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Synthesis of Bridged Steroids. VI.[1] B-Norsteroids having a Gibbane B-C-D Ring System. (1). Synthesis of 5-Cyano-B-norsteroids *via* Hydrocyanation

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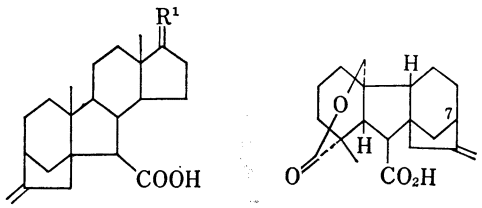
B-Nor-Δ^4-3-ketosteroids such as compounds (**11a, 11b, 11c, 17a, 17b** and **23**) were synthesized starting from Δ^5-3β-hydroxysteroids.

Hydrocyanation of these enones was investigated and by treatment with diethylaluminum cyanide only the 5β-vinyl derivatives (**17a, 17b** and **23**) gave successfully the corresponding 3-keto-5β-cyano compounds (**18a, 18b,** and **24a**), intermediates necessary for the synthesis of B-norsteroids having *cis*-bicyclo[3,2,1]octane ring system.

In a series of papers,[3] we have reported syntheses of cholestane derivatives having a bicyclo[3,2,1]octane ring system of the kaurene type and of the phyllocladene type starting from 5α-cyanocheolstan-3-one. In this and the accompanying[4] paper, the studies are extended to investigate new synthetic methods for preparation of some B-norsteroids (**1**) having the bicyclo[3,2,1]octane ring system with functionalities similar to those of 7-deoxygibberellins. The methods also serve as model experiments for a synthesis of gibberellin A_{15}[5] (**2**) which was isolated from *gibberella fujikuroi* as a minor phytohormone of high potency.[6]

The following approaches for the synthesis of **1** were planned at first. Starting from a B-norsteroid, its derivatives with a conjuga ted enone system and with a functionalized carbon chain at C-6 were first to be synthesized, then the latter might be converted into 5-cyano compounds by using the hydrocyanation recently developed by our group.[7] The introduced cyano group might be lengthened to a three-carbons chain, to be cyclized using a suitable functional group placed at C_3, as depicted in the sequence: (i)→(ii)→(iii)→(iv)→(v). The last two steps will be discussed in detail in Part VII.[4]



1 **2**

$R^1=H_2$, $\begin{matrix}\diagup OH \\ \diagdown H\end{matrix}$

Chart 1

1) Part V: W. Nagata, T. Sugasawa, and T. Aoki, *Chem. Pharm. Bull.* (Tokyo), **16**, 1556 (1968).
2) Location: *Fukushima-ku, Osaka.*
3) *a*) W. Nagata and M. Narisada, *Chem. Pharm. Bull.* (Tokyo), **16**, 867 (1968); *b*) W. Nagata, M. Narisada, and T. Wakabayashi, *ibid.*, **16**, 875 (1968).
4) Part VII: W. Nagata, T. Wakabayashi, M. Narisada, M. Yamaguchi, and Y. Hayase, *Chem. Pharm. Bull.* (Tokyo), **19**, 1582 (1971).
5) J.R. Hanson, *Tetrahedron*, **23**, 733 (1967).
6) B.E. Cross, R.H.B. Galt, and J.R. Hanson, "Regulations Natureles de la Croissance Vegetale," Centre National de la Recherche Scientifique, Paris, 1964, p. 265.
7) *a*) W. Nagata, M. Yoshioka, and S. Hirai, *Tetrahedron Lettets.*, **1962**, 461; *b*) W. Nagata and M. Yoshioka, *ibid.*, **1966**, 1913; *c*) For a full account, see: W. Nagata, M. Yoshioka, and S. Hirai, *J. Am, Chem, Soc.*, in press.

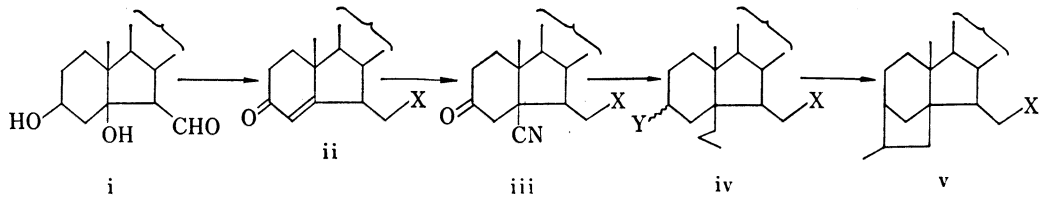


Chart 2

Synthesis of the starting B-norsteroid was carried out by the method of Tanabe, *et al.*[8] and an analog (**3b**), mp 100—102°, of the known formyl-B-norsteroid (**3a**)[8b] was prepared from androst-5-en-3β-ol acetate.[9] Applicability of the method to a 19-nor-compound was examined, as this was believed to be a better model for the synthesis of gibberellin A_{15}. Ozonolysis of estr-5-ene-3β, 17β-diol (**4**), which was synthesized according to the method reported by Hartman, *et al.*[10] with slight modifications, gave the crude *seco*-aldehyde (**5**) similarly, and treatment of (**5**) with neutral alumina in benzene resulted in formation of a by-product (**7a**) besides the major formyl-19, B-bisnorsteroid (**6a**), mp 188.5—190°. Both were acetylated to give the triacetate (**7b**), mp 190—192°, and the diacetate (**6b**), mp 164—167°, respectively. On the basis of similarlity of the infrared (IR) spctrum with that of the formyl-B-nor steroid (**3a**), the structure of (**6b**) was assigned as depicted, where the stereochemistry at C_3, C_5, C_6, and C_{10} was assumed to be the same as that[8c] of the B-norsteroid derivatives (**3a**) and (**3b**) by analogy (*vide infra*). The triacetate (**7b**) showed a shoulder at 1723 cm^{-1} in its IR spectrum indicating the presence of a ketocarbonyl group, supported further by a circular dichro-

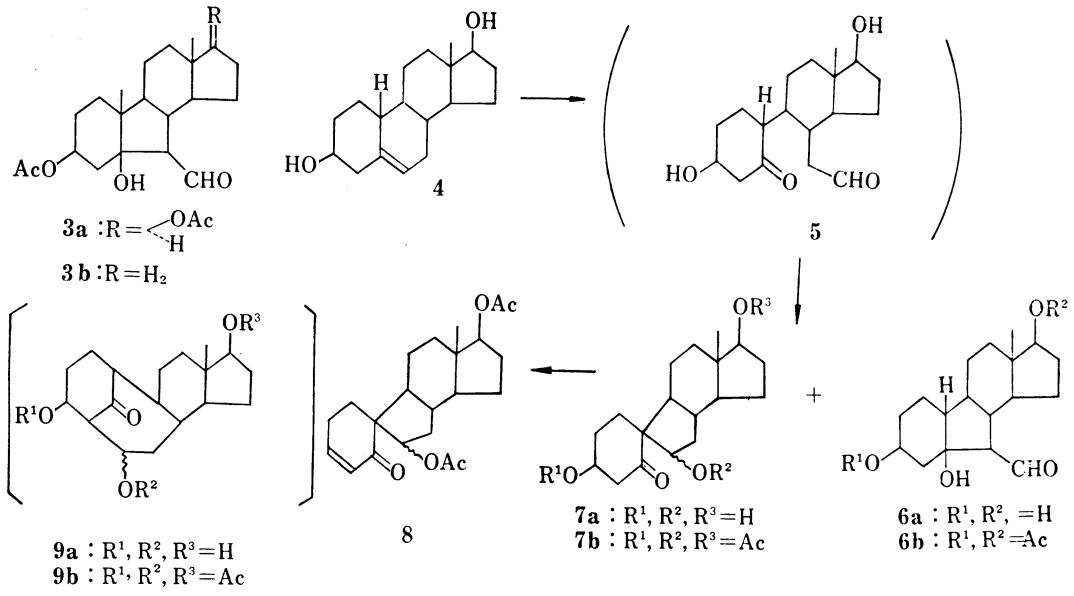


Chart 3

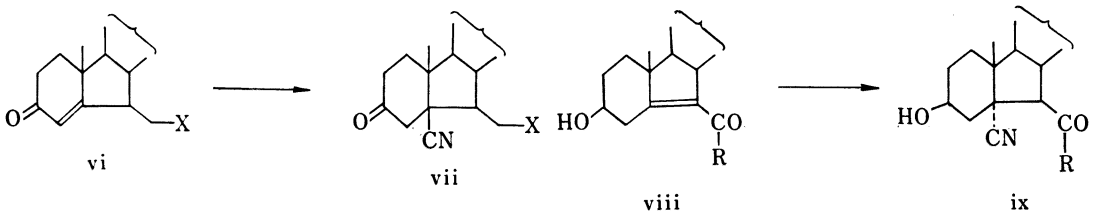
8) *a*) K. Tanabe and Y. Morisawa, *Chem. Pharm. Bull.* (Tokyo), **11**, 536 (1963); *b*) R. Takasaki, *ibid.*, **10**, 439 (1962); *c*) N. Tanabe, R. Hayashi, and R. Takasaki, *ibid.*, **9**, 12 (1961).

9) *a*) A. Butenandt and L.A. Suránvi, *Chem. Ber.*, **75B**, 591 (1942); *b*) R.D.H. Heard and A.F. McKay, *J. Biol. Chem.*, **165**, 677 (1946); *c*) L. Norymberska, J. Norymberski, and A. Dlalde, *J. Am. Chem. Soc.*, **70**, 1256 (1948).

10) *a*) J.A. Hartman, *J. Am. Chem. Soc.*, **77**, 5151 (1955); *b*) J.A. Hartman, A.J. Tomasewski, and A.S. Dreiding, *ibid.*, **78**, 5662 (1956).

ism (CD) maximum at 302 mμ (θ=1830 in chloroform). Lack of an aldehydic band near 2750 cm^{-1} and formation of the triacetyl derivative suggested that the minor product is ketol (**7a** or **9a**). Treatment of **7b** with neutral alumina in benzene at room temperature yielded the conjugated ketone (**8**), mp 170—170.5°, and thus the structure of the triacetate was established as **7b**.

