Hydrocyanation. VI. Application of the New Hydrocyanation Methods to Conjugate Hydrocyanation of α,β-Unsaturated Ketones, Conjugated Dienones, and Conjugated Enamines and to Preparation of α-Cyanohydrins

W. Nagata,* M. Yoshioka, and M. Murakami

Contribution from the Shionogi Research Laboratory, Shionogi and Company, Limited, Fukushima-ku, Osaka, Japan. *Received February 9, 1970*

Abstract: The new hydrocyanation methods using a combination of hydrogen cyanide and an alkylaluminum (method A) and diethylaluminum cyanide (method B) have been applied successfully to conjugate hydrocyanation of the following α,β-unsaturated ketones to the corresponding β-cyano ketones: mesityl oxide, cyclohexenone, bi- and tricyclic enones, and steroidal enones. The methods were applied also to conjugate hydrocyanation of a steroidal 4,6-dien-3-one to the 6α-cyano-4-en-3-one, a 1,4-dien-3-one to the 1α- and 5β-cyano-3-ones, and 19-nortestosterone enamines to the 5-cyano-3-ones (after hydrolysis). Application to preparation of α-cyanohydrins from carbonyl compounds of low reactivity is described also.

Two new hydrocyanation methods have been developed in our laboratory:[1a] method A uses a combination of hydrogen cyanide (HCN) and an alkylaluminum (AlR_3) and method B employs diethylaluminum cyanide (Et_2AlCN). The most useful application of the new methods will be conjugate hydrocyanation of α,β-unsaturated ketones (for significance of the reaction, see ref 1a). The choice of the reagent and reaction conditions depends on structures of enones and affects the stereoselectivity in angular cyanation of polycyclic enones.

In this paper, we report the conjugate hydrocyanation of various types of α,β-unsaturated ketones, the structure–reactivity relationship, preparation of starting enones, and stereochemical proof for hydrocyanation products. Also are reported conjugate hydrocyanation of conjugated dienones and enamines and preparation of α-cyanohydrins from carbonyl compounds of low reactivity.

Results and Discussion

Hydrocyanation of α,β-Unsaturated Ketones. Tables I and II list the results of hydrocyanation of α,β-unsaturated ketones having a bridgehead β-carbon atom (angular cyanation) in the octalin and hydrindene systems, respectively. Conjugate hydrocyanation of α,β-unsaturated ketones having a nonbridgehead β-carbon atom (nonangular cyanation) is shown in Table III. In these tables, there are listed for comparison the data of hydrocyanation by the earlier method using potassium cyanide and ammonium chloride[2a] (referred to as method C). Also, the data already published by us are included with indication of references[3] to give a better understanding of the scope of conjugate hydrocyanation. Preparation of novel starting materials and structure elucidation for products are described in a later section.

The data listed in these tables indicate that most of α,β-unsaturated ketones are hydrocyanated by methods A and B under mild conditions to give β-cyano ketones in good yields. The efficiency of the new methods is demonstrated in hydrocyanation of the tricyclic enones **3** and **7** (Table I, entries 2 and 4) and the Δ^5-7-oxo **29** as well as Δ^8-11-oxo steroids **31** (Table I, entries 15 and 16). Hydrocyanation of these electrically or sterically deactivated enones is not successful by the earlier method C. Hydrocyanation of the tricyclic enone **3** conjugated with an anisole ring is successful only with HCN–Et_2AlCl (a preliminary experiment revealed that a major amount of the enone **3** was recovered unchanged in reaction with Et_2AlCN). The HCN–Et_2AlCl combination is effective for activating the enone system of the electrically deactivated substrate in favor of 1,4 addition. Although data are not given here, one can expect that hydrocyanation by method C would be very difficult for compounds **9**, **25**, **27**, **33**, and **35** (Table I, entries 5, 13, 14, 17, and 18). Smooth introduction of the cyano group at the steroidal 8β position (Table I, entries 16 and 17) is of great significance, because the 8β position is hindered by the C-18 and C-19 angular methyl groups, and direct introduction of a carbon-containing substituent by other known methods such as alkylation is almost impossible.[4a]

Smooth introduction of an angular cyano group into many sterically hindered bridgehead carbons indicates that the steric requirement of the cyanating species in the present new methods is considerably smaller than

(1) (a) W. Nagata, M. Yoshioka, and S. Hirai, *J. Amer. Chem. Soc.*, **94**, 4635 (1972); (b) W. Nagata, M. Yoshioka, and T. Terasawa, *ibid.*, **94**, 4672 (1972); (c) W. Nagata, M. Yoshioka, and M. Murakami, *ibid.*, **94**, 4644 (1972); (d) W. Nagata, M. Yoshioka, T. Okumura, and M. Murakami, *J. Chem. Soc. C*, 2355 (1970).

(2) (a) W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *J. Org. Chem.*, **26**, 2413 (1961); (b) S. Hirai, *Chem. Pharm. Bull.*, **9**, 837 (1961).

(3) (a) W. Nagata, I. Kikkawa, and M. Fujimoto, *ibid.*, 11, 226 (1963); (b) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Amer. Chem. Soc.*, **85**, 2342 (1963); *ibid.*, **89**, 1483 (1967); (c) M. Narisada, Ph.D. Dissertation, Kyoto University, 1964; (d) W. Nagata, T. Terasawa, S. Hirai, and K. Takeda, *Tetrahedron Lett.*, No. 17, 27 (1960); W. Nagata, *Tetrahedron*, 13, 278 (1961); (e) W. Nagata, T. Terasawa, and T. Aoki, *Chem. Pharm. Bull.*, 11, 820 (1963); (f) K. Takeda, K. Igarashi, and M. Narisada, *Steroids*, 4, 305 (1964); (g) W. Nagata and Y. Hayase, *J. Chem. Soc. C*, 460 (1969); (h) W. Nagata, *Proc. Sym. Drug Res.*, 188 (1966); H. Itazaki, Ph.D. Dissertation, Tokyo University, 1969; (i) W. Nagata, M. Narisada, and T. Sugasawa, *Tetrahedron Lett.*, 1041 (1962); *J. Chem. Soc. C*, 648 (1967); (j) W. Nagata, M. Narisada, T. Wakabayashi, Y. Hayase, and M. Murakami, *Chem. Pharm. Bull.*, 19, 1567 (1971); (k) W. Nagata, I. Kikkawa, and K. Takeda, *ibid.*, **9**, 79 (1961); (l) W. Nagata, T. Terasawa, and T. Aoki, *Tetrahedron Lett.*, 856 (1963).

(4) (a) G. Amiard, J. Mathieu, K. Heymes, and T. V. Thuong, *Bull. Soc. Chim. Fr.*, 1031 (1961); 2321 (1965); (b) J. Romo, *Tetrahedron*, 3, 37 (1958).

that in the conventional methods and that of the Grignard reagent. Nevertheless, the steric effect is an important factor to affect the rate of the conjugate hydrocyanation (see the later discussion on steric hindrance).

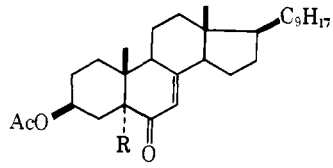
Side reactions such as hydrolysis and dimerization hardly occur in the new methods A and B. Hydrocyanation of compounds **15** (Table I, entry 8) and **39** (Table II, entry 1), which are very susceptible to acid and base, would be never successful by method C or other conventional methods. The use of a neutral reagent, Et_2AlCN, is the key to their successful hydrocyanation. A good yield (72%) of the 16α-cyano compound **54b** in hydrocyanation of the alkali-sensitive 21-acetoxy-Δ^{16}-20-oxo steroid **53b** (Table III, entry 3) by method A contrasts with a poor yield (12%) in the reaction by the conventional method.[4b] In hydrocyanation with $HCN-AlEt_3$ in THF, cyanation at the β carbon greatly predominates over alkylation of the keto function. However, for an α,β-unsaturated ketone having a less reactive β carbon, substitution of Et_2AlCl for $AlEt_3$ is preferable to avoid possible alkylation of the keto function, as can be seen from entry 2 of Table I (stimulation of the 1,4 addition also contributes to the success).

The axial addition principle is borne out throughout all the examples. The trans and cis product ratio in angular cyanation of polycyclic α,β-unsaturated ketones is an important stereochemical problem and discussed in detail in the accompanying paper.[1b] It is noteworthy that the predominant formation of *trans*-cyano ketones in good yields in hydrocyanation of the $\Delta^{13(17)}$-20-oxo steroids **45** and **47** (Table II, entries 4 and 5) is greatly advantageous for the total syntheses of 20-oxo steroids,[3d,3e,3l,3k] latifoline,[5] and conessine.[5,6] The thermodynamic nature of method B and the time dependence of the trans to cis ratio, as shown in hydrocyanation of **19** (Table I, entry 10), **23a** (Table I, entry 12), and **45** (Table II, entry 4), are discussed in detail in the foregoing[1a] and accompanying[1b] papers.

Structure–Reactivity Relationship in Conjugate Hydrocyanation of α,β-Unsaturated Ketones. To examine the dependence of the reactivity on the enone structure, relative rates for conjugate hydrocyanation of various enones with Et_2AlCN in THF were determined. The data are given in Table IV where the rate for the reaction of cholestenone (**23a**) is taken as unity and the favored direction of the cyanide attack is shown in parentheses ("α and β attack" indicates a lack of the favored direction).

These results reveal the following factors affecting the reactivity of α,β-unsaturated ketones.

Steric Hindrance at the β Carbon. Comparison of example 1 with 3 indicates that a methyl group syn-axial to the β carbon of enones decreases the rate by a factor of 200. A smaller rate retardation by a factor of 10 due to a syn-axial hydrogen can be seen by comparing example 5 with 4. The rate retardation is ascribed to the steric hindrance between the entering cyanide and the syn-axial methyl or hydrogen. The steric hindrance depends on the ring distortion[8] which changes the internuclear distance between two syn-axial substituents. The distances can be estimated from molecular models of primary products.[1b] Examination of the models indicates that the internuclear distance between the 9α-methyl and the introduced 5α-cyano group (steriodal numbering) in example 3 is shorter than the distances between the 18- and 19-methyls and the 8β-cyano group in examples 4 and 5. The smaller methyl–cyano steric interaction coupled with instability of the 1,2 adduct (see below) accounts for a higher reactivity of the Δ^8-11-one **33b** than that of the tricyclic enone **7**. Preliminary experiments have shown that conjugate hydrocyanation of the following Δ^7-6-oxo compounds with $HCN-AlEt_3$ was unsuccessful.[3h]



R = H, OH, OAc

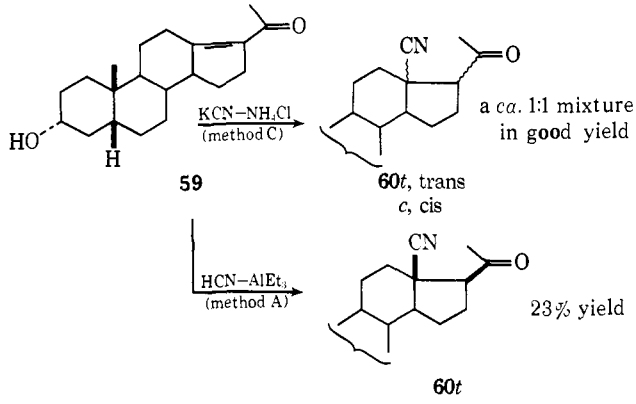
Examination of models revealed that the steric interaction between the 18-methyl and the 8β-cyano group is greater than that in example 4. The greater steric hindrance and considerable stability of the 1,2 adduct (see below) explain the unreactivity of Δ^7-6-oxo compounds.

