphonate and t-butylamine in a similar manner to that described in the literature.[5]

N-(*2-Benzylidene-ethylidene*)-*t-butylamine* (XXI).—A mixture of cinnamaldehyde (2·494 g.), dry methanol (10 ml.), and t-butylamine (2·07 g.) was refluxed under nitrogen for 30 min. and evaporated. The residue was distilled to afford the *imine* (XXI) (2·80 g., 79%), b.p. 132—133°/10 mm., $\lambda_{max.}$ 217, 223, 229, and 284 nm. (ε 15,600, 17,800, 13,700, and 32,300); $\nu_{max.}$ (CCl_4) 1633 (C=N) and 1617 (C=C) cm.$^{-1}$ (Found: C, 83·4; H, 9·3; N, 7·3. $C_{13}H_{17}N$ requires C, 83·35; H, 9·15; N, 7·48%).

N-(*But-2-enylidene*)-*t-butylamine* (XXIII).—Crotonaldehyde (43·4 g.) in methanol (215 ml.) was heated at reflux with t-butylamine (67·56 g.) and acetic acid (0·5 ml.) for 20 min. under nitrogen. Evaporation at 30°/50 mm. followed by vacuum-distillation of the residue yielded N-(*but-2-enylidene*)-*t-butylamine* (XXIII) (25·5 g., 33%), b.p. 72°/65 mm., $\lambda_{max.}$ 221 nm. (ε 19,500); $\nu_{max.}$ 1657 (C=N) and 1626 (C=C) cm.$^{-1}$ (Found: C, 76·2; H, 12·05; N, 11·0. $C_8H_{15}N$ requires C, 76·75; H, 12·1; N, 11·2%).

Treatment of the 3β-Hydroxy-Δ^{16}*-17-carbaldehyde* (Va) *with Diethylaluminium Cyanide at 0°.*—To the enal (Va) (0·15 g., 0·5 mmole) in dry toluene (15 ml.) cooled in ice was added a solution (1·1 ml.) of the cyanide (2·3 mmoles) in toluene; the mixture was kept at 0° under nitrogen for 30 min., poured into a mixture of 2N-hydrochloric acid and ice, and extracted with dichloromethane. Crystallisation of the product from dichloromethane gave *3β,20ξ-dihydroxypregna-5,16-diene-21-nitrile* (Vc) (0·138 g., 84%), m.p. 170—171·5°, $[\alpha]_D^{24}$ −71° (*c* 1·07); $\nu_{max.}$ (KBr) 3450, 3347 (OH), and 2244 (CN) cm.$^{-1}$ (Found: C, 76·1; H, 9·1; N, 4·25. $C_{21}H_{29}NO_2$ requires C, 77·0; H, 9·0; N, 4·3%).

Hydrocyanation of the 3β-Acetoxy-Δ^{16}*-17-carbaldehyde* (Vb) *with Diethylaluminium Cyanide at Room Temperature.*—A solution (1·3 ml.) of the cyanide (2·3 mmoles) in toluene was added to the enal (Vb) (0·20 g., 0·584 mmole) in dry benzene (3 ml.). After 5 hr. at room temperature the mixture was poured into 0·4N-potassium hydroxide in 80% methanol, maintained at −30°. After 10 min., the mixture was mixed with ice–water and extracted with dichloromethane. Crystallisation of the product (0·22 g.) from dichloromethane–ether yielded *3β-acetoxy-16α-cyanoandrost-5-ene-17β-carbaldehyde* (VI) (92 mg., 43%), m.p. 196—199°. The residue from the mother liquor was chromatographed; benzene–dichloromethane (9 : 1) eluted more (VI) (31 mg., 15%), m.p. 194—197°. A pure sample melts at 208—211°, $[\alpha]_D^{24}$ −0·2° (*c* 1·03); $\nu_{max.}$ 2722 (aldehyde CH), 2232 (CN), and 1725 (OAc and CHO) cm.$^{-1}$ (Found: C, 74·85; H, 8·15; N, 4·0. $C_{23}H_{31}NO_3$ requires C, 74·75; H, 8·45; N, 3·8%).

Attempted Conjugate Hydrocyanation of the α-Enals (Xb), (XIIb), (XVc), *and* (XVIIIa).—The α-enals (Xb), (XIIb),[9] (XVc), and (XVIIIa) were treated with an excess (5—8 mol.) of diethylaluminium cyanide in benzene–toluene or dichloromethane–toluene for up to 50 hr. at room temperature. Treatment of the solutions with 2N-hydrochloric acid at low temperature and work-up gave crude products. I.r. spectra and t.l.c. indicated that the 1,2-adduct was a major product in each case. Treatment of the products with N-potassium hydroxide gave the starting enals or their hydrolysis products; only small amounts (if any) of the 1,4-adduct were detected. A similar result was obtained when compound (XVIIIa) was treated with hydrogen cyanide (5 mol.) and ethylaluminium dichloride (7 mol) in tetrahydrofuran.