For introduction of a cyano group into C_5, two different ways were designed: (I) hydrocyanation of hydrindenone-type B-norsteroids (vi)→(vii); (II) hydrocyanation of acetylhydrindene-type B-norsteroids (viii)→(ix). The stereochemistry of the introduced cyano group was expected [11] to be exclusively β-orientated in case (I) and predominantly α-orientated in case (II).



vi vii viii ix

Chart 4

There were some uncertainties about the applicability of the hydrocyanation to the B-norsteroidal enones at that time. However, it was presumed that if the cyano group is introduced into C_5, conversion of either of the epimers into the desired *cis*-bicyclo[3.2.1]octane ring system would be possible by applying the previously described method for the kaurene type ring system[3b] to the 5α-cyano compound or that for the phyllocladene type ring system[3a] to the 5β-cyano compound, respectively. The latter was expected to be transformed to the aimed products (**1**) more directly than the former. Thus, the method (I) was considered preferable one and was examined first.

Syntheses of the hydrindenone-type B-norsteroids, (**11a**, **11b**, and **11c**) were carried out in the following way. The diketoacetal (**10**) obtained[7a] from the formyl-B-norsteroid (**3a**) was dehydrated by mild treatment with thionyl chloride in pyridine to give the ethylenedioxymethylenone (**11a**), mp 181—183°, in a yield of 41% and a by-product, $C_{21}H_{27}O_4Cl$, mp 213.5—215.5° in a yield of 5%. The structure of the by-product was determined as **11d** based on its spectral data (see experimental). The orientation of the introduced chlorine atom was tentatively assigned as α. Reduction of **3a** with lithium aluminum hydride gave a tetrol (**12**), mp 169—171°, in high yield. Selective oxidation of the tetrol (**12**) with N-bromosuccinimide[12] produced the diketodiol (**13a**), mp 178—180°, in a very good yield. This was converted into the acetoxymethylenone (**11b**), mp 119—121°, by dehydration (thionyl chloride in pyridine) of the corresponding acetyl derivative (**13b**), mp 178—179°, in a yield of 48%. Attempts to convert the diketo-diol (**13a**) directly into the hydroxylmethylenone (**11c**) failed and an undesired conjugated dienone was formed. The difficulty of avoiding the ready dehydration of the primary product was eliminated by transformation of **13a** to the corresponding cyclic carbonate (**14**), mp 166.5—169°, in a yield of 76% and by treatment of the latter with one molar equivalent of potassium hydroxide in methanol at room temperature, smoothly yielding the desired hydroxylmethylenone (**11c**), mp 183—184°, in a yield of 88%.

11) W. Nagata, M. Yoshioka, and T. Terasawa, *J. Am. Chem. Soc.*, in press.
12) *a*) W.S. Johonson, J.C. Collins, Jr., R. Pappo, M.B. Rubin, P.J. Kropp, W. F. Johns, J. E. Pike, and W. Bartman, *J. Am. Chem. Soc.*, **85**, 1409 (1963); *b*) H.L. Herzog, M.A. Jevnik, P.L. Perlman, A. Nobile, and E.B. Hershberg, *ibid.*, **75**, 266 (1953).

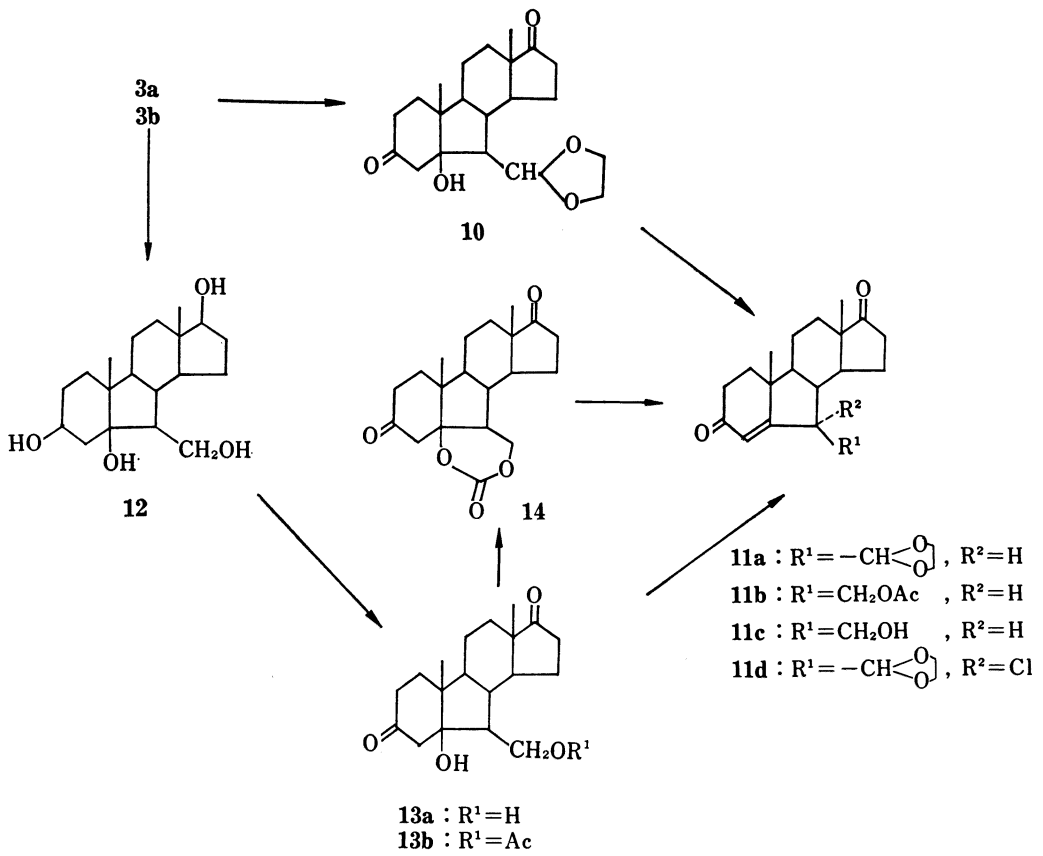


Chart 5

Hydrocyanation of the enones (**11a**, **11b**, and **11c**) was investigated. Treatment of the enones with hydrogen cyanide-triethylaluminum in tetrahydrofuran (process A)[7c] or diethylaluminum cyanide in benzene (process B)[7c] gave unsatisfactory results. The starting materials were mostly recovered under the usual conditions and prolonged treatment caused formation of several unidentified products. In a parallel study[7a] on hydrocyanation of 6β-alkylhydrindenone-type B-norsteroids, successful results using diethylaluminum cyanide were obtained. The yields of 5β-cyano-6β-alkyl-androstane-3,17-diones usually reached 80—85%. An exception was observed for the 6β-ethyl derivative (13%), in which fairly large steric hindrance, caused by the ethyl group, to the introduction of the cyano group was considered to operate. In the present case, the failure of hydrocyanation of the enones (**11a**, **11b**, and **11c**) may be interepreted on the basis of the presumable interaction between the electron deficient C_5 carbon and the electron donating oxygen attached to the C_6-substituting chain in the derivatives (**11a**, **11b**, and **11c**) resulting in a decreased rate of hydrocyanation. The steric effect of the chains was also considered to operate but to be unimportant. To eliminate the electronic interaction, the formyl group was replaced with a vinyl group and the latter was expected to be transformed to the former in the later stage. The conversion of the formyl-B-norsteroid (**3a**) into the 6β-vinyl-B-norsteroid (**15a**) by Wittig reaction and subsequent hydrolysis has been already reported.[7c] The triololefin (**15a**) was oxidized to the diketone (**16a**), mp 135—136°, in a yield of 61% based on **3a**. The diketone (**16a**) was dehydrated with thionyl chloride in pyridine-methylene chloride mixture

at −63° to give the vinylenone (**17a**), mp 145—147°, in a yield of 74%. Hydrocyanation of the vinylenone (**17a**) with diethylaluminum cyanide in tetrahydrofuran was carried out and, as expected, the desired vinylcyanoketone (**18a**), mp 189.5—191°, was isolated from the crude product by a single crystallization. Because of the equilibrium, the hydrocyanation was not completed,[7c] and, therefore, the reaction was repeated with the mother liquor. The increased yield of 61% was thus obtained. In some experiments, a small amount of the 1,6-addition product (**19a**), mp 165—167°, was obtained, whose formation was presumably ascribed to the conjugated dienone contaminating the starting material. The stereochemistry of the introduced cyano group in the B-norsteroids of this type was discussed in the other paper[7c] and confirmed by the CD measurement (*vide infra*). For this purpose, some derivatives of **18a** were synthesized. Partial ketalization of **18a** with methanol and *p*-toluenesulfonic acid gave the 17-keto-3-dimethylketal (**20a**), mp 158—160°, in a yield of 87%, which was then attempted to convert by Huang-Minlon reduction and subsequent acid hydrolysis into the 17-unsubstituted cyanoketone (**18b** *via* **20c**). The yield was unsatisfactory but the compound was considered to be adequatefor the further transformations in Part VII and was prepared through an alternative route.