Another example of rate retardation by steric hindrance is hydrocyanation of 6β-ethyl-B-norandrost-4-en-3-one (**41c**). Although the rates were not measured, a higher temperature (70°) needed for the reaction of **41c** and a poorer yield of the nitrile **42c** as compared with 6β-vinyl and 6β-methyl analogs (Table II, entries 1 and 2) are indicative of a steric interaction between the 6β-ethyl and the 5-cyano groups.

Stability of 1,2 Adduct. Preceding formation of enone α-cyanohydrins (1,2 adducts) retards method-B conjugate hydrocyanation of enones, and the retardation depends on the stability (equilibrium constant) of the 1,2 adduct as discussed in the previous paper.[1c] The greatest retardation is seen in hydrocyanation of α,β-unsaturated aldehydes.[1d] The preceding forma-

(5) W. Nagata, T. Terasawa, and T. Aoki, *Tetrahedron Lett.*, 869 (1963).

(6) In connection with total synthesis of conessine and progesterone, Johnson and his coworkers[7] also reported hydrocyanation of the $\Delta^{13(17)}$-20-oxo steroid **59** according to our methods A and C.



Although the result of method C is reasonable, the poor yield (23%) of the *trans*-cyano ketone **60t** reported for method A should be ascribable to unfit reaction conditions and/or improper work-up, because hydrocyanation of the analogous compounds **45** and **47** by method A in our hands afforded the *trans*-cyano ketones **46t** and **48t** in good yields.

(7) W. S. Johnson, J. A. Marshall, J. F. W. Keana, R. W. Franck, D. G. Martin, and V. J. Bauer, *Tetrahedron, Suppl.*, **8**, 541 (1966).

(8) (a) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, 77, 2505 (1955); (b) R. Bucourt and D. Hainaut, *Bull. Soc. Chim. Fr.*, 1366 (1965).

Table I. Hydrocyanation of Enones Having a Bridgehead β-Carbon Atom in the Octalin System

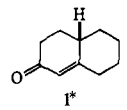
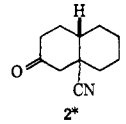
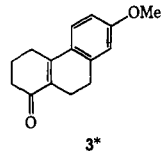
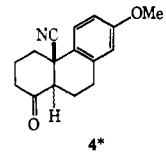
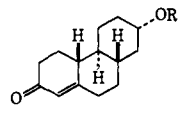
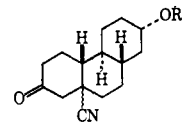
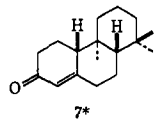
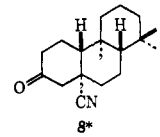
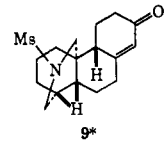
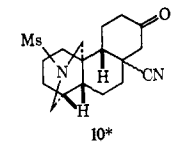
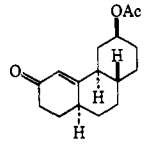
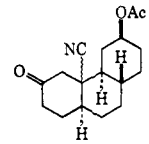
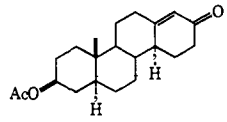
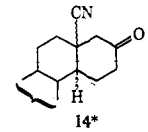
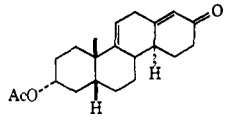
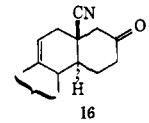
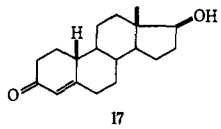
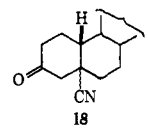
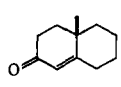
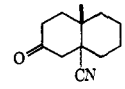
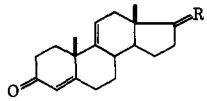
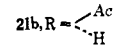
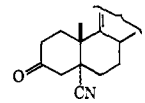
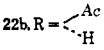
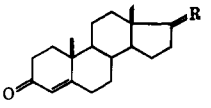
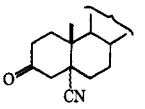
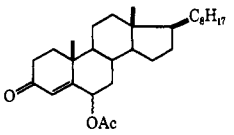
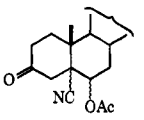
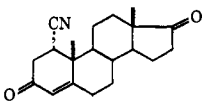
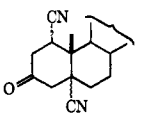
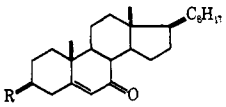
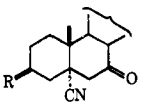
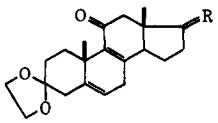
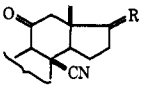
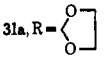
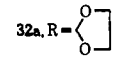
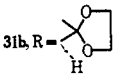
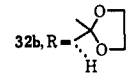
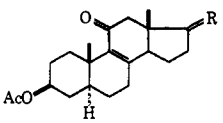
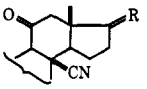
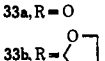
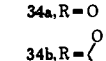
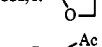
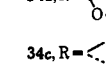
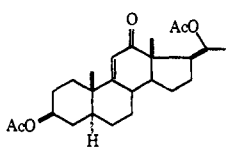
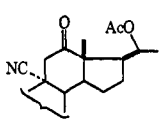
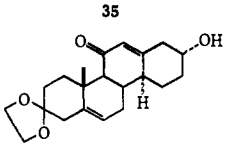
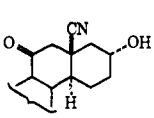
Entry	Enone[a]	Product	Method and conditions[b]	Yields,[c] % Trans	Cis	Ref[d]
1	 1*	 2*	A(THF), rt 1 hr	72	4	3a
			A(THF), 25°, 6 hr	89[e]	11[e]	1b
			A′(THF), rt, 2 hr	70	9	
			B(bz), 25°, 2 min	87[e]	13[e]	1b
			B(bz), 25°, 6 hr	84[e]	16[e]	1b
			C(DMF), 20°, 29 hr	45	22	3a
2	 3*	 4*	A(THF), rt 42 hr	11	0	3b
			A′(THF), rt, 45 hr	45[f]	30[f]	3b
			C(DMF), 100°, 8 hr	0	0	3b
3	 5a*, R = Ac 5b*, R = H	 6a*, R = Ac 6b*, R = H	A(THF), rt, 2.5 hr	65	10	
			C(DMF), 100°, 6 hr	43	32	
4	 7*	 8*	A(THF), rt, 36 hr	72	0	3c
			C(DMF), 100°, 54 hr	14	0	3c
5	 9*	 10*	A(THF), rt, 48 hr	60	1	3b
6	 11*	 12*	A(THF), rt, 3.5 hr	50	30	
			A′(THF), rt, 22 hr[g]	41	27	
7	 13*	 14*	A(THF), rt, 2.5 hr	68	13	
			C(MeOH), reflux, 1.5 hr	41	25	3d
8	 15	 16	A(THF), rt, 15 hr[g]	55[h]	0	3e
9	 17	 18	A(THF), rt 1 hr	67	18	
10	 19*	 20*	A(THF), 25°, 8 hr	71[e]	29[e]	1b
			B(bz), 25°, 2 min	64[e]	36[e]	1b
			B(bz), 25°, 20 hr	13[e]	87[e]	1b
			C(DMF), 100°, 5.5 hr	57[e]	43[e]	1b
11	 21a, R = O 21b, R = 	 22a, R = O 22b, R = 	A(THF), rt, 4 hr	76	8	3f
			C(DMF), 100°, 65 hr	53	15	3f
			A(THF), rt, 2 hr	53	2	

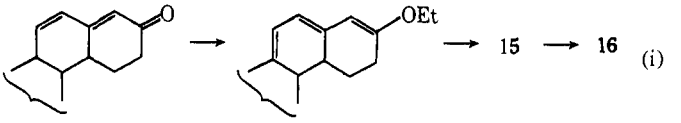
Table I (*Continued*)

Entry	Enone[a]	Product	Method and conditions[b]	Yields,[c] single % Trans	Cis	Ref[d]
12			A(THF), rt, 3.5 hr	49	42	1a
			B(THF), 15°, 4 hr	45	42	1a
			B(bz), rt, 10 min	40	42	1a
			B(bz), 25°, 10 hr	10[e]	90[e]	1a
			C(DMF), 100°, 8 hr	33	51	1a
	23a, R = 	**24a**, R = 				
	23b, R = 	**24b**, R = 	A(THF), rt, 4 hr	47	37	
	23c, R = O	**24c**, R = O	A(THF), rt, 2.5 hr	43	36	
	23d, R = 	**24d**, R = 	A(THF), rt, 16 hr[g]	47	23	3g
	23e, R = 	**24e**, R = 	A′(THF), rt, 23 hr[g]	40	39	
			A″(THF), rt, 17 hr	42	34	
13						
	25a, α-OAc	**26a**, α-OAc	B(bz), rt, 26 min	25	31	
	25b, β-OAc	**26b**, β-OAc	B(bz–tol), rt, 6 hr	15	24	
14			B(THF), rt, 5 hr	12	51	
	27	**28**				
15						
	29a, R = H	**30a**, R = H	A(THF), rt, 4.5 hr	93	0	
	29b, R = OAc	**30b**, R = OAc	A(THF), 25°, 7 hr	93	0	
	29c, R = OH	**30c**, R = OH	C(DMF), 100°, 33 hr	43	0	
16						
			A(THF), rt, 30 hr	74	0	1a
	31a, R = 	**32a**, R = 	B(bz), 0°, 10 min	92[i]	0	1a
			C(DMF), 100°, 8 hr	0	0	1a
			A(THF), rt, 22 hr	52[j]	0	3h
	31b, R = 	**32b**, R = 	B(bz–tol), 0°, 30 min	83[i]	0	3h
	31c, R = BMD[l]	**32c**, R = BMD[l]	B(bz–tol), 0°, 1 hr	82[i]	0	3h
17						
	33a, R = O	**34a**, R = O	A(THF), rt, 16 hr	65	0	3h
	33b, R = 	**34b**, R = 	B(bz), 0°, 10 min	84[i]	0	3h
	33c, R = 	**34c**, R = 	A(THF), rt, 23 hr	78	0	3h
18			B(bz–tol), rt, 3 hr	77	0	
	35	**36**				
19			A(THF), rt, 25 hr[g]	73[k]	0	3i
			C(DMF), 100°, 7 hr	90	0	3i
	37	**38**				

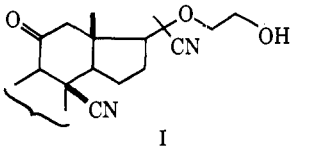
Footnotes to Table I follow on the next page.