Attempted Desulphurisation of the 16α-Cyano-17β-thiocarboxylate (VIIIa).—Compound (VIIIa) in acetone–ethanol (1 : 1) or acetone–water (3 : 1) was refluxed with pre-deactivated or non-deactivated Raney nickel W-1 (ten parts by wt.) for 0·5—1 hr. Work-up gave a mixture, which consisted of either starting material and β-cyanoaldehyde (VIIIb) or an over-reduced material (probably the 16α-aminomethyl-17β-hydroxymethyl derivative) and (VIIIb); the yield of (VIIIb) was <20% in each case. Use of Raney nickel W-2 or W-3 gave a similar result. Only starting material was recovered after treatment with Raney nickel W-2 in the presence of 1,2-dianilinoethane.[7]

In contrast, desulphurisation [6] of 3β-acetoxyandrost-5-ene-17β-thiocarboxylate (IXa) gave the aldehyde (IXb) and a minor amount of the 17β-hydroxymethyl compound.

Hydrocyanation of 2-Cyclohexyliminomethyl-5α-androst-2-en-17β-ol (XIIc).—(a) *With diethylaluminium cyanide.* To compound (XIIc) (0·914 g., 0·00238 mole) in dry tetrahydrofuran (9 ml.) was added a solution (9 ml.) of the cyanide (0·012 mole) in benzene. After 35 min. at room temperature the mixture was poured into a mixture of 2N-hydrochloric acid and ice, and extracted with methanol-free dichloromethane. A mixture of the residue (1·03 g.) from the extracts, benzene (12 ml.), tetrahydrofuran (6 ml.), and 5% oxalic acid (12 ml.) was refluxed with stirring for 1 hr. under nitrogen, cooled, neutralised with sodium hydrogen carbonate, and extracted with dichloromethane. The product (0·925 g.) was chromatographed on acid alumina. Gradient elution with benzene–dichloromethane (1 : 0 to 9 : 1) yielded material (0·14 g.) which was crystallised from dichloromethane–ether to give *2ξ-(1-cyanocyclohexylaminomethyl)-17β-hydroxy-5α-androstane-3α-carbonitrile* (XIVb) (91 mg., 8·8%), m.p. 187—190°, $[\alpha]_D^{23}$ +48° (*c* 1·00), $\nu_{max.}$ 3617, 3312 (OH, NH), and 2225 (CN) cm.$^{-1}$ (Found: C, 77·1; H, 9·9; N, 9·55. $C_{28}H_{43}N_3O$ requires C, 76·85; H, 9·9; N, 9·6%).

Further elution with benzene–dichloromethane (4 : 1) and dichloromethane–methanol (99 : 1) afforded a material (0·44 g.) which yielded *3α-cyano-17β-hydroxy-5α-androstane-2α-carbaldehyde* (XIIIa) (0·345 g., 57%), m.p. 137—143/

191—192° (from dichloromethane–ether), $[\alpha]_D^{23}$ +79° (*c* 1·02); $\nu_{max.}$ 3617, 3424 (OH), 2235 (CN), 2716, and 1728 (CHO) cm.$^{-1}$ (Found: C, 75·2; H, 9·35; N, 4·3. $C_{21}H_{31}NO_2$ requires C, 76·55; H, 9·5; N, 4·25%). To the residue (0·25 g.) from the mother liquor were added 2,4-dinitrophenylhydrazine (0·155 g.) in dimethylformamide (4 ml.) and concentrated hydrochloric acid (1 drop). The mixture was kept at room temperature for 40 min., and 2N-hydrochloric acid was added dropwise until the product started to crystallise. The crystals gave the *2,4-dinitrophenylhydrazone* of (XIIIa) (0·118 g., 9·8%), m.p. 271—272° (from dichloromethane–methanol), $[\alpha]_D^{21}$ +156° (*c* 1·02); $\nu_{max.}$ 3611, 3302 (OH, NH), 2220 (CN), 1621 (C=N), 1595 (aromatic), 1509, and 1335 (NO_2) cm.$^{-1}$ (Found: C, 63·15; H, 6·9; N, 13·5. $C_{27}H_{35}N_5O_5$ requires C, 63·6; H, 6·9; N, 13·75%).

The *semicarbazone* of (XIIIa) had m.p. 268—271°, $\nu_{max.}$ (KBr) 3441 (OH, NH), 2221 (CN), 1640 (C=N), 1690, and 1589 (amide C=O) cm.$^{-1}$ (Found: C, 67·85; H, 8·7; N, 13·15. $C_{22}H_{34}N_4O_2$ requires C, 68·35; H, 8·85; N, 14·5%).