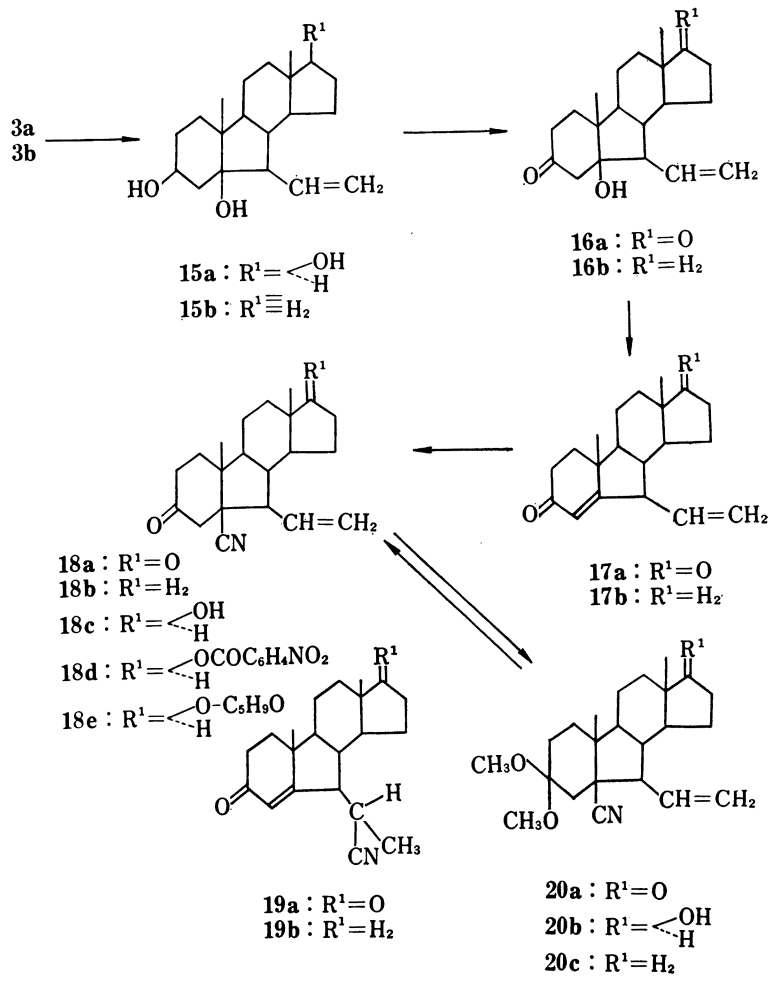


Chart 6

Thus, starting from the formyl-B-norsteroid (**3b**), the same sequence of the reactions as that carried out for the synthesis of **18a** produced (**18b**), mp 123—124°, in a better yield *via* (**15b**, **16b**), mp 131—132°, and **17b**. The 1,6-addition product (**19b**), mp 200—202°, was also obtained in a yield of 2%. The 17β-hydroxyl derivatives were also synthesized. Sodium borohydride reduction of the ketal (**20a**) gave an oily 17β-alcohol (**20b**). Acid hydrolysis of the latter gave the 17β-hydroxyl cyanoketone (**18c**), which was characterized as its *p*-nitrobenzoate (**18d**), mp 170—171°, and its tetrahydropyranylether (**18e**), mp 141—142.5°.

In a similar way, the formyl-B, 19-bisnorsteroid (**6b**) was transformed into a vinyl derivative (**21a**) and further into the vinyldiol (**21b**), mp 176—176.5°. Separation of **21b** from the phosphor compounds arising from the Wittig reagent was satisfactorily effected by conversion of **21b** into its bis-hemisuccinate (**21c**) in a yield of 73% based on **6b**. Oxidation of (**21b**) with Jones' reagent gave the vinyldiketone (**22**), mp 181—182°, in a yield of 75%, which was dehydrated with thionyl chloride–pyridine in methylene chloride at −68° to produce the vinylenone (**23**), mp 127—129°, in a yield of 59%. Hydrocyanation of the enone (**23**) with diethylaluminum cyanide in benzene afforded the desired cyanoketone (**24a**), mp 222—222.5°, in a yield of 55%.

The 3-keto group of **24a** was selectively ketallized with methanol and *p*-toluenesulfonic acid to give ketal (**25a**), mp 152—154°. The latter was reduced with sodium boro-

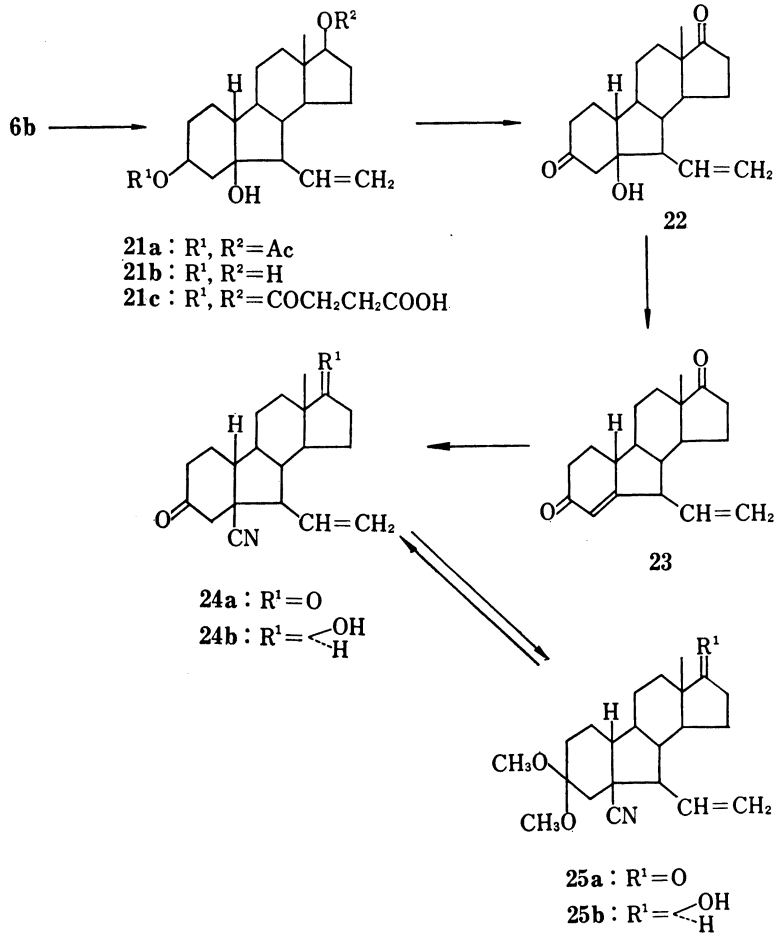


Chart 7

hydride giving the 17β-hydroxyl derivative (**25b**), which was hydrolyzed without isolation to give the cyanoketol (**24b**), mp 125—127°.

For the assignment of the stereochemistry of the cyanoketones, the optical rotatory dispersion (ORD) curves and the CD absorption curves of (**18b** and **24b**) together with the relevant compounds were measured and the results are shown in Table I and Table II. Similarlity of the CD maxima (Table I) or Δ_4-3-keto-B-norsteroid (**17a**) and those of Δ_4-3-keto-B,19-bisnorsteroid (**23**) lead us to a conclusion that the stereochemistry at C_{10} of **23** is β. Thus, the 10β-configuration in (**6b** and **23**) have been established. The molecular amplitudes in methanol of the cyanoketones (**18b**, **18c**, and **18e**) are approximately identical with those of 6β-substituted-3-keto-5β-B-norsteroids[13a] (−40°——65°×10² in methanol) and different from those of 3-keto-5α-B-norcholestane[13b] (+101°×10² in methanol) or from those of 6α-substituted-3-keto-5β-B-norsteroids[13a] (−10—+48°×10² in methanol). Supposing that the substitution of hydrogen at C_5 for a cyano group will cause a small effect on the ORD curves, the 5β,6β-configurations of the cyanoketones (**18b**, **18c**, and **18e**) are considered to be highly reasonable and a similar conclusion was reported[7c] on the hydrocyanation products of 6β-alkyl-Δ_4-3-keto-B-norsteroids. The ORD and CD data of the cyanoketones (**18b**, **18c**, and **18e**) in chloroform are completely different from those in methanol. This suggests conformational mobility in the AB ring of these compounds.[14] The cyanoketo-

Table I. CD Maxima of Δ_4-3-Keto-B-nor- and 19, B-Bisnor-steroids

Compounds	CD (maxima) [θ] (mμ)	Solvent[a]
17a	−86100 (245) +15400 (302) +14900 (335)	C
23	−33500 (245) +11800 (304) +8200 (327 sh)	M
	−75800 (242) +19000 (304) +16300 (332)	C

a) M: methanol, C: chloroform.

Table II. ORD and CD Data of 5β-Cyano-3-keto-B-nor- and 5β-Cyano-3-keto-19,B-bisnor-steroids

Compounds	CD (maxima) [θ] (mμ)	ORD (Molecular amplitude) 10^{-2}	Solvent[a]
18b	−2350 (295)	−37°	M
	+2460 (298)	+29°	C
18c	−1800 (293)	−33°	M
	+2370 (298)	+33°	C
18e	−1900 (295)	−41°	E
	+2070 (304)	+21°	C
24b	−7120 (298)	−121°	M
	−3350 (297.5)	−55°	C

a) M: methanol, C: chloroform, E: ethanol

13) a) J. Fajkoš, J. Joska, and F. Sŏrm, *Collection Czech. Chem. Commun.*, **28**, 605 (1963); b) J. Joska, F. Fajkoš, and F. Sŏrm, *ibid.*, **31**, 2745 (1966).

B,19-bisnorsteroid (**24b**) showed a negative Cotton effect (Table II) in methanol and the 5β-configuration was concluded in spite of some disagreements in the ORD and the CD behaviors in chloroform solution of both series of the cyanoketones. The disagreements might be interpreted[14] by changes in the distortion and/or conformational mobility in the AB rings of the 19-nor-series.

In parallel with the successful studies on the above-described hydrocyanation of the hydrindenone-type B-norsteroids, hydrocyanation of the acetylhydrindene-type B-norsteroids have been also investigated. The formyl-B-norsteroid (**3a**) was dehydrated by mild treatment with alkali and subsequent reacetylation to produce the conjugated aldehyde (**26**), mp 194—196°, in a yield of 64%. Preliminary investigation of 1,4-hydrocyanation of the conjugated aldehyde (**26**) failed and thus, the aldehyde was converted into the conjugated acid cyanide (**28**), mp 163—164.5°, by 1,2-addition of hydrogen cyanide to give the cyanohydrin (**27**) using hydrogen cyanide–diethylaluminum chloride[15] in tetrahydrofuran and successive oxidation with manganese dioxide in dry benzene. Hydrocyanation of the conjugated acid cyanide (**28**) with diethylaluminum cyanide gave an unstable cyano acid cyanide, which without isolation was reduced with sodium borohydride *in situ* to yield the cyanoalcohol (**29**), mp 175—176° in a yield of 39%. The relative configuration of 3β-acetoxyl-, 5α-cyano-, and 6β-hydroxylmethyl-groups was assigned, as depicted, because neither iminolactone nor lactone band could be observed in the IR spectrum of the product after 4 hr's refluxing in 1,3N-hydrochloric acid in aqueous ethanol.[16] The crude product showed IR bands at 3312 and 2238 cm^{-1} and was considered to be consisted mainly of a cyanotriol (**30**).