Table I (*Continued*)

[a] The compound marked with asterisk indicates the *dl* form. The *d* form is not marked. [b] Method A, HCN–$AlEt_3$; A′, HCN–Et_2AlCl; A″, HCN–$EtAlCl_2$; B, Et_2AlCN; C, KCN–NH_4Cl. Solvent THF, tetrahydrofuran (in method B, it contains a small amount of isopropyl ether or toluene coming from a reagent stock solution); bz, benzene; tol, toluene; DMF, dimethylformamide–water (8:1); rt, room temperature. [c] Isolated yields unless otherwise stated. [d] Reference in which data are reported already by Nagata, *et al.* [e] Estimated by gas-liquid chromatography. [f] There was obtained a *ca.* 1:1.5 mixture of the cis and trans isomers in 75% yield from which the trans isomer was isolated in 69% yield by repeated isomerization and crystallization. [g] The reaction mixture was let stand overnight, though the reaction was complete in several hours. [h] This value is for the overall yield of the equation below (i).



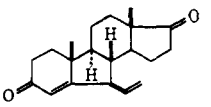
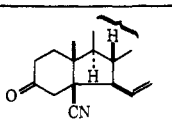
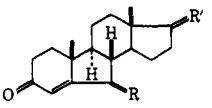
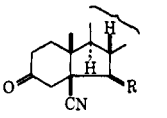
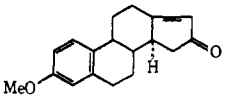
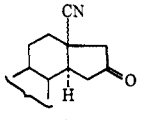
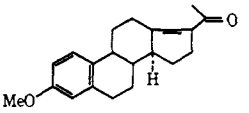
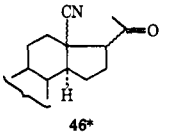
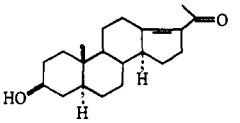
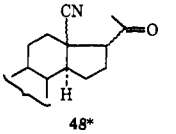
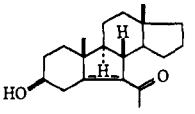
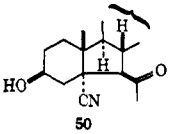
(i)



I

[i] Since the product contained *ca.* 20% of the unchanged enone, hydrocyanation was repeated on the recovered enone. [j] By-product I (above) was obtained in 8% yield. [k] In this case, 20 and 13 molar equiv of HCN and $AlEt_3$ were used. The yield of 73% lower than that in method C may be attributed to the use of an unfavorable excess of the reagent coupled with the unnecessary extension of the reaction time. [l] BMD = 17a,20:20,21-bismethylenedioxy.

Table II. Hydrocyanation of α,β-Unsaturated Ketones Having a Bridgehead Carbon Atom in the Hydrindene System

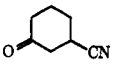
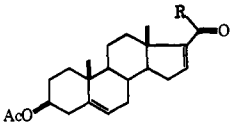
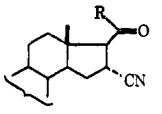
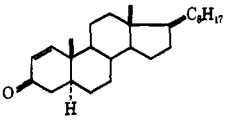
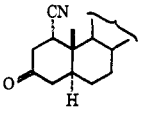
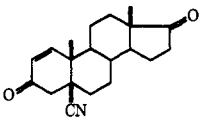
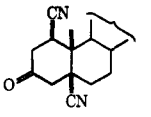
Entry	Enone[a]	Product	Method and conditions[b]	Yields,[c] % Trans	Cis	Ref[d]
1	 **39**	 **40**	A(THF), rt, 6 hr	0	16	3j
			B(bz–CH_2Cl_2), rt, 3 hr	0	61	3j
2						
	41a, R = H; R′ = O	**42a**, R = H; R′ = O	B(THF), rt, 2 hr	0	85	
	41b, R = Me; R′ = O	**42b**, R = Me; R′ = O	B(THF), rt, 2 hr	0	80	
	41c, R = Et; R′ = O	**42c**, R = Et; R′ = O	B(THF), 70°, 1 hr	0	13	
	41d, R = H; R′ = H_2	**42d**, R = H; R′ = H_2	B(THF), rt, 2 hr	0	72	
	41e, R = Me; R′ = H_2	**42e**, R = Me; R′ = H_2	B(THF), rt, 2.5 hr	0	54	
3	 **43***	 **44***	A(THF), rt, 3.5 hr	16	65	
4	 **45***	 **46***	A(THF), rt, 12 hr	67[f]	9[f]	1a
			B(bz), 25°, 3 min	69[e]	31[e]	1a
			B(bz), 25°, 10 hr	46[e]	54[e]	1a
			C(DMF), 100°, 8 hr	22	57	3k
5	 **47***	 **48***	A(THF), rt, 2.5 hr	80	0	3i
			B(bz–CH_2Cl_2), rt, 20 min	77[g]	3[g]	
6	 **49**	 **50**	B(bz–tol), rt, 30 min	93[g]	0	

[a–e] The same as footnotes *a–e* of Table I. [f] A mixture of the cis and trans isomers was isolated in 8% yield. [g] The same as footnote *i* of Table I.

tion of the 1,2 adducts in about 95% yields was observed in examples 1–3 and 6–9, whereas the Δ^8-11-oxo compounds having a hindered oxo group (examples 4 and 5) did not form the 1,2 adducts (the adducts are unstable). Thus, the conjugate hydrocyanation is much favored for the Δ^8-11-ones as compared with the other enones having a less hindered oxo group.

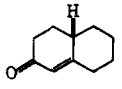
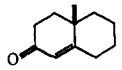
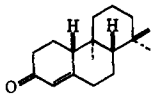
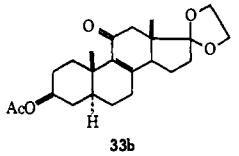
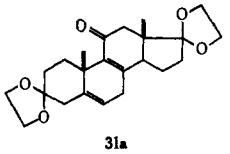
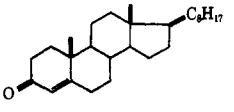
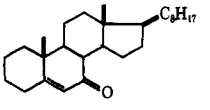
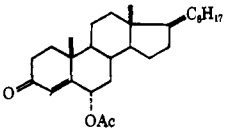
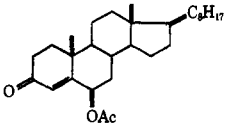
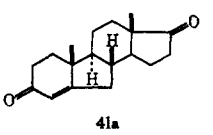
Rigidity. Comparison of examples 1, 2, 6, 7, and 10 indicates the rate is reduced by introduction of an angular methyl group, increase in the number of rings, transfer of the enone system to an intermediate ring, and the fusion of a five-membered ring. Since the β carbons in these examples are subject to a similar steric hindrance, this rate retardation is ascribed to an

Table III. Hydrocyanation of α,β-Unsaturated Ketones Having Nonbridgehead β Carbon

Entry	Enone[a]	Product	Method and conditions[b]	Yield,[c] %
1	$CH_3COCH{=}C(CH_3)_2$ **51a**	$CH_3COCH_2C(CN)(CH_3)_2$ **52a**	A(THF), rt, 3.5 hr A′(THF), rt, 3.5 hr	88 86
2	 **51b**	 **52b***	A(ether), −15°, 22 hr B(bz–hexane), −15°, 1 hr	80 57[d]
3	 **53a**, R = Me **53b**, R = CH_2OAc	 **54a**, R = Me **54b**, R = CH_2OAc	A(THF), rt, 2.5 hr A(THF), rt, 7.5 hr	69 72
4	 **55**	 **56**	A(THF), rt, 1.3 hr	90
5	 **57**	 **58**	B(THF), rt, 5 hr	78

[a–c] The same as footnotes *a–c* of Table II. [d] The starting enone was recovered in 13% yield.

Table IV. Relative Reactivities for Conjugate Hydrocyanation of Various Enones with Diethylaluminum Cyanide in Tetrahydrofuran

Example no.	Enone	Relative rate
1	 **1** (α attack)	10
2	 **19** (α attack)	1.7
3	 **7** (α attack)	0.053
4	 **33b** (β attack)	0.17
5	 **31a** (β attack)	1.8
6	 **23a** (α and β attack)	1.0
7	 **29a** (α attack)	0.26
8	 **25a** (α and β attack)	0.12
9	 **25b** (α and β attack)	0.016
10	 **41a** (β attack)	0.13

energy increase in the transition state by conformational rigidity (strains) of a polycyclic system.[1b]

Neighboring Group Participation. The rate retardation observed for the 6-acetoxy-Δ^4-3-oxo steroids (examples 8 and 9) would be due to a steric interaction and participation of the neighboring acetoxyl group to deactivate the reaction center C-5. The eightfold rate retardation for the 6β-acetoxy enone **25b** as compared with the 6α epimer **25a** will be due to a greater electronic participation of the 6β- than the 6α-acetoxyl group.[9]

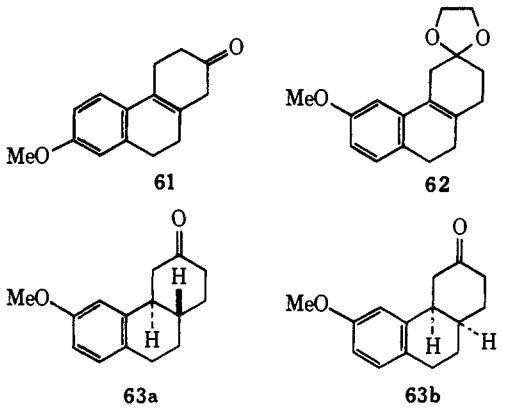
These factors discussed here are useful for selection of the reaction conditions which are illustrated in Tables I–III.