Treatment of the 3α-cyano-2α-formyl-17β-ol (XIIIa) with benzoyl chloride in pyridine afforded *17β-benzoyloxy-3α-cyano-5α-androstane-2α-carbaldehyde* (XIIIb), m.p. 237—240° (from acetone), $[\alpha]_D^{23}$ +101° (*c* 0·81); $\nu_{max.}$ 2230 (CN), 2718, 1727 (CHO), 1714, 1604, and 1586 (OBz) cm.$^{-1}$; δ 0·867 (3H, s, 19-H), 0·934 (3H, s, 18-H), 2·542 (1H, td, J_t 4, J_d 13 Hz, 2β-H), 3·250 (1H, m, $W_{\frac{1}{2}}$ 8 Hz, 3β-H), 6·157 (1H, m, 17α-H), and 10·366 (1H, s, 2α-CHO) p.p.m. (Found: C, 77·65; H, 8·25; N, 3·0. $C_{28}H_{35}NO_3$ requires C, 77·55; H, 8·15; N, 3·25%).

(b) *With hydrogen cyanide–triethylaluminium.* To compound (XIIc) (1·327 g., 0·00346 mole) in dry tetrahydrofuran was added a solution of hydrogen cyanide (0·011 mole) and triethylaluminium (0·017 mole) in tetrahydrofuran (10 ml.). After 20 min. at room temperature the mixture was poured into a mixture of ice and 2N-hydrochloric acid, and extracted with dichloromethane. The product (1·58 g.) yielded 2ξ-(1-*cyanocyclohexylaminomethyl*)-17β-*hydroxy-5α-androstane-3α-carbonitrile* (XIVa′) (1·519 g., 96%), m.p. 125—127° (from dichloromethane–ether), $\nu_{max.}$ 3690, 3620 (OH), 3483 (NH, H_2O), 2220 (CN), and 1603 (H_2O) cm.$^{-1}$ (Found: C, 74·45; H, 10·2; N, 9·4. $C_{28}H_{43}N_3O,H_2O$ requires C, 73·8; H, 9·95; N, 9·9%).

Hydrocyanation of 2-Cyclohexyliminomethyl-5α-androst-2-en-17β-ol 17-Benzoate (XIId).—(a) *With diethylaluminium cyanide.* To the benzoate (XIId) (85 mg., 0·21 mmole) in tetrahydrofuran (0·7 ml.) was added a solution (0·7 ml.) of the cyanide (1·05 mmoles) in benzene. After 23 hr. at room temperature the mixture was poured into a mixture of 2N-hydrochloric acid and ice, and extracted with chloroform. The product showed $\nu_{max.}$ 3400 (NH), 2230 (CN), 1710, 1604, and 1587 (OBz) cm.$^{-1}$. Treatment with 5% oxalic acid in benzene–tetrahydrofuran as before yielded material (70 mg.) identical (i.r. spectrum and t.l.c.) with authentic 17β-benzoyloxy-5α-androst-2-ene-2-carbaldehyde.

(b) *With diethylaluminium cyanide and propan-2-ol.* A solution (4·1 ml.) of the cyanide (5 mmoles) in benzene was added to the imine (XIId) (0·488 g., 1·0 mmole) in tetrahydrofuran (5·7 ml.) containing propan-2-ol (1·0 mmole). After 30 min. at 25° the mixture was poured into a mixture of 2N-hydrochloric acid and ice, and extracted with ether–dichloromethane (3 : 1). A solution of the residue (0·5 g.) from the extracts in tetrahydrofuran (8 ml.), ethanol (8 ml.), and 5% oxalic acid (8 ml.) was refluxed under nitrogen for 40 min., poured into ice–water, and neutralised with sodium hydrogen carbonate in the presence of dichloromethane with stirring. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layer and the extracts yielded material (0·43 g.) which afforded the β-cyano-aldehyde (XIIIb) (0·253 g.), m.p. 236—239° (from dichloromethane–acetone). The residue from the mother liquor was chromatographed on acid alumina. Gradient elution with benzene–dichloromethane (1 : 0 to 2 : 1) yielded more (XIIIb) (45 mg.), m.p. 236—238° (total yield 69%).

(c) *With hydrogen cyanide–triethylaluminium.* To the imine (XIId) (0·488 g., 1·0 mmole) in tetrahydrofuran (3 ml.) was added a solution of hydrogen cyanide (3 mmoles), and triethylaluminium (5 mmoles) in tetrahydrofuran (2·5 ml.). After 20 min. at 25° the mixture was worked up as in (*b*). Purification of the product (0·45 g.) as in (*b*) gave the nitrile (XIIIb) (0·291 g., 67%), m.p. 237—240°.