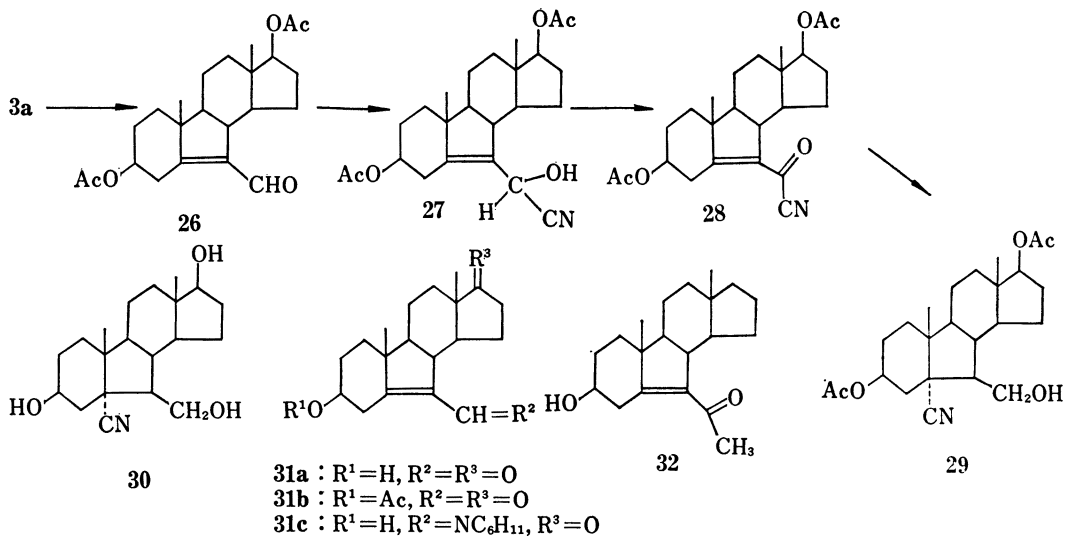


Chart 8

A detailed investigation along this line has been carried out in our laboratory[7c,17] and it was revealed that successful hydrocyanation was achieved not with conjugated formylhydrindene-type B-norsteroids (**31a** and **31b**) but with the cyclohexylimino derivative (**31c**)[17]

14) Details of the phenomena will be discussed separately: K. Kuriyama, S. Hagishita, T. Iwata, and M. Moriyama, to be published.
15) *a*) W. Nagata, M. Yoshioka, and S. Hirai, *Tetrahedron Letters*, **1962**, 461; *b*) W. Nagata and M. Yoshioka, *ibid.*, **1966**, 1913.
16) S. Hirai, *Chem. Pharm. Bull.* (Tokyo), **9**, 837 (1961).
17) W. Nagata, M. Yoshioka, T. Okumura, and M. Murakami, *J. Chem. Soc.* (*C*), **1970**, 2355.

by using hydrogen cyanide–ethylaluminum dichloride and with the acetylhydrindene–type B-norsteroid (**32**)[7c] by using diethylaluminum cyanide to give the corresponding 5α-cyano derivatives in 55 and 93% yields respectively. The orientation of the cyano group introduced was proved as expected to be 5α, which is considered to be less suitable for the further elaboration of the synthesis of the *cis*-bicyclo[3.2.1]octane ring. In addition, during experiments directed to the total synthesis[18] of gibberellin A_{15}, difficulties were encountered in preparation of a conjugated aldehyde similar to the conjugated aldehyde (**26**). So we abandoned this route.

Further investigation using the vinyl cyano ketone (**18b**) will be described in Part VII.

Experimental

Preparation of Estr-5-ene-3β,17β-diol (4)——A suspension of 10.154 g of 19-nortestosterone and 0.802 g of p-toluenesulfonic acid monohydrate in 60 ml of isopropenyl acetate was heated under reflux for 170 min cooled, mixed with 0.42 g of powdered sodium acetate, and stirred for 10 min. The resulting mixture was poured into ice water containing 5 g of sodium bicarbonate and extracted with ether–methylene chloride (3:1). The washed and dried organic solution, on removal of the solvent under reduced pressure, gave 13.1 g of a mixture of the dienol acetates. This was suspended in 600 ml of 95% ethanol and, after addition of a solution of 13.1 g of sodium borohydride in 100ml of 70 % ethanol at 0°, was heated undur reflex for 13 min. One hundred millilitres of 5% sodium hydroxide was added dropwise to the boiling mixture over 6 min and after further 20 min reflux the mixture was concentrated under reduced pressure, diluted with 500 ml of salt solution and treated with 220 ml of 2 N hydrochloric acid. Extraction of the mixture with chloroform–methanol (5:1) gave the crude product. This was purified by fractional recrystallization from methylene chloride–methanol–ether to produce 5.192 g of estr-5-ene-3β, 17β-diol (**4**), mp 167—168° (loc. cit.,[10] mp 161—162°).

Ozonolysis if Estr-5-ene-3β,17β-diol (4)——A stream of ozonized oxygen (65.8 mg of ozone/min) was introduced into a solution of 10.12 g of the diol (**4**) in 900 ml of a 4:1 mixture of methylene chloride–methanol with cooling in a dry ice–acetone bath until the solution turned pale blue. The resulting solution was treated with 28.3 g of zinc powder then 64.0 ml of acetic acid was added dropwise at 0°. The mixture was stirrred with ice–cooling for 2 hr. The zinc and zinc salts were filtered off and washed well with methylene chloride–methanol. The filtrate was diluted with salt solution and extracted with the methylene chloride–methanol washings. The organic layer was shaken with water, dried, and on removal of the solvent under reduced pressure gave 11.01 g of the crude *seco*-aldehde (**5**). This substace was dissolved in 1.00 ml of benzene and 500 ml of methylene chloride and the solution was stirred with 110 g of neutral alumina (Woelm II) at room temperature for 9 hr and then introduced into a column filled with 110 g of neutral alumina and benzene and chromatographed. Fractions eluted with benzene-methylene chloride (1:1) were combined and crystallized from methylene chloride–ether to produced 3.37 g of 6β-formyl-B-norestrane-3β,5β,17β-triol (**6a**), mp 186—187°. A pure sample melts at 188.5—190°. *Anal.* Calcd. for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.23; H, 9.05. Substances eluted with methylehe chloride-methylene chloride–methanol (9:1) were chromatographed again on 35 g of neutral alumina. Elution with methylene chloride–methanol (97:3—9:1) and recrystallization of the residues from methanol–methylene chloride gave 1.094 g of the *spiro*-ketone (**7a**), mp 250—254°. Recrystallization of the crystals from ethyl acetate-methanol gave a sample melting at 246.5—248°.

Acetylation of 6a——A mixture of 820 mg of **4**, 15 ml of pyridine, and 8 ml of acetic anhydride was allowed to stand at room temperature for 12 hr and concentrated under reduced pressure to complete dryness. The residue was recrystallized from acetone–ether to afford 697 mg of 6β-formyl-β-norestrane-3β,5β,17β-triol 3β,17β-diacetate (**6b**), mp 164—167°. A pure sample melts at the same temperature. *Anal.* Calcd. for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 66.84; H, 8.24. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3580, 2756, 1741, and 1242. $[\alpha]_D^{22}$ +9.7±2° (*c*=1.008, methanol). CD [θ] (mμ): −3280 (295) (*c*=1.008, methanol).

Acetylation of 7a——A solution of 361 mg of **7a** in 10 ml of pyridine was treated with 3 ml of acetic anhydride at room temperature for 12.5 hr. Working up the reaction mixture in the usual way gave foams, which were crystallized from methylene chloride–ether to give the acetate (**7b**), mp 188—191°. A pure sample meltsat 190—192°. *Anal.* Calcd. for $C_{24}H_{34}O_7$: C, 66.34; H, 7.89. Found: C, 66.71; H, 7.93. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1744, 1723 (sh), 1237, and 1036. $[\alpha]_D^{22}$ +42±2° (*c*=1.033, chloroform). CD[θ] (mμ): −1830 (302) (*c*=1.033, chloroform). NMR ($CDCl_3$) τ: 4.77, 5.24 (3H, C**H**–OAc), 7.96, 8.01 (9H, OCOC**H**$_3$), and 9.227 (3H, 18–H).

18) *a*) W. Nagata, T. Wakabayashi, Y. Hayase, M. Narisada, and S. Kamata, *J. Am. Chem. Soc.*, **92**, 3220 (1970); *b*) W. Nagata, T. Wakabayashi, M. Narisada, Y. Hayase, and S. Kamata (in part), *J. Am. Chem. Soc.*, in press.

Treatment of (7b) with Alumina——A solution of 97.5 mg of **7b** in 16 ml of benzene was stirred with 1.00 g of neutral alumina (Woelm II) at room temperature for 9 hr. The mixture was chromatographed using an additional 3 g of alumina. Fractions eluted with benzene wee crystallized from methylene chloride–ether to give 46.3 mg of the enone (**8**), mp 168—169° One recrystallization from the same solvent raised the mp to 170—170.5°. *Anal.* Calcd. for $C_{22}H_{30}O_5$: C, 70.10; H, 9.15. Found: C, 70.61; H, 8.05. NMR ($CDCl_3$) τ: 3.17 (1H, m, C**H**=CH–C=O), 3.98 (1H, d, CH=C**H**–C=O), 4.67 (1H, t, J=7 cps, 6–H), 5.35 (1H, m, 17–H), 7.97 (3H, O–COC**H**$_3$), 8.10 (3H, O–COC**H**$_3$), and 9.22 (3H, 18–H).