Preparation of Starting Enones and Structural Elucidation for β-Cyano Ketones. Preparation of new α,β-unsaturated ketones and structural elucidation for new hydrocyanation products listed in Tables I–III are given below. References for known compounds are cited in the Experimental Section.

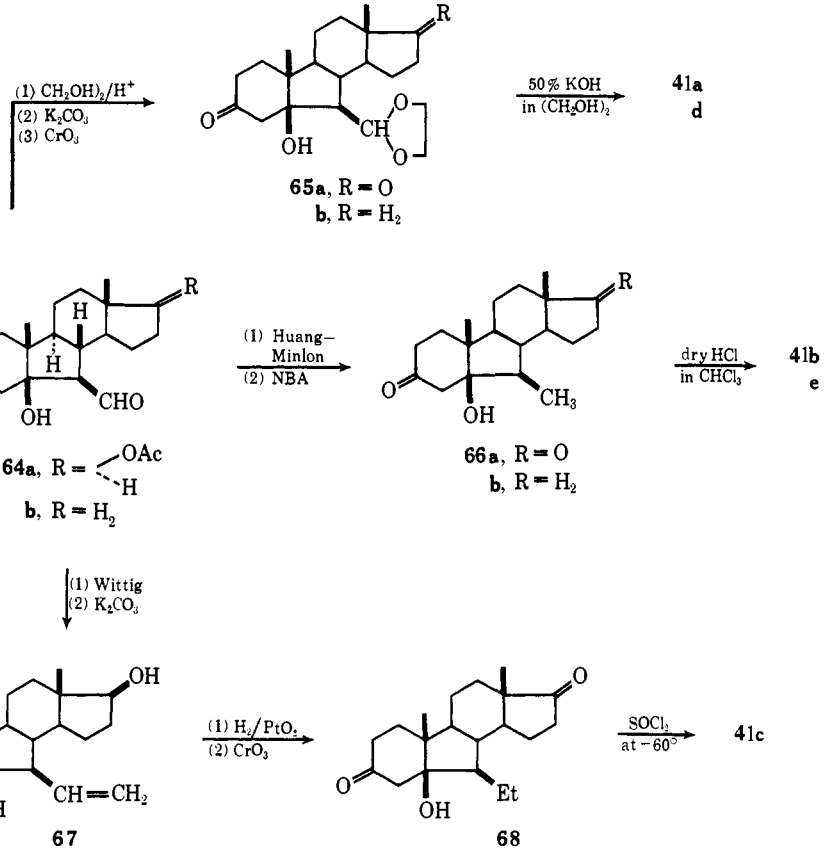
A. α,β-Unsaturated Ketones. The tricyclic ketones **5a** and **b** were prepared from compounds **61**[10a] by the Birch reduction and subsequent acid treatment followed by acetylation. Treatment of the unsaturated ketal **62**[10b] with sodium in liquid ammonia in the presence of aniline followed by acid treatment afforded the B,C-*trans*-ketone **63a** and the cis epimer **63b** in 51 and 26% yields, respectively. The trans and cis assignment to these ketones is based on the fact that the catalytic hydrogenation of the ketal **62** followed by acid treatment gave only the epimer **63b**. The Birch reduction of the *trans*-ketone **63a** followed by acid treatment and acetyla-

(9) K. Kuriyama, M. Moriyama, T. Iwata, and K. Tori, *Tetrahedron Lett.*, 1661 (1968).

(10) (a) W. S. Worall, Ph.D. Thesis, Harvard University, Cambridge, Mass., 1949; W. Nagata, T. Terasawa, I. Kikkawa, and K. Takeda, *Chem. Pharm. Bull.*, **9**, 756 (1961). (b) The material **62** was provided by Dr. H. Tada of this laboratory, to whom we express our appreciation.



Scheme I



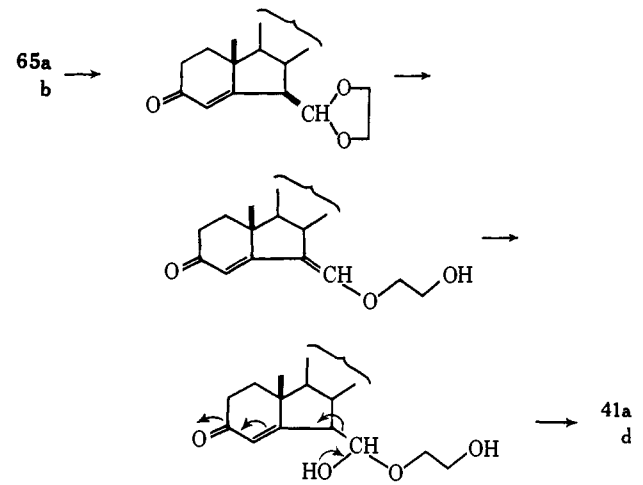
tion gave the tricyclic enone **11**. The assigned ring juncture and the equatorial hydroxyl in **5** and **11** are deduced from the thermodynamic nature of the Birch reduction. Compounds **27** and **57** were prepared by hydrocyanation of androsta-1,4-diene-3,17-dione, the details of which are described in the next section.

The Δ^4-3-oxo-B-nor steroids **41a–e** were prepared from the B-nor-6β-formyl-5β-ols **64a** and **b** as shown in Scheme I. Of these compounds, compounds **41a** and **b** are known, but the preparation procedures are different from those reported.[11,12] Conversion of the 6β-ethylenedioxymethyl derivatives **65a** and **b** into the 6-unsubstituted enones **41a** and **d** is unique and would follow the path shown in Scheme II. Assignment of the 6β-alkyl configuration to **41b**, **c**, and **e** is based on the nonisomerizable reaction conditions employed for dehydration of the corresponding 5β-hydroxyl compounds.

The Δ^5-6-acetyl-B-norsteroid **49** was prepared from the 6β-formyl-5β-ol **64b** by dehydration, Grignard reaction of the resulting enal **69**, and selective oxidation of the thus obtained diol **70** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

B. Hydrocyanation Products. In this paper, the subscripts *t* and *c* in products indicate trans and cis epimers, respectively. Configurations of the tricyclic *trans*- and *cis*-cyano ketones, **6a***t*, **6b***t*, **6a***c*, and **6b***c*, were determined by comparison of hydrolysis rates for the corresponding tetrahydropyranyl ethers **71***t* and *c*, the rate for the latter being *ca.* 15 times that of the former.

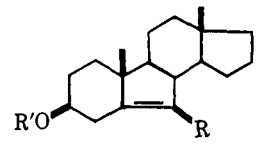
Scheme II



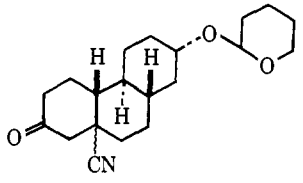
The more reactive cyano group in **71***c* should be equatorial (β).[2a] The assignment was confirmed by com-

(11) (a) K. Tanabe, R. Hayashi, and R. Takasaki, *Chem. Pharm. Bull.*, **9**, 12 (1961); (b) K. Tanabe and Y. Morisawa, *ibid.*, 11, 536 (1963).

(12) R. Takasaki, *ibid.*, **10**, 439 (1962). The 6β-methyl configuration in **66a** has been established. We are grateful to him for supplying us with an authentic sample of **66a**.



69, R = CHO; R′ = Ac
70, R = CH(OH)CH$_3$; R′ = H
49, R = COCH$_3$; R′ = H

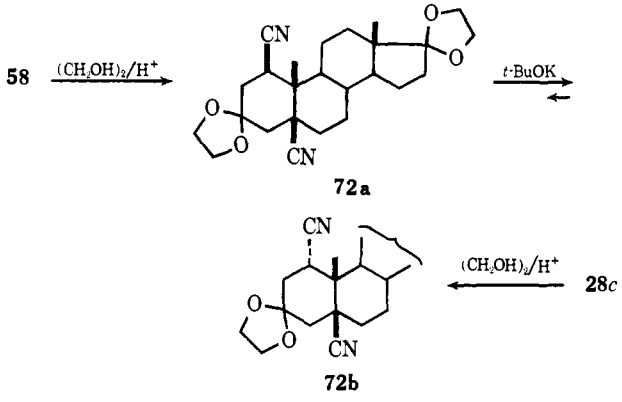


71*t*, α-CN
c, β-CN

parison of the cyano band intensities of **6a***t* and *c* in the infrared.[13] The structures of compounds **12***t* and *c* also are based on comparison of their cyano band intensities.

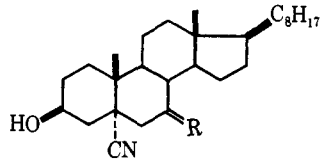
Configurations of the 3-oxo-5-carbonitriles, **22b***t* and *c*, **24c***t* and *c*, **26a***t* and *c*, and **26b***t* and *c*, were determined by comparing[2a] their ORD and CD data with those of 5α- and 5β-3-oxo steroids.[14-16] The assignments for compounds **22b** and **24c** were confirmed by comparison of cyano band intensities.[13]

Configurations of the 1,5-dicyano-3-oxo steroids, **28***t* and *c*, and **58**, are based on the following evidence: the ketal **72a** derived from the dicyano ketone **58** was



epimerized with potassium *tert*-butoxide to the other ketal which was identical with compound **72b** derived from the other dicyano ketone **28***c*. Since the 5β-cyano structure in **58** and the 1α-cyano configuration in **28***c* have been established (see next section), the 1α,5β-dicyano structure is definitely assigned to compound **72b** and also to **28***c*. Then, the epimeric dicyano compounds **72a** and **58** are assigned the 1β,5β-dicyano structure. The 5α-cyano configuration of **28***t* epimeric to **28***c* was confirmed from the nmr signal of the C-19 methyl group appearing at 1.22 ppm (calcd 1.26 ppm).