5-Cyano-3β-hydroxy-B-nor-5α-androstane-6β-carbaldehyde (XI).—To the B-nor-imine (Xd) (0·50 g., 1·35 mmole) was added a solution of hydrogen cyanide (6·8 mmoles) and ethylaluminium dichloride (9·5 mmoles) in tetrahydrofuran (5·5 ml.). After 20 hr. at room temperature in a sealed ampoule, the mixture was worked up and the residue (0·58 g.) from the extracts was treated with 5% oxalic acid in ethanol–tetrahydrofuran as before. The product (0·43 g.) was chromatographed on acid alumina. Gradient elution with benzene–dichloromethane and dichloromethane gave the *B-nor-cyano-aldehyde* (XI) (0·21 g., 49%), m.p. 141·5—143·5° (from ether–petane), $[\alpha]_D^{23}$ −71° (*c* 1·06); $\nu_{max.}$ 3630 (OH), 2724, 1728 (CHO), and 2210 (CN) cm.$^{-1}$ (Found: C, 75·95; H, 9·3; N, 4·4. $C_{20}H_{29}NO_2$ requires C, 76·15; H, 9·25; N, 4·45%). Preparative t.l.c. of the mother liquor gave more (XI) (23 mg., 6%), m.p. 139—141°.

Hydrocyanation of 17-Cyclohexyliminomethylandrosta-5,16-diene-3β-ol 3-Acetate (Vd).—(a) *With hydrogen cyanide–triethylaluminium.* Compound (Vd) (0·37 g., 0·873 mmole) was treated with a solution of hydrogen cyanide (2·6 mmoles) and triethylaluminium (3·5 mmoles) in tetrahydrofuran (2·1 ml.) at 25° for 30 min. The usual work-up followed by treatment of the residue from the extracts with 5% oxalic acid as before afforded a non-crystallisable material which was chromatographed. Gradient elution with benzene–dichloromethane (1 : 0 to 1 : 1) gave the 16α-cyano-17β-formyl compound (VI) (80 mg., 25%), m.p. 208—211° (from dichloromethane–acetone). Fractions (0·15 g.) eluted with dichloromethane and dichloromethane–methanol (100 : 1 and 75 : 1) were rechromatographed. Dichloromethane–methanol (200 : 1) eluted *3β-acetoxy-1′-cyclohexyl-5′-imino-16β,17β-androst-5-eno*[16,17-c]*pyrrolidine-2′ξ-carbonitrile* (VII) (26 mg., 6·2%), m.p. 193—195° (from ether), $[\alpha]_D^{20}$ −123° (*c* 0·47); $\nu_{max.}$ 3333 (OH), 2241 (CN), 1729 (OAc), and 1614 (C=N) cm.$^{-1}$ (Found: C, 75·4; H, 9·3; N, 8·8. $C_{30}H_{43}N_3O_2$ requires C, 75·45; H, 9·05; N, 8·8%).

(b) *With diethylaluminium cyanide and propan-2-ol.* A solution (5·6 ml.) of the cyanide (5·9 mmoles) in toluene was added to the imine (Vd) (0·498 g., 1·17 mmole) in tetrahydrofuran (5·3 ml.) containing propan-2-ol (1·2 mmole). After 1 hr. at 21° the mixture was worked up in the usual way. Treatment of the residue from the extracts with 5% oxalic acid and chromatography as described in (*a*) afforded the β-cyano-aldehyde (VI) (0·203 g., 47%), m.p. 204—208°.

Hydrocyanation of 3-Cyclohexyliminomethyl-5α-androst-2-en-17β-ol 17-Benzoate (XVf).—Compound (XVf) (2·501 g., 5·13 mmoles) in dry tetrahydrofuran (10 ml.) was treated with a solution of hydrogen cyanide (15 mmoles) and tri-