Preparation of 6β-Ethylenedioxymethyl-B-norandrost-4-ene-3,17-dione (11a)——Thionyl chloride (280 mg) was added by syringe over 30 sec to a stirred solution of 6β-ethylenedioxymethyl-B-norandrostan-5β-ol-3,17-dione (**10**)[7c] in 2.8 ml of pyridine cooled in an ice–water bath. After a further 3 min stirring at 0°, the suspension was poured onto ice water and extracted with methylene chloride. The organic solution was washed at 0° successively with water, 2 N hydrochloric acid, water, 2 N sodium carbonate solution, and water, dried, and the solvent was evaporated under reduced pressure. The resulting crystalline residue was recrystallized from acetone to yield 129 mg of crystals, mp 171—173°. The crystals were proved to be contaminated with a small amount of a non-polar material. Seventy four milligram of the crystals and the mother liquor were applied on a 20×20 cm silica gel plete and developed with ethyl acetate. The two main bands were cut off and extracted with methylene chloride–methanol (9:1). The major polar band gave 102 mg of a crystalline residue, which was recrystallized from acetone-egher to give 83 mg of 6β-ethylenedioxymethyl-B-norandrost-4-ene-3,17-dione (**11a**), mp 181—183°. A pure sample has the same up. *Anal.* Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.04; H, 8.39. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 and 1664. UV λ_{max}^{EtOH} mμ (ε): 241.4 (15,400). NMR ($CDCl_3$) τ: 4.01 (1H, d, J=1.8 cps, 4–H), 5.01 (1H, d, J=3.0 cps, 6a–H) 6.11 (4H, m, OC**H**$_2$C**H**$_2$O), 8.87 (3H, s, 19–H), and 9.05 (3H, s, 18–H). The non polar band produced 21 mg of a crystaline residue. Recrystallization from acetone ether yielded 11 mg of 6α-chloro-6β-ethylenedioxymethyl-B-norandrost-4-ene-3,17-dione (**11d**), mp 210—216°. A pure sample, obtained from another experiment and melting at 213.5—215.5°, was analyzed. *Anal.* Calcd. for $C_{21}H_{27}O_4Cl$: C, 66.57; H, 7.18; Cl, 9.36. Found: C, 66.77; H, 7.32; Cl, 9.52. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1737 and 1667. UV λ_{max}^{EtOH} mμ (ε): 245 (12,700). NMR ($CDCl_3$) τ: 3.74 (1H, s, 4-H), 4.87 (1H, s, 6a-H), 6.04 (4H, OC**H**$_2$C**H**$_2$O), 8.88 (3H, s, 19-H), and 9.05 (3H, s, 18-H).

6β-Hydroxylmethyl-B-norandrostane-3β,5β,17β-triol (12)——A stirred solution of 2.00 g of 6β-formyl-B-norandrostane-3β,5β,17β-triol 3β, 17β-diacetate (**3a**)[8b] in 200 ml of tetrahydrofuran was mixed with a suspension of 1.00 g of lithium aluminium hydride in 40 ml of tetrahydrofufan at room temperature and the stirring was continued for 80 min. After decomposition of the excess of the reagent, the mixture was made acid with ice–cold hydrochloric acid, salted out, and extracted well with ethyl acetate–methylene chloride–methanol (5:2:1). The organic solution, on removal of the solvent under reduced pressure and on crystallization of the residue from methanol–ether containing a small volume of methylene chloride, produced 1.384 g of 6β-hydroxylmethyl-B-norandrostane-3β, 5β, 17β-triol (**12**), mp 170—172.5°. Recrystallization from acetone gave an analytical sample, mp 169—171°. *Anal.* Calcd. for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94. Found: C, 69.96; H, 9.95. IR ν_{max}^{KBr} cm^{-1}: 3408, 1085, and 1038.

Hydroxylmethyl-B-norandrostan-5β-ol-3,17-dione (13a)——To a stirred solution of 2.845 g of 6β-hydroxylmethyl-B-norandrostane-3β,5β,17β-triol (**12**) in a mixture of 445 ml of acetone, 142 ml of *t*-butanol, and 71 ml of water, cooled to 5—10°, was added 6.06 g of N-bromoacetamide and the resulting mixture was stirred for 3 hr at 5—10°, cooled in an ice–water bath, the solution was then mixed with 143 ml of 5% of sodium sulfite solution, diluted with ice water, and extracted with methylene chloride. The residue obtained was recrystallized from methanol to afford 2.573 g of 6β-hydroxylmethyl-B-norandrostan-5β-ol-3,17-dione (**13a**), mp 178—180°. A sample melting at 174.5—177° was analyzed. *Anal.* Calcd. for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.29; H, 8.96. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3415, 1730, 1716 (sh), 1088, and 1004.

6β-Acetoxylmethyl-B-norandrostan-5β-ol-3,17-dione (13b)——A mixture of 1.50 g of 6β-hydroxylmethyl-B-norandrostan-5β-ol-3,17-dione (**13a**), 30 ml of pyridine, and 15 ml of acetic anhydride was allowed to stand at room temperature for 15 hr. Working up the resulting mixture in the usual way and recrystallization of the residue from methanol yielded 1.623 g of 6β-acetoxylmethyl-B-norandrostan-5β-ol-3,17-dione (**13b**), mp 176—177.5°. A pure sample melts at 178—179°. *Anal.* Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.12; H, 8.34. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1734 and 1719 (sh).

6β-Acetoxymethyl-B-norandrost-4-ene-3,17-dione (11b)——To an ice–cold solution of 900 mg of 6β-acetoxymethyl-B-norandrostan-5β-ol-3,17:dione (**13b**) in 18 ml of absolute pyridine was added 4.7 ml of a 20% solution of thionyl chloride in pyridine and the resulting mixture, kept in a stoppered flask, was allowed to stand at o° for 3 min, poured into ice water, and extracted with benzene. The organic layer was washed successively with 2N hydrochloric acid, water, sodium bicarbonate solution, and water, dried, and the solvent was removed under reduced pressure to give 504 mg of a residue, which was crystallized from ether to produce 430 mg of 6β-acetoxymethyl-B-norandrost-4-ene-3,17-dione (**11b**), mp 121.5—122.5°. A sample melting at 122.5—123.5° was analyzed. *Anal.* Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.00; H, 8.10. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1738 and 1662. UV λ_{max}^{EtOH} mμ (ε): 240 (15,100).

Preparation of 6β-Hydroxylmethyl-B-norandrost-4-3,17-ene-dione (11c)——To a stirred solution of 680 mg of 6β-hydroxylmethyl-B-norandrostan-5β-ol-3,17-dione (**13a**) in 10.2 ml of absolute pyridine 8.6 ml of a

cold 7.27 % solution of phosgene in toluene was added dropwise with ice-cooling and the resulting mixture was kept at 0° for 1 hr, poured onto ice water, and extracted with methylene chloride. The residue obtained in the same way as described in preparation of **11b** was crystallized from methanol containing a small volume of methylene chloride to afford 560 mg of the cyclic carbonate (**14**), mp 167.5—169.5°. One recrystallization from the same solvent afforded an analytical sample melting at 166.5—169°. *Anal.* Calcd. for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.32; H, 7.80. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1766 and 1738.

A solution of 500 mg of the cyclic carbonate (**14**) dissolved in 50 ml of absolute methanol was mixed with a solution of 81 mg of potassium hydroxide in 8.6 ml of the solvent and the resulting mixture was stirred at room temperature for 90 min. This was poured into ice water and extracted with methylene chloride. The washed and dried solution, on removal of the solvent under reduced pressure, gave foams, which were crystallized from methylene chloride–ether to yield 383 mg of 6β-hydroxylmethyl-B-norandrost-4-ene-3, 17-dione (**11c**), mp 181.5—183°. A pure sample melts at 183—184°. *Anal.* Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.77; H, 8.82. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3629, 3478, 1735, and 1660. UV λ_{max}^{EtOH} mμ (ε): 243 (14,200).

Attempted Hydrocyanation of the Enones (11a), (11b), and (11c)——To a solution of 30—50 mg of an enone in 0.6—3.0 ml of pure tetrahydrofuran or dry methylene chloride was added under nitrogen stream 1.6 M toluene or 1.0 M isopropyl ether solution containing 5—10 molar equivalents of diethylaluminum cyanide and the resulting mixture was kept in a sealed ampule. After standing the reaction mixture at room temperature for 12—54 hr, it was poured into ice-cold 2N sodium hydroixde solution and extracted with methylene chloride. The organic solution was shaken well with the alkaline solution at 0°, washed well with water, dried, and the solvent was removed completely. The residue was examined by IR spectrum and thin-layer chromatography (TLC). In a case of the enone (**11a**), triethylaluminum-hydrogen cyanide was used instead of diethylaluminum cyanide. In typical cases using the enone (**11a**), a major part of the starting enone was recovered and only a very small amount of the desired cyanoketone was seemed to be formed. Under more drastic conditions, the yield of the latter was improved slightly and formation of a fairly large amount of a polar by-product was observed. In the case of the enone (**11b**), formation of more than four products accompanied by recovery of moderate amount of the starting enone was observed. In one experiment using the enone (**11c**), two less polar by-products were formed besides a large amount of the recovered enone and the former were proved not to be the desired cyanoketone after separation of the products.

6β-Vinyl-B-nor-5β-androstan-5β-ol-3,17-dione (16a)——The crude triololefin (**15a**)[7c] (2.64 g) was dissolved in acetone (100 ml). The solution was treated with Jones' reagent[19] (62 ml) at 0° for 7 min. The mixture was poured into ice-water and extracted with methylene chloride. The methylene chloride extract was washed with water, dried, and evaporated to leave 2.07 g of a residue which was chromatographed on neutral alumina (60 g). Fractions eluted with petroleum ether–benzene (1:1)–benzene were crystallized to give 1.260 g (61% from (**3a**)) of the diketone (**16a**), mp 121—123°. An analytical sample melts at 135—136°. *Anal.* Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.56; H, 9.06. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3560, 1743, 1723, 924. $[\alpha]_D^{22}+90.2\pm2°$ ($c=1.052$, $CHCl_3$).