The structure of the 7-oxo-5-carbonitrile **30c** is based



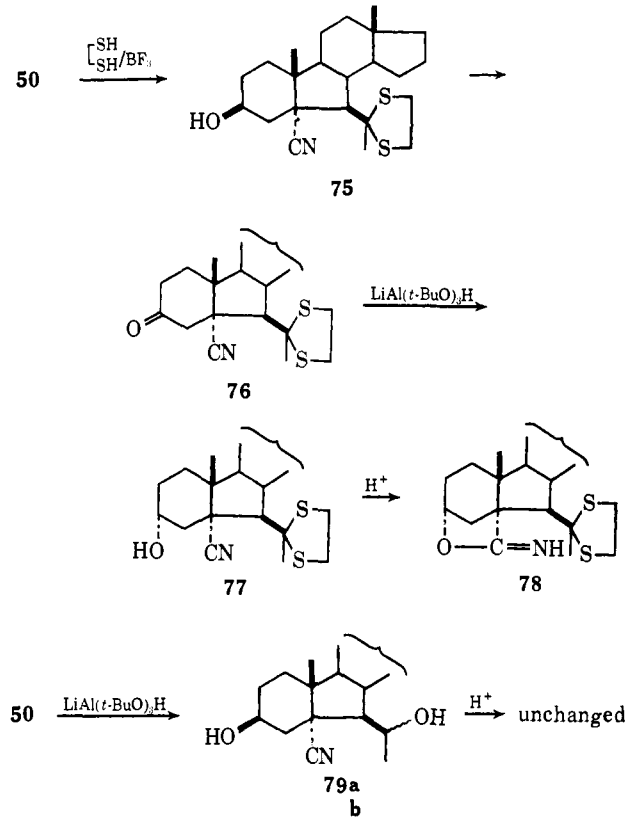
30c, R = O
73, R = 
74, R = H$_2$

on its conversion into the known 5α-cyano compound **74**[2b] *via* the thioketal **73**. The 5α-configuration of the 3-desoxy analog **30a** was confirmed from a negative Cotton effect in its CD curve.[14]

Structural assignment for the B-nor steroids **42d** and **e** is based on their negative Cotton effect curves.[17] The structures of the 17-oxo analogs **42a-c** are deduced by analogy. The configurations of the 13-cyano-16-oxo compounds **44***t* and *c* are determined by comparison of their cyano band intensities.

Structural elucidation for the 5-cyano-6-acetyl-B-nor steroid **50** was carried out as shown in Scheme III.

Scheme III



Namely, the 5α configuration was proved by conversion of compound **50** into the imino lactone **78** *via* the cyano thioketals **75-77** and supported by a positive Cotton effect in the CD curve of the 3-oxo compound **76**. The β configuration of the 6-acetyl group in **50** was deduced

(13) For differentiation of *trans*- and *cis*-cyano ketones by cyano band intensities, see W. Nagata, M. Yoshioka, M. Narisada, and H. Watanabe, *Tetrahedron Lett.*, 3133 (1964).

(14) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill, New York, N. Y., 1960; Leon Velluz, "Optical Circular Dichroism," Academic Press, New York, N. Y., 1965.

(15) For ORD and CD data, see Experimental Section.

(16) For pairs of compounds having an additional carbonyl group at C-17 or C-20, the isomer which showed a stronger positive Cotton effect was assigned the α configuration on a reasonable assumption that little vicinal effect is present between the 3-oxo and the 17- or 20-oxo groups and the additivity rule holds.[14]

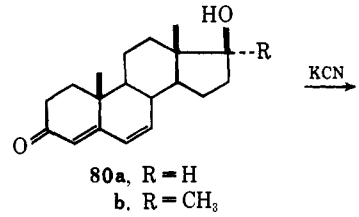
(17) T. Fajkoš, J. Joska, and F. Šorm, *Collect. Czech. Chem. Commun.*, 28, 605 (1963); J. Joska, J. Fajkoš, and F. Šorm, *ibid.*, 31, 2745 (1966).

from stability of the 6α-hydroxyl derivatives **79a** and **b** to acid-catalyzed cyclization.

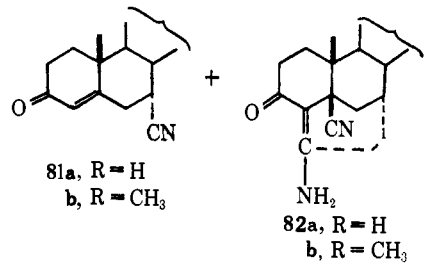
Hydrocyanation of Conjugated Dienones. Christiansen and Johnson[18] have studied hydrocyanation of the steroidal 4,6-dien-3-ones **80a** and **b** with potassium cyanide and obtained the 7α-cyano-Δ^4-3-ketones **81a** and **b** in only 6–13% yields in addition to 33–36% yields of the amino derivatives **82** which probably are formed from 5,7-dicyano derivatives. Komeno and Hayashi of our laboratory[19a] also have examined hydrocyanation of **80a** by method C (KCN–NH_4Cl) and obtained **81a** and **82a** in 55 and 10% yields, respectively. They assigned the 7α configuration to the nitrile **81a** on the basis of conversion into the known 17β-hydroxy-7α-methylandrost-4-en-3-one.[20]

The low yields of the 7α-cyano compounds **81** by the conventional methods prompted us to investigate hydrocyanation of the dienone **80a** by the new methods A and B. A preliminary experiment showed that method A (HCN–$AlEt_3$) was not preferable owing to the formation of by-products, probably dicyano compounds. On the other hand, method B afforded a *ca.* 8:2 equilibrium mixture of the nitrile **81a** and the starting material **80a** with little by-products. The nitrile **81a** was isolated in 77% yield by crystallization of the mixture, and additional crops of **81a** (15% yield) were obtained by rehydrocyanation of the residue from the mother liquor. The result is quite satisfactory.

To our knowledge, hydrocyanation of $\Delta^{2,4}$-3-oxo steroids has not been reported.[21] We tested the new hydrocyanation methods on androsta-1,4-diene-3,17-dione **83**. Treatment of **83** with Et_2AlCN (method B) afforded the two monocyano ketones, **27** and **57**, in 52 and 26% yields, respectively. The dicyano ketones **28***t* and *c* and **58** were produced as by-products in hydrocyanation of **83** by method A. The positions of the cyano groups in **27** and **57** were deduced from the fact that compound **27** showed an ultraviolet absorption at 241.5 mμ (calcd 244 mμ) and the 5-cyano isomer **57** at



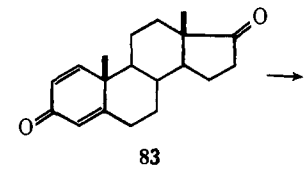
80a, R = H
b, R = CH_3



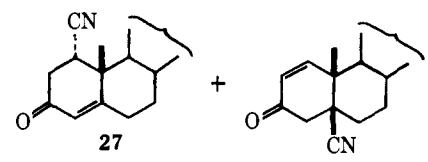
81a, R = H
b, R = CH_3

82a, R = H
b, R = CH_3

229 mμ (calcd 227 mμ). The 1α-cyano configuration is evident from its nmr signal of the C-19 methyl group appearing at 1.32 ppm (calcd for 1α- and 1β-cyano



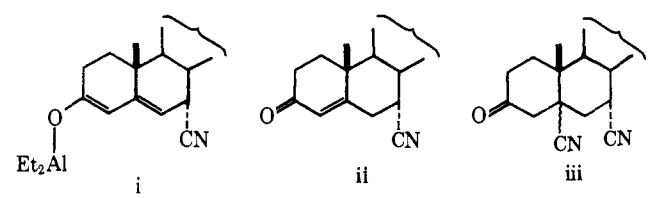
83



27 **57**

forms: 1.35 and 1.47 ppm[22]) coupled with a triplet pattern (J = 4 cps) for the 1β hydrogen. The structure of the 5β nitrile **57** is based on its hydrogenation into the known 5β-cyano ketone **24cc**.

In hydrocyanation of conjugated dienones, method B is advantageous over method A and KCN methods in that method B does not yield dicyano compounds as by-products which are produced by the other methods. Exclusive formation of monocyano compounds in method B is rationalized by the consideration that the cyanated product is present in the form of an enolate such as i in the reaction mixture.[1a,1c] In method A and



i ii iii

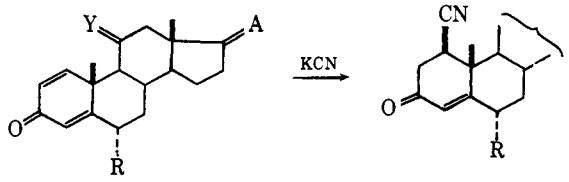
conventional methods, a monocyano ketone such as ii is formed, partly or entirely, in the reaction mixture and suffers the second hydrocyanation to produce a dicyano compound such as iii. The stereochemistry of hydrocyanation of conjugated dienones is discussed in a subsequent paper.[1b]

(18) R. G. Christiansen and W. S. Johnson, *Steroids*, 1, 620 (1963). They did not assign the configuration of the cyano group.

(19) (a) T. Komeno and S. Hayashi, private communication; (b) After completing the writing of this manuscript, we noticed that O. R. Rodig and N. J. Johnston, *J. Org. Chem.*, 34, 1949 (1969), had studied conjugate addition of tetrahydro-1,4a-dimethyl-2-naphthalenone with potassium cyanide in the absence or presence of ammonium chloride. In the absence of ammonium chloride, the products are two lactamols, while in the presence of this salt they are three ketodinitriles. These results well demonstrate the difficulty in obtaining 1,6 adducts in hydrocyanation of α,β,γ,δ-unsaturated ketones.

(20) J. A. Campbell and J. C. Babcock, *J. Amer. Chem. Soc.*, 81, 4069 (1959).

(21) A. Bowers and H. J. Ringold, U. S. Patent 3,054,809 (1962), have claimed the following conversion. We doubt their result, because



R = H, CH_3, F

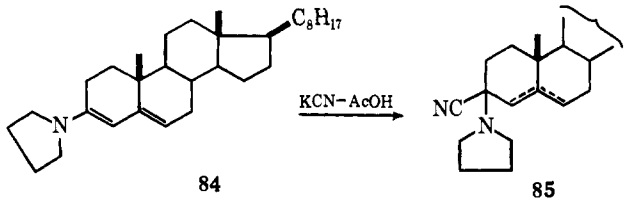
Y = H_2, O, 

A = O, 

they gave no physical properties for the products and 1α-cyano compounds would be expected.

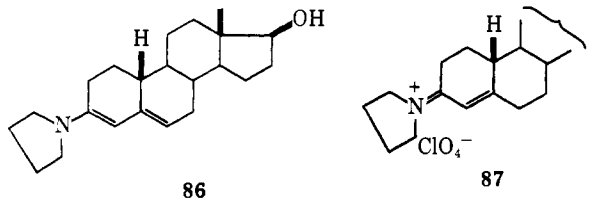
(22) *Cf.* A. T. Glen and J. McLean, *Tetrahedron Lett.*, 1387 (1964); A. T. Glen, W. Lawrie and J. McLean, *J. Chem. Soc.*, 661 (1966).