ethylaluminium (25 mmoles) in tetrahydrofuran (12 ml.) at 25° for 1 hr. The usual work-up and treatment of the residue from the extracts with 5% oxalic acid in ethanol–tetrahydrofuran as before afforded material (2·6 g.) which was chromatographed on acid alumina. Benzene eluted the Δ^2-3-formyl compound (XVd) (0·283 g.). Fractions (0·42 g.) eluted with benzene–dichloromethane (9 : 1 to 1 : 1) were crystallised from dichloromethane–ether to give 17β-*benzoyloxy*-2β-*cyano*-5α-*androstane*-3β-*carbaldehyde* (XVIb) (0·143 g., 7·2%), m.p. 248—252°, $[\alpha]_D^{23}$ +54° (*c* 0·97); $\nu_{max.}$ 2714, 1728 (CHO), 2212 (CN), 1714, 1604, and 1587 (OBz) cm.$^{-1}$; δ 0·934 (3H, s, 18-H), 1·134 (3H, s, 19-H), 2·220 (1H, q, $J_{app.}$ 1·4 and 2·5 Hz, 3α-H; on irradiation at δ 3·267 p.p.m., the quartet collapsed to a doublet, *J* 14 Hz), 3·267 (1H, m, 2α-H; on irradiation on 3α-H, the multiplet changed to a triplet, *J* 5 Hz), 6·500 (1H, m, 17α-H), and 10·333 (3α-CHO) p.p.m. (Found: C, 77·1; H, 8·2; N, 3·3. $C_{28}H_{35}NO_3$ requires C, 77·55; H, 8·15; N, 3·25%). More (XVIb) (65 mg., 3·3%), m.p. 236—240°, was obtained from the mother liquor by rechromatography. Fractions (0·9 g.) eluted with dichloromethane–methanol (75 : 1 and 50 : 1) from the initial column were rechromatographed. Elution with benzene–dichloromethane (1 : 1) and dichloromethane–methanol (100 : 1) afforded 17β-*benzoyloxy*-1′-*cyclohexyl*-5′-*imino*-2α,3α,5α-*androstano*[2,3-c]*pyrrolidine*-2′-α-*carbonitrile* (XVIIa) (0·282 g., 12%), m.p. 274—276° (from dichloromethane–acetone), $[\alpha]_D^{20}$ +58° (*c* 0·54); $\nu_{max.}$ 3308 (NH), 2216 (CN), 1629 (C=N), 1711, 1602, and 1585 (OBz) cm.$^{-1}$; δ 0·717 (3H, s, 19-H), 0·917 (3H, s, 18-H), 2·734 (1H, t, *J* 7 Hz, 2α-H), 3·834 (1H, s, 2′β-H), 4·034 (m, 1H, cyclohexyl proton on the carbon adjacent to the nitrogen atom), 4·717 (1H, m, 17α-H), and 5·384br (1H, s, NH) p.p.m. (Found: C, 77·2; H, 8·95; N, 7·4. $C_{35}H_{47}N_3O_2$ requires C, 77·6; H, 8·75; N, 7·75%). Elution of the initial column with dichloromethane–methanol (25 : 1) gave material (0·82 g.) which was rechromatographed. Elution with dichloromethane and dichloromethane–methanol (100 : 1 and 50 : 1) yielded the 2′β-*cyano*-*analogue* (XVIIb) (0·395 g., 17%), m.p. 266—268° (from dichloromethane–ether). A pure sample melts at 275—276°, $[\alpha]_D^{20}$ +5·2° (*c* 0·21); $\nu_{max.}$ 3306 (NH), 2215 (CN), 1629 (C=N), 1712, 1602, and 1585 (OBz) cm.$^{-1}$; δ 0·767 (3H, s, 19-H), 0·917 (3H, s, 18-H), 2·467 (1H, m, 2α-H), 4·000 (1H, m, cyclohexyl proton on the carbon adjacent to the nitrogen atom), 4·334 (1H, d, *J* 6 Hz, 2′α-H), 4·817 (1H, m, 17α-H), and 5·284br (1H, s, NH) p.p.m. (Found: C, 77·5; H, 8·9; N, 7·75. $C_{35}H_{47}N_3O_2$ requires C, 77·6; H, 8·75; N, 7·75%).

Hydrocyanation of N-(2-*Cyclohexylidene-ethylidene*)*cyclohexylamine* (XVIIIb).—To the imine (XVIIIb) (2·423 g., 0·0118 mole) in dry tetrahydrofuran (14 ml.) at −10° was added a solution of hydrogen cyanide (0·035 mole) and triethylaluminium (0·059 mole) in tetrahydrofuran (30 ml.). After 2·5 hr. at −10° the mixture was poured into a mixture of 2N-sodium hydroxide (100 ml.) and ice–water (500 ml.), and extracted with dichloromethane. A mixture of the residue (3·0 g.) from the extracts, benzene (60 ml.), and 5% oxalic acid (180 ml.) was refluxed with stirring for 70 min. The benzene layer was separated, and the aqueous layer was extracted twice with ether. The neutral portion (1·19 g.) from the organic layers was dissolved in dimethylformamide (10 ml.) and to the solution were added 2,4-dinitrophenylhydrazine (1·55 g.) in dimethylformamide (20 ml.), concentrated hydrochloric acid (3 drops), and finally 2N-hydrochloric acid until the product started to crystallise. The crystals were filtered off, washed with cold methanol, and dried to give the 2,4-*dinitrophenylhydrazone* of 1-formylmethylcyclohexanecarbonitrile (XIX) (1·536 g., 39%), m.p. 143—146·5°. A pure sample melts at 146—148°, $\nu_{max.}$ 3412 (NH), 2222 (CN), 1618 (C=N), 1597 (aromatic), 1513, and 1336 (NO_2) cm.$^{-1}$ (Found: C, 54·55; H, 5·45; N, 20·85. $C_{18}H_{17}N_5O_4$ requires C, 54·35; H, 5·15; N, 21·15%). The aqueous layer from the isolation of the neutral product was made alkaline with 2N-sodium hydroxide and extracted with dichloromethane. The basic product (1·13 g.) was crystallised from ether–pentane to give 2-*cyclohexyl*-1-*imino*-2-*azaspiro*[4,5]*decane*-3-*carbonitrile* (XXa) (0·746 g., 24%), m.p. 115·5—117°, $\nu_{max.}$ 3320 (NH), 2234 (CN), and 1630 (C=N) cm.$^{-1}$ (Found: C, 74·4; H, 9·7; N, 16·0. $C_{16}H_{25}N_3$ requires C, 74·1; H, 9·7; N, 16·2%).