6β-Vinyl-B-norandrost-4-ene-3,17-dione (17a)——To a cold (−63°) solution of the diketone (**16a**) (1.00g) in a mixture of dry methylene chlorie (3 ml) and dry pyridine (4 ml) a solution of thionyl chloride (0.3 ml) in dry methylene chloride (0.7 ml) was added with stirring over 15 sec under nitrogen. After the resulting solution had been stirred for 90 sec, a cold (−15°) solution (5 ml) of ethylene glycol–water (1:1) was added. The mixture was made acid with cold 2N hydrochloric acid (30 ml) and extracted with methylene chloride. The methylene chloride extract was washed with water, dried, and evaporated to leave 979 mg of a residue which was chromatographed on alumina (15 g). Fractions eluted with benzene–methylene chloride (9:1) were crystallized from ether to give 507.3 mg of the vinylenone (**17a**), mp 130—133°, and 191.8 mg of the second crop, mp 113—119°. An analytical sample melts at 132—134°. *Anal.* Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.51; H, 8.66. IR ν_{max}^{KBr} cm^{-1}: 3080, 1734, 1661, 1634, 924. UV λ_{max}^{EtOH} mμ (ε): 244 (12,600). $[\alpha]_D^{22}+162\pm2°$ ($c=0.992$, $CHCl_3$). ORD ($CHCl_3$) [φ] (mμ): +103800 (235), −71100 (262.5) (trough), −6829 (325) (trough), +12515 (364) (peak). CD ($CHCl_3$) [θ] (mμ): −86100 (245) (max), +15380 (302) (max).

5β-Cyano-6β-vinyl-B-nor-5β-androstane-3,17-dione (18a)——A: To a solution of te vinylenone (**17a**) (600 mg) in dry methylene chloride (6 ml) wzs added a solution (6 ml) of diethylaluminum cyanide in dry benzene (1.26 mmole/ml) at room temperature under nitrogen. The solution was allowed to stand for 2 hr, poured into cold 2N sodium hydroxide, and extracted with ether–methylene chloride (3:1). The organic extract was wahsed with water, dried, and evaporated to leave 688 mg of a residue which was crystallized from methylene chloride–ether to afford 184 mg of the vinylcyanoketone (**18a**), mp 185—189°. The mother liquor was evaporated to dryness, and the resudie was again treated with the benzene solution (3 ml) of diethylaluminum cyanide (1.26 mmole/ml) to afford 480 mg of a residue which was chromatographed on neutral alumina (15 g). Fractions eluted with benzene and benzene–chloroform (9:1) were crystallized to give 217 mg of **18a**, mp 189—191°. The total yield was 401 mg (61%). An analytical sample melts

19) K. Bowden, I.M. Heilbron, E.R. Jones, and C.L. Weedon, *J. Chem. Soc.*, **1945**, 39.

at 189.5—191°. *Anal.* Calcd. for $C_{21}H_{27}O_2N$: C, 77.50; H, 8.36; N, 4.30. Found: C, 77.52; H, 8.49; N, 4.10. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2236, 1733, 1643, 927. $[\alpha]_D^{25}+144.1\pm2°$ ($c=1.002$, $CHCl_3$).

B: To a cold (3°) solution of crude vinylenone (**17a**) (231 mg) in dry tetrahydrofuran (1.4 ml) a solution (2.6 ml) of diethylaluminum cyanide in dry toluene (0.902 mmole/ml) was added under nitrogen. The reaction mixture was allowed to stand at room temperature for 7 hr, poured into ice–2N hydrochloric acid, and extracted with ether–methylene chloride (3:1). The organic layer was washed successively with 2N sodium hydroxide and woter and warked up as above to leave 234 mg of a residue which was chromatographed on alumina (8 g). Fractions eluted with benzene and benzene–chloroform (9:1) were collected, and subjected to preparative TLC (silica gel, ethyl acetate–benzene, 1:2), which afforded 58.7 mg of the 1,6-addition product (**19a**) mp 165—167°. *Anal.* Calcd. for $C_{21}H_{27}O_2N$: C, 77.50; H, 8.36; N, 4.30. Found: C, 77.85; H, 8.33; N, 4.04. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240, 1740, 1667, 1636. UV ν_{max}^{EtOH} $m\mu$ (ε): 239 (14,000). $[\alpha]_D^{25}+60.0$ ($\pm2°$) ($c=0.949$, $CHCl_3$). ORD (CH_3OH) [ϕ] ($m\mu$): +81000 (222), −58000 (254). CD (CH_3OH) [θ] ($m\mu$): −62000 (237) (max).

3,3-Dimethoxy-5β-cyano-6β-vinyl-B-nor-5β-androstan-17-one (20a)—— A mixture of the vinylcyanoketone (**18a**) (1.899 g), *p*-toluenesulfonic acid (260 mg), and dry methanol (80 ml) was refluxed for 6 hr under nitrogen. The mixture was cooled and then poured into ice–2N sodium carbonate, and extracted with methylene chloride. The methylene chloride extract was washed with water to leave 2.137 g of a residue, which was crystallized from methylene chloride–ether to give 1.391 g of the 17-keto-3-dimethylketal (**20a**), mp 158—160°. The mother liquor was evaporated to dryness, and the residue mixed with *p*-toluenesulfonic acid (143 mg), dry methanol (60 ml), and dry benzene (70 ml). The mixture was refluxed for 3.5 hr under removal of 50 ml of an azeotropic distillate, and worked up as above to leave 780 mg of a residue which was chromatographed on alumina (30 g). Fractions eluted with petroleum ether–benzene (2:1—1:1) were crystallized to give 448 mg of (**20a**), mp 156—159°. The total yield was 87%. An analytical sample melts at 158—160°. *Anal.* Calcd. for $C_{23}H_{33}O_3N$: C, 74.36; H, 8.95; N, 3.77. Found: C, 73.77; H, 9.06; N, 3.51. IR ν_{max}^{KBr} cm^{-1}: 3080, 2283, 1737, 1645, 1104, 1047. $[\alpha]_D^{25}+91.5\pm2°$ ($c=1.002$, $CHCl_3$).

Ozonization of Androst-5-en-3β-ol 3β-Acetate[9]——Through a cold (−73°) solution of androst-5-en-3β-ol 3β-acetate (48.1 g) in dry methylene chloride (2000 ml) and dry methanol (30 ml) was introduced oxygen containing ozone until the solution acquired bluish violet color. A mixture of zinc dust (90 g) and acetic acid (320 ml) was added to this solution and the mixture was stirred at −5° for 1.5 hr. The precipitate was filtered off, the filtrate was poured into a cold solution of sodium bicarbonate (460 g) in water (4000 ml). The organic layer was washed with water, dried, and evaporated to leave 57 g of a residue, 2.89 g of which was dissolved in benzene (80 g). To the solution was added neutral alumina (20 g, Woelm activity II). The suspension was stirred at room temperature for 5 hr, filtered to remove alumina. The filtrate was evaporated to dryness. The residue was crystallized from ether–pentane to give 1.80 g of the aldo-B-norsteroid (**3b**), mp 100—102°, and 36 mg of second crop, mp 98—100°, in a yield of 68.4%. An analytical sample melts at 100—102°. *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.13; H, 9.38. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3578, 2764, 1721. $[\alpha]_D^{25}+17.3\pm2°$ ($c=1.003$, $CHCl_3$). ORD ($CHCl_3$) [ϕ] ($m\mu$): +3998 (273) (peak), −1890 (319.5) (trough). CD ($CHCl_3$) [θ] ($m\mu$): −4111 (296) (max).

6β-Vinyl-B-nor-5β-androstan-5β-ol-3-one (16b)——To a suspension of methyltriphenylphosphonium bromide (111.8 g) in dry ether (700 ml) was added potassium *t*-butoxide (29.7 g) at 3° under nitrogen. The mixture was stirred at room temperature for 2 hr. To the resulting ylid solution a solution of the aldo-B-norsteroid (**3b**) (26.362 g) in dry tetrahydrofuran (350 ml) was added dropwise at 3° with stirring over a period of 10 min. The reaction mixture was stirred at room temperature for 3 hr, poured into ice-water, and extracted with ether–methylene chloride (3:1). The organic extract was washed with water, dried, and evaporated to leave 72 g of a residue which was treated with dry pyridine (150 ml) and acetic anhydride (50 ml). Usual wrking up gave 65.5 g of a residue which was chromatographed on alumina (250 g) to remove polar phosphorus containing compounds. Fractions eluted with petroleum ether–benzene (2:1) were collected to afford 32.0 g of a residue which was dissolved in methanol (250 ml). To the solution was added 2N potassium carbonate (150 ml). The mixture was refluxed for 2 hr, concentrated *in vacuo*, diluted with ice-water, and extracted with chloroform. The chloroform extract was washed with water, dried, and evaporated to leave 29.4 g of crude vinylalcohol (**15b**) which was dissolved in acetone (300 ml). The solution was treated with Jones' reagent[10] (21 ml) at 0° for 5 min. The mixture was poured into ice–water and extracted with ether–chloroform (3:1). The organic extract was washed with water, dried, and evaporated to leave 25.4 g of a residue which was chromatographed on alumina (250 g). Fractions eluted with petroleum ether–benzene (2:1) were crystallized from ether–pentane to give 14.231 g (63% from **3b**) of the vinylketone (**16b**), mp 124—129°. An analytical sample melts at 131—132°. *Anal.* Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.71; H, 10.28. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560, 1714, 1637, 922. $[\alpha]_D^{24}-3.1\pm2°$ ($c=1.097$, $CHCl_3$). ORD (CH_3OH) [ϕ] ($m\mu$): +4841 (262) (peak), −2057 (307) (trough). CD (CH_3OH) [θ] ($m\mu$): −4402 (289) (max).