Hydrocyanation of Conjugated Enamines. Johnson and his coworkers[23] have examined hydrocyanation of cholestenone pyrrolidine enamine (**84**) with potassium

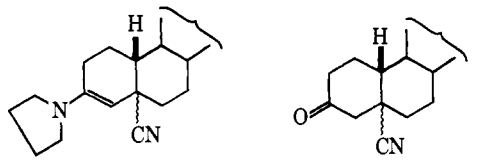


84 **85**

cyanide and acetic acid, and obtained only the 3-cyano-3-pyrrolidinyl-$\Delta^{4 \text{ or } 5}$-olefin **85**. We have carried out hydrocyanation of 19-nortestosterone pyrrolidine enamine (**86**) and its perchlorate **87** by the new methods.

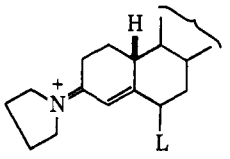


86 **87**



88*t*, α-CN
c, β-CN

18*t*, α-CN
c, β-CN

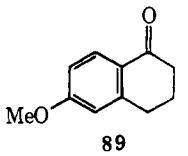


iv
L = H or Et_2Al

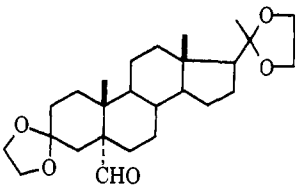
In contrast to the result of the Johnson group, the enamine **86** reacted with HCN–$AlEt_3$ under mild conditions (room temperature, 3.5 hr) to give a mixture of the 5α- and 5β-cyano enamines **88***t* and *c*. The mixture was not separated and underwent acid hydrolysis to afford the *trans*- and *cis*-cyano ketones **18***t* and *c* in 62 and 15% yields, respectively. The result is comparable to that obtained in the hydrocyanation of 19-nortestosterone (**17**) with HCN–$AlEt_3$. Hydrocyanation of **86** with Et_2AlCN also proceeded smoothly to give, after acid hydrolysis of the product, the *trans*-cyano ketone **18***t* in 57% yield. The enamine perchlorate **87** reacted with HCN–$AlEt_3$ under the same conditions as used for the enamine **86** to afford, after hydrolysis of the product, the nitrile **18***t* and *c* in 43 and 19% yields.

Comparable results obtained in reaction of the enone **17** and its enamine **86** with HCN–$AlEt_3$ coupled with smooth hydrocyanation of the enamine perchlorate **87** would suggest intermediacy of the quaternary iminium salt iv in the hydrocyanation of the conjugated enamine **86** by the new methods.

Hydrocyanation of Carbonyl Compounds of Low Reactivity. Usual ketones and aldehydes are known to be converted easily into their α-cyanohydrins by the conventional methods.[24] However, electrically deactivated or sterically hindered carbonyl compounds resist the addition of hydrogen cyanide. For example, hydrocyanation of 6-methoxy-1-tetralone (**89**) has



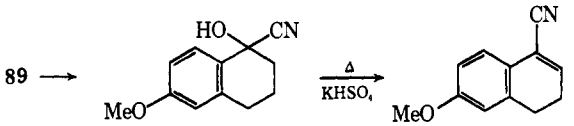
89



90

never been successful by earlier methods,[25] because the reactivity of the carbonyl group is greatly lowered by conjugation with the *p*-anisole-type grouping. We have observed that addition of hydrogen cyanide to the sterically hindered 5α-carboxaldehyde **90** by conventional methods failed. Application of the new hydrocyanation methods seemed promising and turned out to be successful.

Preliminary experiments showed that the α-tetralone **89** reacted with Et_2AlCN at low temperature, but not with method-A reagents, and the α-cyanohydrin product was unstable. Then, hydrocyanation of **89** was performed with varied molar ratios of Et_2AlCN at varied reaction temperatures, and the unstable α-cyanohydrin **91**, without purification, was converted into



91 **92**

the conjugated nitrile **92**. The results are summarized in Table V. Since the product **92** can be easily separated by crystallization or column chromatography from the unchanged **89**, which can be recycled, the results of Table V are quite satisfactory.

Table V. Results of Hydrocyanation of 6-Methoxy-1-tetralone (**89**)

Molar equiv of Et_2AlCN	Temp, °C	Time, min	Isolated yields, % 92	Unchanged 89
3.3	−35 ± 3	80	79	19
2.8	−28 ± 3	90	83	14
2.3	−24 ± 2	80	85	12
1.8	−15 ± 2	80	85	12

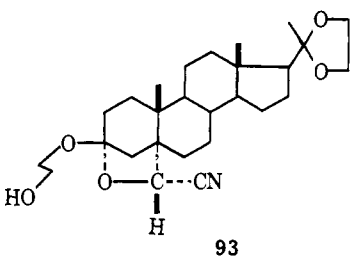
Method A was applied to hydrocyanation of the 5α-formyl steroid **90**. Treatment of **90** with HCN–Et_2AlCl in THF at room temperature for 4 hr afforded the bridged nitrile **93** in 83% yield. The result has been reported already.[26a]

(23) J. L. Johnson, M. E. Herr, J. C. Babcock, A. N. Fonken, J. E. Stafford, and F. W. Heyl, *J. Amer. Chem. Soc.*, **78**, 431 (1956).

(24) C. Djerassi, "Steroid Reactions," Holden-Day, San Francisco, Calif., 1963, p 54.

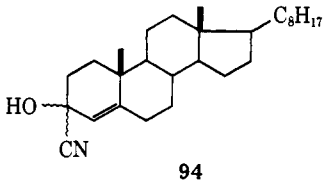
(25) A. J. Birch and R. Robinson, *J. Chem. Soc.*, 503 (1944).

(26) (a) W. Nagata, T. Sugasawa, Y. Hayase, and K. Sasakura, *Proc. Chem. Soc.*, 241 (1964); (b) W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *Justus Liebigs Ann. Chem.*, **641**, 184 (1961); (c) ref 3h and 3l; W. Nagata and I. Kikkawa, *Chem. Pharm. Bull.*, 11, 289 (1963); W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *Justus Liebigs Ann. Chem.*, **641**, 196 (1961); W. Nagata, The 2nd International Symposium on the Chemistry of Natural Products, Prague, 1962, Symposium Papers,



93

Selective 1,2-addition of HCN to cholest-4-en-3-one (**23a**) was accomplished by reaction with Et_2AlCN in THF at −60° for 15 min. The α-cyanohydrin **94** was obtained in 92% yield.



94

Conclusions

Hydrocyanation of various types of α,β-unsaturated ketones to β-cyano ketones are successful by new methods A and B. Also successful are conjugate hydrocyanation of conjugated dienones and enamines and preparation of α-cyanohydrins from carbonyl compounds of low reactivity. These results verify high efficiency, high uniformity, and high selectivity of the new methods. In other words, difficulties encountered in conventional methods on steric and electronic grounds are overcome, undesirable side reactions scarcely occur, and the reaction can be carried out in the presence of other functional groups such as olefinic (isolated), hydroxyl, alkoxyl, acyloxyl, cyano, and amido. As to choice of the method and reaction conditions, the general features of the two methods discussed in the previous papers[1a,1c] and the structure–reactivity relationship are indicative. Because of its reversible nature, the more efficient method-B hydrocyanation does not go to completion in certain cases where the β carbon of the enone system is electrically or sterically deactivated. In such cases, the reaction should be repeated on the unchanged enone or performed with a method-A reagent, the HCN–Et_2AlCl combination being preferable. It should be pointed out that method B is an excellent way to prepare α-cyanohydrins of α,β-unsaturated or aromatic ketones. Preparation of these α-cyanohydrins has been difficult by conventional methods. A relation between the substrate structure and the cis to trans product ratio in angular cyanation of polycyclic α-enones exists and is the subject of the accompanying paper.[1b]

The β-cyano ketones are important synthetic intermediates, and we have been successful in converting angular cyano ketones into polycyclic compounds having various angular carbon substituents such as carboxyl,[3d,3h,3i,26b] aldimino,[26c] aminomethyl,[26c] formyl,[26c] hydroxymethyl,[3h] methyl,[3h,26d] formylmethyl,[26e] 2-formylvinyl,[3g,3j] and vinyl[26e] or having various bridged ring systems.[3b,3j,26e–k]

Experimental Section

All solvents used for method-A and -B hydrocyanations are anhydrous. For handling of alkylaluminums and preparation of Et_2AlCN, see a preceding paper.[1a]

Melting points were measured on a Kofler block and are not corrected. Unless otherwise stated, specific rotations were determined in chloroform with a Perkin-Elmer 141 polarimeter, ir spectra in chloroform with a Koken DS-201B or DS-402G spectrophotometer, and uv spectra in 95% ethanol with a Hitachi EPS-2 or EPS-3T spectrophotometer. ORD and CD curves were obtained with a Rudolf spectropolarimeter and a JASCO model ORD/UV-5 spectropolarimeter. Nmr spectra were recorded with a Varian A-60 or A-60A spectrometer, unless otherwise stated, on chloroform-*d* with tetramethylsilane as an internal standard. Tlc were performed on Merck Kieselgel G and GF_{254}, unless otherwise stated, in benzene–ethyl acetate or acetone–chloroform mixtures in different proportions. For checking purities of products, plates were sprayed with concentrated sulfuric acid and developed on a hot iron plate, and for preparative tlc, plates were examined in uv light (for uv-absorbing materials on GF_{254} plates) or detected after being sprayed with water or a solution of iodine in dichloromethane. Column chromatography was performed according to the method of Reichstein and Shoppee[27] using, unless otherwise stated, Woelm alumina (activity II). Extraction was carried out three times in a countercurrent manner, and extracts were washed with water twice or thrice and dried over anhydrous sodium sulfate. Solvents were evaporated *in vacuo* with a rotatory evaporator at 40–80°. Unless otherwise indicated, acetylation was effected by mixing a substrate with a *ca.* tenfold amount of pyridine and a *ca.* fivefold amount of acetic anhydride and allowing the mixture to stand overnight. Identity with an authentic sample was established by mixture melting point determination and/or comparison of ir spectra and thin layer chromatograms.

Recommended Procedure for Method-A Hydrocyanation.[28] To 40 ml of THF placed in a flask was added 8.9 ml (7.4 g, 0.065 mol) of $AlEt_3$. To the solution was added 13 ml of an 8.1% solution of HCN (1.05 g, 0.039 mol) with stirring and ice cooling. After the stirring was continued for 5 min, the mixture was added quickly through a funnel to a mixture of 5.76 g (0.013 mol) of 3β-acetoxycholest-5-en-7-one (**29b**), 0.12 ml (0.0067 mol) of water, and 40 ml of THF. The resulting mixture was kept at 25° with occasional swirling under nitrogen atmosphere. After 3 hr, a solution of 0.1 ml (0.0056 mol) of water in 2 ml of THF was added, and the mixture was allowed to stand for an additional 4 hr. The reaction mixture was poured slowly into a vigorously stirred mixture of 65 ml of concentrated hydrochloric acid (HCl) and 800 ml of ice water. The mixture was stirred for 20 min with ice cooling and extracted with three 500-ml portions of a 3:1 mixture of ether and dichloromethane. The extracts were washed with three 200-ml portions of ice cold 2 *N* sodium hydroxide (NaOH) and two 200-ml portions of water, dried, and evaporated to give 6.15 g of a crystalline residue. Purification and characterization of the product are given later.