Reaction of the Δ^{16}-*t-Butyliminomethyl Steroid* (Ve) *with Hydrogen Cyanide–Triethylaluminium*.—Compound (Ve) (0·138 g., 0·347 mmole) in tetrahydrofuran (1·8 ml.) containing water (0·35 mmole) was treated with a solution of hydrogen cyanide (1·0 mmole) and triethylaluminium (1·7 mmole) in tetrahydrofuran (1 ml.) at room temperature for 1·5 hr. Work-up as described for the *N*-cyclohexyliminoanalogue (Vd) followed by crystallisation from dichloromethane–ether afforded the 16α-cyano-17β-carbaldehyde (VI) (63 mg., 47%), m.p. 209—211°. The residue from the mother liquor was rechromatographed. Benzene eluted more (VI) (9 mg., 8%), m.p. 192—195°. Fractions (31 mg.) eluted with dichloromethane and dichloromethane–methanol (98 : 2) had an i.r. spectrum consistent with the iminopyrrolidine structure (VII; *N*-Bu^t instead of *N*-C_6H_{11}), but were not purified.

Hydrocyanation of the Δ^2-3-*t-Butylimino-derivative* (XVg).—The imine (XVg) (0·366 g., 0·793 mmole) was hydrocyanated, as described for the reaction of (Ve), for 2 hr. The product (0·37 g.) obtained after treatment with 5% oxalic acid was crystallised from dichloromethane–ether to give the 2β-cyano-3β-formyl steroid (XVIb) (0·222 g., 64%), m.p. 231·5—233°.

Hydrocyanation of N-(2-*Cyclohexylidene-ethylidene*)-*t-butylamine* (XVIIIc).—Compound (XVIIIc) (0·345 g., 1·92 mmole) in dry tetrahydrofuran (1 ml.) was treated with hydrogen cyanide (5·8 mmoles) and triethylaluminium (9·6 mmoles) in tetrahydrofuran (4·5 ml.) at room temperature for 30 min. Work-up as described for compound (XVIIIb) afforded a neutral portion (0·255 g.) and a basic portion (61 mg.). Crystallisation of the neutral product from ether–pentane yielded 1-*formylmethylcyclohexanecarbonitrile* (XIX) (0·158 g., 54%), m.p. 37°, $\nu_{max.}$ (CCl_4) 2725, 1736 (CHO), and 2216 (CN) cm.$^{-1}$ (Found: C, 71·3; H, 8·6; N, 9·4. $C_9H_{13}NO$ requires C, 71·5; H, 8·65; N, 9·25%). The residue (89 mg.) from the mother liquor was treated with 2,4-dinitrophenylhydrazine (117 mg.) as already described to give the 2,4-dinitrophenylhydrazone of (XIX) (0·114 g., 18%), m.p. 146—148°. The basic portion afforded 1-*imino*-2-*t-butyl*-2-*azaspiro*[4,5]*decane*-3-*carbonitrile* (XXb) (50 mg., 11%), m.p. 108—109° (from ether–pentane), $\nu_{max.}$ (CCl_4) 3303 (NH), 2216 (CN), and 1632 (C=N) cm.$^{-1}$ (Found: C, 72·05; H, 9·9; N, 18·0. $C_{14}H_{23}N_3$ requires C, 72·05; H, 9·95; N, 18·0%).