5β-Cyano-6β-vinyl-B-nor-5β-androstan-3-one (18b)——To a cold (−73°) solution of the vinylketone (**16b**) (3.860 g) in dry methylene chloride (24 ml) and dry pyridine (5 ml) a solution of thionyl chloride (1.1 ml) in dry methylene chloride (7 ml) was added with stirring over 15 sec under nitrogen. After the resulting solution had been stirred for 1 min, a cold (−15°) solution (20 ml) of ethylene glycol–water (1:1) was

added. The mixture was made acid with cold 2N hydrochloric acid (70 ml), and extracted with methylene chloride. The methylene chloride solution was washed with water, dried, concentrated *in vacuo* to *ca.* 10 ml volume, then diluted with petroleum ether–benzene (2:1, 180 ml). The resulting solution was chromatographed on alumina (27 g). Fractions eluted with same solvent mixture were collected to afford 3.581 g of crude enone (**17b**) which, without purification, was dissolved in dry benzene (30 ml). To the solution was added a solution (27 ml) of diethylaluminum cyanide in dry toluene (1.626 mmole/ml) at room temperature. The mixture was allowed to stand for 30 min, poured into cold–2 N hydrochloric acid (70 ml), and extracted with ether–methylene chloride (3:1). The organic extract was washed successively with 2N sodium hydroxide and water, and worked up as usual to leave 4.39 g of a residue which was chromatographed on alumina (125 g). Fractions eluted with petroleum ether–benzene (4:1—1:1) were crystallized from ether–pentane to give 1.355 g (34% from (**16b**)) of the vinylcyanoketone (**18b**), mp 121—123°. An analytical sample melts at 123—124°. *Anal.* Calcd. for $C_{21}H_{29}ON$: C, 80.98; H, 9.38; N, 4.50. Found: C, 80.68; H, 9.23; N, 4.24. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2242, 1724, 1642, 926. $[\alpha]_D^{25}+59.4\pm2°$ ($c=1.102$, $CHCl_3$). ORD ($CHCl_3$) [ϕ] (mμ): −576 (277) (trough), +2297 (323) (peak). CD ($CHCl_3$) [θ] (mμ): +2459 (298) (max), CD (MeOH) [θ] (mμ): −2348 (295) (max). Fractions eluted with benzene–chloroform (9:1) were crystallized from ether–methylene chloride to give 66 mg (2%) of the 1,6-addition type compound (**19b**), mp 200—202°. *Anal.* Calcd. for $C_{21}H_{29}ON$: C, 80.98; H, 9.38; N, 4.50. Found: C, 80.76; H, 9.26; N, 4.76. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2238, 1664, 1635. UV λ_{max}^{EtOH} mμ (ε): 241 (14,400). $[\alpha]_D^{25}+44.4\pm2°$ ($c=1.068$, $CHCl_3$). ORD ($CHCl_3$) [ϕ] (mμ): −15170 (304) (trough), +6372 (370) (peak). CD ($CDCl_3$) [θ] (mμ): +13870 (337.5) (max).

Preparation of 5β-Cyano-6β-vinyl-B-nor-5β-androstan-17β-ol (18c)——To a solution of the ketal (**20a**) (13.3 mg) in methanol (1 ml) was added sodium borohydride (11 mg). The reaction mixture was stirred at room temperature for 2 hr, poured into ice–water, and extracted with methylene chloride. The methylene chloride extract was washed with saturated sodium chloride solution to leave 15.4 mg of crude 17β-alcohol (**20b**) which was dissolved into dioxane (1 ml). To the resulting solution was added 20% perchloric acid (2 drops). The mixture was allowed to stand at room temperature for 30 min, poured into ice–2 N sodium carbonate, and extracted with methylene chloride. The methylene chloride extract was washed with water, dried, and evaporated to leave 11.1 mg of a residue which was purified by preparative TLC (silica gel, benzene–ethyl acetate, 1:2) to afford 6 mg of the 17β-hydroxy cyanoketone (**18c**). The *p*-nitrobenzoate (**18d**) of (**18c**) was crystallized from methylene chloride–ether to give an analytically pure material, mp 170—171°. *Anal.* Calcd. for $C_{28}H_{32}O_5N_2$: C, 70.57; H, 6.77; N, 5.88. Found: C, 70.28; H, 6.52; N, 5.77. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2238, 1725, 1641, 1611, 1530, 1350, 926. $[\alpha]_D^{25}+61.9\pm5°$ ($c=0.202$, $CHCl_3$).

5β-Cyano-6β-vinyl-17β-tetrahydropyranyloxy-B-nor-5β-androstan-3-one (18e)——To a solution of the crude 17β-hydroxy cyanoketone (**18c**) (1.474 g) in dry tetrahydrofuran (25 ml), dihydropyrane (1.5 ml) and conc. HCl (1 drop) were added successively. The mixture was refluxed for 3.5 hr, cooled, poured into ice–2N sodium carbonate and extracted with methylene chloride. The methylene chloride extract was washed with water, dried, and evaporated to leave 2.253 g of residue which was crystallized from methylene chloride–ether to give 1.202 g of the tetrahydropyranylether (**18e**), mp 167—172°. The mother liquor was evaporated to dryness to leave 1.05 g of a residue which was chromatographed on alumina (30 g). Fractions eluted with petroleum ether–benzene (2:1) and petroleum ether–benzene (1:1) were crystallized from methanol to give 279 mg of (**18e**), mp 138—142° (dimorphism). The total yield was 1.481 g (>81%). An analytical sample melts at 141—142.5°. *Anal.* Calcd. for $C_{26}H_{37}O_3N$: C, 75.87; N, 9.06; N, 3.40. Found: C, 75.54; H, 8.90; N, 3.48. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3090, 2248, 1725, 1642, 1135, 1117, 926. $[\alpha]_D^{25}+111.9\pm2°$ ($c=$ 1.033, $CHCl_3$). ORD (ethanol) [ϕ] (mμ): +4812 (260) (peak), +720 (312) (trough). CD (ethanol) [θ] (mu): −1904 (295) (max).

Preparation of 6β-Vinyl-B-norestrane-3β,5β,17β-triol (21b) A——To a stirred suspension of 3.21g of methyl, triphenylphosphonium bromide in 23 ml of absolute ether was added 0.673 g of potassium *t*-butoxide under nitrogen steam and with ice-cooling and the resulting mixture was stirred at room temperature for 30 min. A solution of 590 mg of the diacetate (**6b**) in 15 ml of freshly distilled tetrahydrofuran was added to the ylide solution at 0°. The resulting mixture was stirred in stoppered flask with ice-cooling for 4 hr. It was poured onto ice water and extracted with methylene chloride. The organic solution was washed with water and dried. On removal of the solvent 2.14 g of a residue was obtained, which was purified by column chromatography using 30 g of neutral alumina (Woelm II). Petroleum ether–benzene (2:1—1:2) fractions gave 415 mg of the crude 6β-vinyl-B-norestrane-3β,5β,17β-triol 3β,17β-diacetate (**21a**). The crude (**21a**), dissolved in 20 ml of methanol, was refluxed, after addition of 4.0 ml of 2N potassium carbonate solution, for 40 min, concentrated under reduced pressure, diluted with salt solution, and extracted with methylene chloride. The organic solution was shaken with water, dried, and the solvent was evaporated to give 308 mg of a crystalline residue. On recrystallization of the residue from methylene chloride–ether 270 mg of 6β-vinyl-B-norestrane-3β,5β,17β-triol (**21b**), mp 175—176° was obtained. A pure sample melts at 176—176.5°. *Anal.* Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.44; H, 10.04. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580, 3485, 1640, and 917. $[\alpha]_D^{22}$ $+55.9\pm2°$ ($c=1.067$, chloroform).

B: Starting from 3.92 f the diacetate (**6b**), 14.7 g of a crude product was obtained by the Wittig traction carried out as described in A. The product was dissolved in 280 ml of methanol, mixed with 57 ml of 2N potassium carbonate solution, heated under reflux for 40 min, poured onto ice water, and extracted with me-

thylene chloride. The organic layer was washed with water, dried, and the solvent was removed, and finally co-distilled with toluene under reduce pressure to complete dryness. The residue was heated with 5.80 g succinic anhydride and 50 ml of absolute pyridine at 80—85° for 4.5 hr. The readtion mixture was mixed with ice–water and allowed to stand for 30 min to destroy the excess of the anhydride, diluted with water, and extracted with ether–methylene chloride (3:1). The organic layer was washed successively with 2N hydrochloric acid, water, 2N potassium carbonate solution, and water. The alkaline aqueous layers were made acid by addition of 6N hydrochloric acid, saturated with salt, and extracted with methylene chloride. The methylene chloride solution gave the crude bis-hemisuccinate (**21c**), which was hydrolyzed by 1 hr's reflux in 400 ml of methanol and 200 ml of 2N potassium carbonate solution and extracted with methylene chloride–methanol (9:1). The crystalline residue was recrystallized from methylene chloride–ether to afford 2.263 g of 6β-vinyl-B-norestrane-3β,5β,17β-triol (**21b**), mp 174—175°. This was identified with the specimen described in A by comparison of their IR spectra and by m.xture melting point.

6β-Vinyl-B-norestrad-5β-ol-3,17-dione (**22**)——To an nice-cold solution of 152 mg of 6β-vinyl-B-norestrane-3β,5β,17β-triol (**21b**) in 10 ml of acetone, 0.37 ml of 8N chromic anhydride 3.3N sulfuric acid solution was added with stirring and the resulting solution was stirred at 0° for 10 min. Working up the reaction mixture in the usual way and recrystallization of the crystalline residue from methylene chloride-acetone produced 114 mg of 6β-vinyl-B-norestran-5β-ol-3,17-dion (22), mp 180—181°. One reacrystallization from the same solvent raises the mp to 181—182°. *Anal.* Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.70; H, 8.69. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3536, 1723 (br), and 1639. $[\alpha]_D^{22}$ +28.7±2° (c=1.041, chloroform). CD [θ] (mμ): +4370 (215), −2870 (277), +2650 (309) (C=0.0377, methanol), −2690 (284), +2320 (310) (c=1.041, chloroform).