The preparation of the HCN–$AlEt_3$ reagent and the reaction were carried out under nitrogen with vigorous exclusion of moisture and oxygen. However, the above operations may be carried out without protection from moisture except for the standing of the reaction mixture provided the operations are made quickly. In this case, the addition of the water as described above is not necessary. Many method-A hydrocyanations described hereinafter were carried out in this way.

The acid treatment of the reaction mixture followed by alkaline washing of the extracts prevents possible hydrolysis of the acetoxyl and the cyano groups. The alkaline treatment to convert α-cyanohydrins to ketones may be replaced by passage of a product solution through neutral alumina. The latter treatment is preferred for isolation of an alkali-sensitive product. In many cases described hereinafter, the reaction mixture has been poured directly into a mixture

p 37; (d) W. Nagata and H. Itazaki, *Chem. Ind.* (London), 1194 (1964); (e) W. Nagata, M. Narisada, T. Sugasawa, and T. Wakabayashi, *Chem. Pharm. Bull.*, **16**, 885 (1968); (f) W. Nagata and M. Narisada, *ibid.*, **16**, 867 (1968); (g) W. Nagata, M. Narisada, and T. Wakabayashi, *ibid.*, **16**, 857 (1968); (h) W. Nagata, T. Wakabayashi, M. Narisada, M. Yamaguchi, and Y. Hayase, *ibid.*, **19**, 1582 (1971); (i) W. Nagata, T. Wakabayashi, Y. Hayase, M. Narisada, and S. Kamata, *J. Amer. Chem. Soc.*, **92**, 3202 (1970); W. Nagata, T. Wakabayashi, M. Nirisada, Y. Hayase, and S. Kamata, *ibid.*, **93**, 5740 (1971); (j) W. Nagata and S. Hirai, *Chem. Pharm. Bull.*, **16**, 1550 (1968); (k) W. Nagata, T. Sugasawa, and T. Aoki, *ibid.*, **16**, 1556 (1968).

(27) T. Reichstein and C. W. Shoppee, *Discuss. Faraday Soc.*, **7**, 305 (1949).

(28) Procedures for hydrocyanation of **29b** with HCN–$AlEt_3$ and the reaction of **89** with Et_2AlCN will appear in *Org. Syn.* soon.

of 2 *N* NaOH and ice. This operation is inferior to that described above, unless the product is sensitive to acid.

Method-B Hydrocyanation Procedure. The method-B hydrocyanation was carried out in the same way as described in the recommended method-A procedure, except that the HCN–$AlEt_3$ solution was replaced by an Et_2AlCN solution and the water was not added. Vigorous exclusion of moisture is preferred for the reaction.

Hydrocyanation of $\Delta^{1(9)}$-Octalin-2-one (1).[29] A reagent solution consisting of 3.6 mmol of HCN, 6.0 mmol of Et_2AlCl, and 3 ml of THF was added to a solution of 300 mg (2.0 mmol) of enone **1** in 3 ml of THF. The mixture was kept at room temperature for 2 hr, poured into a mixture of 2 *N* NaOH and ice and extracted with dichloromethane. The oily product (343 mg) was crystallized from ether–petroleum ether to give 161 mg (mp 51–53.5°; lit.[3a] mp 55–58°) and 16 mg (mp 44–48°) of 2-oxo-*trans*-decalin-9-carbonitrile (**2***t*).[29] Preparative tlc of the mother liquor followed by crystallization and treatment with semicarbazide gave 62 mg (8.8%) of the semicarbazone of the *cis*-nitrile **2***c*, mp 201–204° (admixture with an authentic sample[3a] of the *cis*-semicarbazone, mp 200–205°), 25 mg of the *trans*-nitrile **2***t*, mp 47–52°, and 60 mg of its semicarbazone, mp 190–198° (admixture with an authentic sample[3a] of the trans semicarbazone, mp 199–203°). The total yield of the trans isomers is 69.8%.

Hydrocyanation of *dl*-7α-Acetoxy-2,3,4,4aβ,4bα,5,6,7,8,8aβ,9,10-dodecahydrophenanthren-2-one (5a) and Its 7β-Hydroxy Compound 5b.[29] **A. Reaction of 5a with HCN–$AlEt_3$.** To a solution of 142 mg (0.541 mmol) of the enone **5a** and 0.54 mmol of water in 1.4 ml of THF was added a reagent solution consisting of 1.6 mmol of HCN, 2.7 mmol of $AlEt_3$, and 1.6 ml of THF. After being kept at room temperature for 2.5 hr, the reaction mixture was poured into a mixture of 2 *N* NaOH and ice and extracted with chloroform. The partly hydrolyzed product was acetylated to give 164 mg of a mixture of *dl*-7α-acetoxy-2-oxo-1,2,3,4,4aβ,4bα,5,6,7,8,8aβ,9,10,10aα-tetradecahydrophenanthrene-10a-carbonitrile (**6a***t*)[29] and the cis epimer.[29] Preparative tlc of the product (160 mg) followed by crystallization from dichloromethane–ether gave 100 mg (65.0%) of the *trans*-nitrile **6a***t*, mp 146–147.5°, and 15 mg (9.8%) of the *cis*-nitrile **6a***c*, mp 181–185°.

An analytical sample of the *trans*-nitrile **6a***t* had mp 153–154°; ir 2238 (ε 13.1) (CN) and 1725 cm^{-1} (C=O and ester C=O).

Anal. Calcd for $C_{17}H_{23}O_3N$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.71; H, 7.86; N, 4.70.

An analytical sample of the *cis*-nitrile **6a***c* had mp 190–193°; ir 2237 (ε 21.6) (CN) and 1725 cm^{-1} (C=O and ester C=O).

Anal. Calcd for $C_{17}H_{23}O_3N$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.44; H, 8.09; N, 4.79.

Glpc analysis of the above reacetylation product showed that the trans to cis ratio was 85:15. The glpc conditions were 1.5 m × 4 mm glass column, 3% QF-1 (FS 1265) Gaschrom Q; column temperature, 220°; N_2, 60 cc/min; Shimazu GC-4A-PF gas chromatograph; hydrogen flame ionization detector. The trans and the cis isomers **6a***t* and **6a***c* had retention times of 13.7 and 15.7 min, respectively.

B. Reaction of 5b with KCN–NH_4Cl. A mixture of 5.0 g (0.0227 mol) of the hydroxy enone **5b**, 2.95 g (0.0454 mol) of KCN, 1.72 g (0.034 mol) of NH_4Cl, 100 ml of dimethylformamide, and 10 ml of water was heated at 100° for 6 hr, cooled, neutralized with acetic acid, concentrated *in vacuo*, mixed with water, and extracted with chloroform to give 5.9 g of a crystalline residue. Recrystallization from acetone–ether afforded 1.773 g (31.6%) of the *trans*-cyano ketone **6b***t*, mp 198–203°; ir (Nujol) 3525 (OH), 2242 (CN), and 1710 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{21}O_2N$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.68; H, 8.50; N, 5.82.

Chromatography of the residue from the mother liquor gave 0.794 g (14.1%) of the *cis*-cyano ketone **6b***c*; mp 175.5–178° (from acetone–ether); ir (Nujol) 3615, 3525 (br) (OH), 2243 (CN), and 1716 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{21}O_2N$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.66; H, 8.46; N, 5.84.

The noncrystalline parts (2.6 g) were combined and ketalized in the usual way. Repeated chromatography of the ketalization product gave 0.861 g of the ketal of **6b***t*, mp 170–172.5°, which on deketalization afforded an additional 0.659 g (11.8%) of **6b***t*, mp 196–201°. The residual ketal portion was deketalized, and the product was crystallized from acetone–ether to yield an additional 1.016 g (18.1%) of **6b***c*, mp 175–178°.

Hydrocyanation of *dl*-6β-Acetoxy-1,2,3,4bα,5,6,7,8,8aβ,9,10,10aα-dodecahydrophenanthren-3-one (11).[29] **A. With HCN–$AlEt_3$.** To a solution of 0.2 g (0.762 mmol) of the enone **11** in 1.8 ml of THF containing 0.762 mmol of water was added a reagent solution consisting of 2.29 mmol of HCN, 3.81 mmol of $AlEt_3$, and 2.2 ml of THF. After being kept at room temperature for 3.5 hr, the mixture was poured into a mixture of 2 *N* NaOH and ice and extracted with chloroform. Acetylation of the major part (218 mg) of the residue (225 mg) gave 220 mg of a mixture of the *trans*- and *cis*-cyano ketones **12***t* and *c*. Preparative tlc of the mixture (213 mg) followed by crystallization from dichloromethane–ether afforded 102 mg (49.6%) of *dl*-6β-acetoxy-1,2,3,4,4aβ,4bα,5,6,7,8,8aβ,9,10,10aα-tetradecahydrophenanthrene-4a-carbonitrile (**12***t*),[29] mp 153–156°, and 62.6 mg (30.4%) of the cis epimer **12***c*, mp 179–182°. Glpc analysis[30] of the crude product indicated the trans to cis ratio was 63.4:36.6.

An analytical sample of the *trans*-cyano ketone **12***t* had mp 161–162°: ir 2232 (ε 16.0) (CN) and 1729 cm^{-1} (C=O and ester C=O).

Anal. Calcd for $C_{17}H_{23}O_3N$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.33; H, 8.12; N, 4.52.

An analytical sample of the *cis*-cyano ketone **12***c* melts at 199–200°: ir 2232 (ε 23.9) (CN) and 1732 cm^{-1} (C=O and ester C=O).

Anal. Calcd for $C_{17}H_{23}O_3N$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.65; H, 7.77; N, 5.11.

B. With HCN–Et_2AlCl. A reagent solution consisting of 2.7 mmol of Et_2AlCl, 1.9 mmol of HCN, and 1.7 ml of THF was added to a solution of 100 mg (0.381 mmol) of enone **11** in 0.3 ml of THF. After being kept overnight at room temperature, the reaction mixture was worked up in the same way as described in **A** to give 45 mg (41%) of the *trans*-cyano ketone **12***t*, mp 159.5–161°, and 30 mg (27%) of the cis isomer **12***c*, mp 196.5–197°.