2-*Phenylsuccinaldehydronitrile* (XXII).—To *N*-(2-benzylidene-ethylidene)-t-butylamine (XXI) (1·026 g., 0·00548 mole) in dry tetrahydrofuran (3 ml.) was added a solution of hydrogen cyanide (0·016 mole) and triethylaluminium (0·027 mole) in tetrahydrofuran (14 ml.). After 26 hr. at room temperature the mixture was treated as described

for compound (XVIIIb) to give a neutral portion (0·58 g.) as an oil and a basic portion (0·28 g.). Distillation of the neutral product afforded the cyano-aldehyde (XXII) (0·474 g., 54%), b.p. 129—132°/6 mm.; $\nu_{max.}$ (CCl_4) 2723, 1735 (CHO), and 2238 (CN) cm.$^{-1}$ (Found: C, 74·55; H, 5·85; N, 8·65. $C_{10}H_9NO$ requires C, 75·45; H, 5·7; N, 8·8%). The 2,4-dinitrophenylhydrazone melted at 146—147° (from dichloromethane–methanol); $\nu_{max.}$ 3308 (NH), 2236 (CN), 1620, 1598 (C=N and aromatic), 1512, and 1337 (NO_2) cm.$^{-1}$. The basic portion was not examined further.

2-*Methylsuccinaldehydronitrile*.—To *N*-(2-butenylidene)-t-butylamine (XXIII) (1·90 g., 0·0152 mole) in dry tetrahydrofuran was added a solution of hydrogen cyanide (0·046 mole) and triethylaluminium (0·076 mole) in tetrahydrofuran (36 ml.) at 0°. After 1 hr. at 0° the mixture was poured into a mixture of 2N-sodium hydroxide (400 ml.) and ice, and extracted with ether. The residue (2·42 g.) from the extracts was heated with 10% oxalic acid (100 ml.) at 60° for 1 hr. under nitrogen. The mixture was cooled, salted out, and extracted with dichloromethane. The combined extracts were washed with water, dried, and divided into two equal portions. Each was distilled through a Vigreux column below 75° to remove the bulk of the dichloromethane, and the residue was evaporated at 25°/20 mm. The resulting oil showed $\nu_{max.}$ (CCl_4) 2726, 1732 (CHO), and 2247 (CN) cm.$^{-1}$, consistent with structure (XXIV). The product (0·265 g.) from one portion in dimethylformamide (1 ml.) was treated with 2,4-dinitrophenylhydrazine (0·54 g.) in dimethylformamide (5·4 ml.) to give the 2,4-*dinitrophenylhydrazone* of the β-cyano-aldehyde (XXIV) (0·321 g., 15%), m.p. 125—127°. Recrystallisation from dichloromethane–methanol afforded a pure sample, m.p. 127—128·5°, $\nu_{max.}$ 3308 (NH), 2240 (CN), 1620, 1597 (C=N and aromatic), and 1510 and 1340 (NO_2) cm.$^{-1}$ (Found: C, 47·65; H, 4·0; N, 24·95. $C_{11}H_{11}N_5O_4$ requires C, 47·65; H, 4·0; N, 25·25%). To the crude compound (XXIV) (0·215 g.) from the other portion in ethanol (3 ml.) was added a hot solution of thiosemicarbazide (0·20 g.) in water (4 ml.), and the resulting turbid mixture was set aside for 2 weeks. The crystals formed were washed with cold ethanol, and dried to give the *thiosemicarbazone* of (XXIV) (0·131 g., 10%), m.p. 151·5—153°. A sample obtained by recrystallisation from dichloromethane–methanol melted at 151·5—152·0°; $\nu_{max.}$ (Nujol) 3423, 3262 (NH, NH_2), 2232 (CN), 1616, 1602, and 1550 (C=N, and thioamide) cm.$^{-1}$ (Found: C, 42·55; H, 6·1; N, 32·85; S, 18·45. $C_6H_{10}N_4S$ requires C, 42·35; H, 5·9; N, 32·9; S, 18·85%). The oxalic acid layer from the isolation of the β-cyano-aldehyde (XXIV) was made alkaline with 2N-sodium hydroxide and extracted with dichloromethane to give a basic product (0·76 g., 28%), which was not examined further.

3β-*Acetoxy*-20ξ,21-*dihydroxypregn*-5-*ene*-16α-*carbonitrile* (XXVII).—Sodium borohydride (29 mg.) was added to 3β-acetoxy-21-hydroxy-20-oxopregn-5-ene-16α-carbonitrile (XXVI) [1] (0·20 g.) in methanol (15 ml.). The mixture was stirred at room temperature for 25 min., mixed with acetic acid (3 drops), poured into water, and extracted with chloroform. The product (0·22 g.) afforded the 20,21-*diol* (XXVII) (0·143 g.), m.p. 238—240° (from acetone–methanol), $[\alpha]_D^{22}$ −70° (*c* 1·05); $\nu_{max.}$ 3615, 3559 (OH), 2244 (CN), and 1736 (OAc) cm.$^{-1}$ (Found: C, 71·05; H, 8·45; N, 3·55. $C_{24}H_{35}NO_4$ requires C, 71·8; H, 8·8; N, 3·5%).