6β-Vinyl-B-norestr-4-ene-3,17-dione (**23**)——To a stirred solution of 199 mg of 6β-vinyl-B-norestran-5β-ol-3,17-dione (**22**) in a mixture of 1.5 ml of absolute pyridine and 1.2 ml of dry methylene chloride cooled in a bath of −68°, 0.06 ml of thionyl chloride diluted with 0.14 ml of dry methylene chloride was added under nitrogen in one portion. The resulting solution was stirred for 110 sec, transfered into 30 ml of 50% ethylene glycol cooled to −50°, and stirred for 5 min. After dilution with water, the solution was extracted with methylene chloride. The residue obtained was chromatographed on 3 g of neutral alumina (Woelm II). The eluates of benzene–methulene chloride (9:1) were crystallized from methylene chloride–ether to afford 105 mg of 6β-vinyl-B-norestr-4-ene-3,17-dione (**23**), mp 122—125°. A pure sample melts at 127—129°. *Anal.* Calcd. for $C_{19}H_{24}O$: C, 80.24; H, 8.51. Found: C, 80.65; H, 8.47. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1736, 1667, and 914. $[\alpha]_D^{22}$ 147.6±2° (c=1.034, chloroform). CD [θ] (mμ): +24400 (210), −33500 (245), ,+11800 (304), +8250 (327) (c=0.0128, 0.128, methanol), −75800 (242), ×19000 (304), +15600 (323), +16300 (332) (c=0.1034, cholroform).

5β-Cyano-6β-vinyl-β-norestrane-3,17-dione (**24a**)——A solution of 692 mg of 6β-vinyl B-norestr-4-ene-3,17-dione (**23**) in 30 ml of dry methylene chloride was treated with 9.35 ml of 1.3 M/liter solution of diethylaluminum cyanide in benzene under nitrogen stream and sllowed to stand at room temperature for 1 hr. The resulting mixture was poured into ice-cold 2N hydrochloric acid and extracted with ether–methylene chloride (3:1). The organic solution was washed successively with water, 2N sodium hydroxide solution, and water, dried, and on complete removal of the solvent under reduced pressure yielded the crude enone (**24a**) as a crystalline residue, which was purified by column chromatography using 34 g of neutral alumina (Woelm II). The column was eluted with a large volume of benzene and the residue was recrystallized from methanol to produce 322 mg of 5β-cyano-6β-vinyl-B-norestrane-3,17-dione (**24a**), mp 220—222°. The mother liquors were purified by silica gel layer chromatography, developed with benzene–ethyl acetate (1:4) and an additionsl 20 mg of (**24a**), mp 213—218°, was obtained. A pure sample melts at 222—222.5°. *Anal.* Calcd. for $C_{20}H_{25}O_2N$: C, 77.13; H, 8.09; N, 4.50. Found: C, 77.08; H, 8.10; N, 4.54. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2237, 1732, 1642, and 930. $[\alpha]_D^{22}$ +87.7±2° (c=1.041, chloroform). CD [θ] (mμ): +6520 (301) (c=1.041, chloroform).

3,3-Dimethoxy-5β-cyano-6β-vinyl-B-norestran-17-one (**25a**)——A solution of 204 mg of 5β-cyano-6β-vinyl-B-norestrane-3,17-dione (**24a**) and 20 mg of *p*-toluenesulfonic acid monohydrate in 20 ml of absolute methanol was heated under reflux for 4 hr, cooled, poured onto ice–cold 2N sodium carbonate solution, and extracted with methylene chloride. The extracts were crystallized from ether to give 156 mg of 3,3-dimethoxy-5β-cyano-6β-vinyl-B-norestran-17-one (**25a**), mp 147—149°. The crystals were recrystallized from ether to give an analytical sample, mp 152—154°. *Anal.* Calcd. for $C_{22}H_{31}O_3N$: C, 73.91; H, 8.74; N,3. 92. Found: C, 74.02; H, 8.73; N, 4.04. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2235, 1744, 1642, 1112, 1054, and 726.

Preparation of 5β-Cyano-6β-vinyl-B-norestran-17β-ol-3-one (**24b**)——To a solution of 205 mg of 3,3-dimethoxy-5β-cyano-6β-vinyl-B-norestran-17-one (**25a**) in 10 ml of methanol was added 205 mg of sodium borohydride in three portions with ice–cooling and the resulting mixture was stirred at room temperature for 2 hr and then for further 1 hr after addition of a further 100 mg of the reagent. The reaction mixture was poured into ice–water and extracted with methylene chloride. On removal of the solvent the extract gave a crude residue of the 17β-hydroxyl derivative (**25b**), which was used for further reaction without purification. The residue dissolved in 8 ml dioxane was mixed with 1 ml of 30% perchloric acid, allowed to stand at room temperature for 15 hr, poured into ice–cold 2N sodium carbonate solution, and extracted with methylene chloride. The methylene chloride solution was washed with water, dried, and the solvent was removed under

reduced pressure to give a residue. The residue was chromatographed on 4 g of neutral alumina (Woelm II) and the eluates of benzene–benzene–methylene chloride (9:1) were crystallized from ether, producing 89 mg of 5β-cyano-6β-vinyl-B-norestran-17β-ol-3-one (**24b**), mp 125—127°. A sample melting at 125—127° was analyzed. *Anal.* Calcd. for $C_{20}H_{27}O_2N$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.85; H, 8.71; N, 4.36. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620, 3463, 1726, 1641, and 923. $[\alpha]_D^{22}$ + 14.4 ±2° (*c*=1.111, chloroform). CD [θ] (mμ): −7120 (298) (*c*=0.0896, methanol), −3350 (297.5) (*c*=1.111, chroroform).

6-Formyl-B-norandrost-5-ene-3β,17β-diol 3β,17β-diacetate (**26**)——A mixture of the aldo-B-norsteroid (**3a**) (2.034 g), methanol (230 ml), potassium carbonate (7 g), and water (70 ml) was stirred at room temperature for 4.5 hr, concentrated *in vacuo*, diluted with water, and extracted with chloroform–methanol (4:1). The organic extract was worked up to leave 1.688 g of a residue which was reacetylated with acetic anhydride (3 ml) and pyridine (9 ml). The mixture was worked up as usual to leave 1.854 g of a residue which was crystallized from methylene chloride–pentane to give 834 mg of the conjugated aldehyde (**26**), mp 194—196°, and 405 mg of the second crop, mp 188—194°, in 64% yield. *Anal.* Calcd. for $C_{23}H_{35}O_5$: C, 71.10; H, 8.30. Found: C, 71.17; H, 8.38. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2740, 1739, 1681, 1607. $[\alpha]_D^{24.5}$ −90.2±2° (*c*=1.062, $CHCl_3$).

6-Formyl-B-norandrost-5-ene-3β,17β-diol 3β,17β-diacetate 6a-cyanohydrin (**27**)——To a suspension of the conjugated aldehyde **26** (3.353 g) in tetrahydrofurau (15 ml) a solution of hydrogen cyanide (700 mg) and diethylalumium chloride (5.2 g) in tetrahydrofuran (35 ml) was added at 3° under nitrogen. The mixture was stirred for 10 min, cooled to −55°, diluted with 2N hydrochloric acid (40 ml), stirred for 1 hr, poured into ice-water, and extracted with methylene chloride. The methylene chloride extract was washed with water, dried, and evaporated to leave 3.76 g of a residue whfich was crystallized from ether-pentane to give 3.287 g (92%) of the cyanohydrin (**27**), mp 151—154°. An analytical sample melts at 161—163°. *Anal.* Calcd. for $C_{24}H_{33}O_5N$: C, 69.37; H, 8.01; N, 3.39. Found: C, 69.27; H, 8.05; N, 3.43. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1727. $[\alpha]_D^{25}$ −97.6 ±3.3° (*c*=0.423, $CHCl_3$).

6-Cyanoformyl-B-norandrost-5-ene-3β,17β-diol 3β,17β-diacetate (**28**)——To a solution of the cyanohydirn (**27**) (311 mg) in dry benzene (20 ml) was added manganese dioxide (3 g). The suspension was stirred at room temperature for 3 hr, and filtered. The filtrate was evaporated to leave 234 mg of a residue which was crystallized from dry ether–pentane to give 119.5 mg of the conjugated acid cyanide (**28**), mp 158—161°, and 59.2 mg of second crop, mp 140—146°, in 58% yiels. An analytical sample melts at 163—164.5°. *Anal.* Calcd. for $C_{24}H_{31}O_5N$: C, 69.71; H, 7.56; N, 3.39. Found: C, 69.69; H, 7.50; N, 3.46. IR ν_{max}^{Nujol} cm^{-1}: 2226, 1737, 1657, 1599. $[\alpha]_D^{25}$ −92.8±6° (*c*=0.207, $CHCl_3$).

5α-Cyano-6β-hydroxylmethyl-β-nor-5α-androstane-3β,17β-diol 3β,17β-diacetate (**29**)——A mixture of the conjugated acid cyanide (**28**) (920 mg) and a solution (11 ml) of diethylaluminum cyanide in toluene (0.90 mmole/ml) was stirred at room tempe rature for 1 hr. The mixture was added to a solution of sodium borohydride (2 g) in tetrahydrofuran (50 ml) and water (25 ml) at room temperature. The reaction mixture was stirred for 30 min, poured into ice–2N-hydrochloric acid, and extracted with methylene chloride. The methylene chloride extract was washed with water, dried, and evaporated to leave 998 mg of a residue which was chromatographed on alumina (30 g). Fractions eluted with benzene and benzene–chloroform (9:1—2:1) were crystallized from ether–pentane to give 357 mg (39%) of the *trans*-cyanoaclcohol (**29**), mp 170—172°. An analytical sample melts at 175—176°. *Anal.* Calcd. for $C_{24}H_{35}O_5N$: C, 69.03; H, 8.45; N, 3.35. Found: C, 68.54; H, 8.84; N, 3.46. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2236, 1729. $[\alpha]_D^{25}$ −1.5±1.0° (*c*=0.406, $CHCl_3$), $[\alpha]_{365}^{25}$ −9.1±1.2° (*c*=0.406, $CHCl_3$).