3β-*Acetoxy*-16α-*cyanoandrost*-5-*ene*-17β-*carbaldehyde* (VI).—Periodic acid dihydrate (0·1 g.) in water (0·3 ml.) was added to the 20,21-diol (XXVII) (0·079 g.) in methanol (45 ml.), and the mixture was kept at room temperature for 80 min. The crystals deposited were filtered off, washed with water, and dried to give the 16α-cyano-17β-formyl steroid (VI) (0·070 g., 96%), m.p. 200—203°. Recrystallisation from dichloromethane–ether afforded a sample, m.p. 206—210°, identical with the samples of (VI) prepared from the enal (Vb) and the imines (Vd) and (Ve).

Reaction of the 5α-*Cyano*-6β-*formyl*-B-*nor-steroid* (XI) *with Methylmagnesium Iodide*.—Compound (XI) (82 mg.) in tetrahydrofuran (8 ml.) was treated with an ethereal solution of methylmagnesium iodide (3 mol.) at 0° for 35 min. The mixture was poured into a mixture of 2N-hydrochloric acid and ice, and extracted with dichloromethane. Preparative t.l.c. of the product as reported previously [3b] afforded two types of crystal, m.p. 185·5—186·0° (21 mg.) and m.p. 189—191° (8 mg.), identical with samples of the two epimeric 3β-hydroxy-6β-(1ξ-hydroxyethyl-B-nor-5α-androstane-5-carbonitriles (XXVIIIa and b).[3b]

Conversion of the 3α-*Cyano*-2α-*formyl Derivative* (XIIIb) *into* 17β-*Benzoyloxy*-3α-*cyano*-5α-*androstane*-2α-*carboxylic Acid* (XXIXa) *and the* 17-*Hydroxy*- (XXIXb) *and* 17-*Acetoxy-analogues* (XXIXc).—To the aldehyde (XIIIb) (0·217 g.) in acetone (50 ml.) cooled in ice was added Jones reagent (0·2 ml.). The mixture was stirred at 0° for 30 min., then poured into ice–water and extracted with dichloromethane. Crystallisation of the product from dichloromethane–methanol afforded the *acid* (XXIXa) (0·17 g., 76%), m.p. 274—275·5°, $[\alpha]_D^{23}$ +110° (*c* 1·02 in pyridine); $\nu_{max.}$ (KBr) 2228 (CN), 3400, 1755 (CO_2H), and 1716 (OBz) cm.$^{-1}$ (Found: C, 75·05; H, 7·85; N, 3·15. $C_{28}H_{35}NO_4$ requires C, 74·8; H, 7·85; N, 3·1%).

A mixture of compound (XXIXa) (0·15 g.), potassium carbonate (0·3 g.), methanol (25 ml.), and water (4·4 ml.) was refluxed for 5 hr., cooled, poured into 2N-hydrochloric acid, and extracted with dichloromethane–methanol (20 : 1). The crystalline product (0·143 g.) gave the 3α-*cyano*-17β-*hydroxy*-2α-*carboxylic acid* (XXIXb) (0·105 g., 92%), m.p. 253—254·5° (from dichloromethane–methanol), $[\alpha]_D^{22}$ +68° (*c* 0·98 in pyridine); $\nu_{max.}$ (KBr) 3447 (OH), 2230 (CN), and 1736 (CO_2H) cm.$^{-1}$ (Found: C, 72·9; H, 9·2; N, 4·35. $C_{21}H_{31}NO_3$ requires C, 73·0; H, 9·05; N, 4·05%).

Acetylation of compound (XXIXb) with acetic anhydride in pyridine yielded the acetate (XXIXc), m.p. 268—270°, identical with an authentic sample.[1]

3α-*Cyano*-17-*oxo*-5α-*androstane*-2α-*carboxylic Acid* (XXIXd).—(a) *From the* 2α-*formyl*-17β-*ol* (XXIXb). Compound (XXIXb) (35 mg.) was treated with Jones reagent as just described and the product (30 mg.) was chromatographed on alumina. Elution with dichloromethane–methanol–ethyl acetate (4·5 : 1 : 4·5) containing acetic acid (1%) afforded the *keto-acid* (XXIXd) (10 mg.), m.p. 236—238° (from dichloromethane–methanol–ether), $[\alpha]_D^{23}$ +122° (*c* 0·88 in pyridine); $\nu_{max.}$ (KBr) 2220 (CN), 3400, 1735 (CO_2H), and 1712 (C=O) cm.$^{-1}$ (Found: C, 73·65; H, 8·6; N, 4·35. $C_{21}H_{29}NO_3$ requires C, 73·45; H, 8·5; N, 4·1%).

(b) *From the* 2α-*formyl*-17-*ketone* (XIIIa). Compound (XIIIa) (20 mg.) was treated with Jones reagent. The product (20 mg.) afforded crystals, m.p. 242—243°, identical with the keto-acid (XXIXd) obtained in (a).

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