Reaction of *dl*-3β-Acetoxy-D-homo-18-nor-5α-androst-13(17a)-en-17-one (13) with HCN–$AlEt_3$. The enone **13** (0.480 g, 1.45 mmol) in 6 ml of THF was treated with a reagent solution consisting of 3.4 mmol of HCN, 4.35 mmol of $AlEt_3$, and 4 ml of THF at room temperature for 2.5 hr. The reaction mixture was poured into 2 *N* NaOH–ice and extracted with ether–chloroform (3:1). Recrystallization of the crystalline product from chloroform–acetone afforded 0.302 g of *dl*-3β-acetoxy-17-oxo-D-homo-5α-androstane-18-nitrile (**14***t*), mp 223–225°. The residue from the mother liquor was chromatographed. Elution with petroleum ether–benzene (1:1) gave 29.2 mg of the cis epimer **14***c*, mp 227–231° (from chloroform–acetone). Further elution afforded 19.2 mg of the *trans*-cyano ketone **14***t*, mp 215–220°. Ketalization of the residual portions and subsequent chromatography as described in the literature[3d] gave 36.6 mg of the ketal of **14***t* and 43.9 mg of the ketal of **14***c*. All the products isolated were identified with authentic samples.[3d] The total yield of the *trans*-cyano ketone **14***t* and its ketal is 68%, and that of the cis epimer **14***c* and its ketal is 13%.

Hydrocyanation of 19-Nortestosterone (17). To 0.414 g (1.5 mmol) of 19-nortestosterone (**17**) was added a reagent solution consisting of 4.5 mmol of HCN, 6 mmol of $AlEt_3$, and 7 ml of THF. After being kept at room temperature for 1 hr, the mixture was poured into 2 *N* NaOH–ice and extracted with chloroform. Fractional recrystallization of the product from acetone–ether afforded 0.288 g (63.8%) of 17β-hydroxy-3-oxo-19-nor-5α-androstane-5-carbonitrile (**18***t*), mp 242–245° ($[\alpha]^{21}D$ +54° (*c* 1.05) (lit.[31a] mp 240–243°, $[\alpha]^{21}D$ +55°)), and 69 mg (15.3%) of the cis epimer **18***c*, mp 189–193° ($[\alpha]^{21}D$ +20° (*c* 1.14) (lit.[31a] mp 192–195°, $[\alpha]^{24}D$ +21°)). Chromatography of the residue from the mother liquors afforded 15 mg (3.3%) of **18***t* and 14 mg (3.1%) of **18***c*.

Reaction of Pregna-4,9(11)-diene-3,20-dione (21b) with HCN–$AlEt_3$. To a solution of 50.0 g (0.16 mol) of the enone **21b** in 600 ml of THF was added a reagent solution consisting of 0.48 mol of HCN, 0.64 mol of $AlEt_3$, and 400 ml of THF. After being kept at room temperature for 2 hr, the mixture was poured into a mixture of 76.4 g of NaOH and 8 l. of ice water and extracted with ether–chloroform (3:1). Of 53.1 g of the product, a 1.52 g portion was subjected to recrystallization from methanol–ether and repeated chromatography on alumina and silica gel to give 0.810 g of 3,20-

(29) The structures given in Table IV are depicted upside down for convenience.

(30) Glpc conditions were 1.5 m × 4 mm glass column, 1% QF-1 Gaschrom Q; column temp, 205°; N_2, 60 cc/min; Shimazu GC-4A-PF gas chromatograph; hydrogen flame ionization detector. The trans and cis isomers **12***t* and **12***c* had retention times of 5.8 and 8.6 min, respectively.

(31) (a) J. Fishman and T. Torigoe, *Steroids*, **5**, 599 (1965); (b) A. Bowers, *J. Org. Chem.*, **26**, 2043 (1961).

dioxo-5α-pregn-9(11)-ene-5-carbonitrile (**22bt**), mp 204–208°, and 36 mg of the cis epimer **22bc**, mp 210–212°. The estimated yield of the *trans*-cyano ketone **22bt** was 53.3%, and that of the *cis*-cyano ketone **22bc** is 2.4%.

An analytical sample of the *trans*-nitrile had mp 208–210°; $[\alpha]^{24}D$ +109° (*c* 1.05); ir 2226 (ε 19.1) (CN), 1715, and 1702 cm^{-1} (C=O); ORD (*c* 0.212, dioxane) $[\alpha]^{25}_{315}$ +1197° (peak), $[\alpha]^{25}_{270}$ −1202° (trough).

Anal. Calcd for $C_{22}H_{29}O_2N$: C, 77.84; H, 8.61; N, 4.13. Found: C, 77.48; H, 8.55; N, 4.17.

The *cis*-nitrile **22bc** showed the following physical properties: $[\alpha]^{26}D$ +93° (*c* 1.03); ir 2226 (ε 24.0) (CN), 1722, and 1703 cm^{-1} (C=O); ORD (*c* 0.218, dioxane) $[\alpha]^{25}_{315}$ +683° (peak), $[\alpha]^{25}_{270}$ −645° (trough).

Anal. Calcd for $C_{22}H_{29}O_2N$: C, 77.84; H, 8.61; N, 4.13. Found: C, 77.37; H, 8.54; N, 4.32.

Reaction of 17β-Acetoxyandrost-4-en-3-one (23b) with HCN–$AlEt_3$. The enone **23b** (0.500 g, 1.52 mmol) in 6.3 ml of THF was allowed to react with a reagent solution consisting of 3 mmol of HCN, 4.6 mmol of $AlEt_3$, and 3 ml of THF at room temperature for 4 hr. The reaction mixture was poured into 2 *N* NaOH–ice and extracted with dichloromethane. Recrystallization of the crystalline product from ethyl acetate gave 0.132 g (24.4%) of 17β-acetoxy-3-oxo-5α-androstane-5-carbonitrile (**24bt**), mp 234–236° (lit.[31b] mp 231–233°). Preparative tlc of the mother liquor afforded an additional 0.123 g (22.8%) of the *trans*-nitrile **24bt**, mp 234–236°, and 0.198 g (36.7%) of the *cis*-nitrile **24bc**, mp 198–200° (from methanol) (lit.[31b] mp 195–197°).

Reaction of Androst-4-ene-3,17-dione (23c) with HCN–$AlEt_3$. To a solution of 9.92 g (0.0346 mol) of the enone **23c** in 50 ml of THF was added a reagent solution consisting of 0.103 mol of HCN, 0.138 mol of $AlEt_3$, and 70 ml of THF. After being kept at room temperature for 2.5 hr, the reaction mixture was poured into a mixture of 15.2 g of NaOH and 1 l. of ice water. Extraction with chloroform followed by repeated recrystallization of the product (11.3 g) from methanol gave 1.35 g (12.5%) of 3,17-dioxo-5α-androstane-5-carbonitrile (**24ct**), mp 220–227°. The residue from the mother liquor was chromatographed. Elution with petroleum ether–benzene (1:1) to benzene afforded 3.28 g (30.2%) of the *trans*-nitrile **24ct**, mp 220–225°. Further elution gave 3.95 g (36.3%) of the *cis*-nitrile **24cc**.

An analytical sample of the *trans*-nitrile **24ct** showed mp 217–220°; $[\alpha]^{23}D$ +114° (*c* 0.356); ir 2240 (ε 20.0) (CN), 1735, and 1720 cm^{-1} (C=O); CD (*c* 0.356, $CHCl_3$) $[\theta]^{23}_{332}$ 0, $[\theta]^{23}_{299}$ +14322, $[\theta]^{22}_{240}$ 0.

Anal. Calcd for $C_{20}H_{27}O_2N$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.43; H, 8.67; N, 4.35.

An analytical sample of the *cis*-nitrile **24cc** showed mp 227–231°; $[\alpha]^{23}D$ +92° (*c* 0.41); ir 2236 (ε 28.4) (CN), 1733, and 1721 cm^{-1} (C=O); CD (*c* 0.41, $CHCl_3$) $[\theta]^{23}_{332}$ 0, $[\theta]^{23}_{302}$ +9368, $[\theta]^{23}_{250}$ 0.

Anal. Calcd for $C_{20}H_{27}O_2N$: C, 76.64; H, 8.68; H, 4.47. Found: C, 76.37; H, 8.74; N, 4.43.

Hydrocyanation of Testosterone (23e). A. With HCN–Et_2AlCl. To a solution of 100 mg (0.348 mol) of testosterone (**23e**) in 0.4 ml of THF was added a reagent solution consisting of 2.4 mmol of Et_2AlCl, 1.7 mmol of HCN, and 1.6 ml of THF. After being kept overnight (23 hr) at room temperature, the reaction mixture was poured into 2 *N* NaOH–ice and extracted with chloroform. Preparative tlc of the product (108 mg) followed by crystallization from methanol gave 44 mg (40%) of 17β-hydroxy-3-oxo-5α-androstane-5-carbonitrile (**24et**), mp 234–236°, and 42 mg (39%) of the cis isomer (**24ec**), mp 216–216.5°.

The trans isomer **24et** was identical with an authentic sample, mp 229–231°, prepared by hydrolysis of the 17β-acetoxy compound **24bt** with potassium carbonate in methanol.

B. With HCN–$EtAlCl_2$. The enone **23e** (144 mg, 0.5 mmol) in 1.5 ml of THF was treated with a reagent solution consisting of 2.5 mmol of $EtAlCl_2$, 1.5 mmol of HCN, and 1 ml of THF at room temperature overnight (17 hr). The same work-up as described in A gave 66 mg (42%) of the *trans*-nitrile **24et** and 54 mg (34%) of the cis isomer **24ec**.

Reaction of 6α-Acetoxycholest-4-en-3-one (25a) with Et_2AlCN. The enone **25a**[32] (0.202 g, 0.456 mmol) in 2.2 ml of benzene was allowed to react with 1.9 ml of a 1.2 *M* solution of Et_2AlCN in benzene at room temperature for 26 min. The reaction mixture was poured into 2 *N* NaOH–ice and extracted with dichloromethane, and the product (0.215 g) was chromatographed. Elution with petroleum ether–benzene (2:1) gave 40.4 mg (18.8%) of 6α-acetoxy-3-oxo-5β-cholestane-5-carbonitrile (**26ac**), mp 144–148° (from methanol). Additional **26ac** (26.1 mg (12.2%), mp 134–136°), was obtained from the mother liquor. Further elution afforded 53.3 mg (24.8%) of the trans epimer **26at**, mp 164–166° (from methanol). Recrystallization gave an analytical sample of **26at**, mp 166.0–166.5°; $[\alpha]^{23}D$ + 28° (*c* 1.09, CH_3OH); ir 2244 (CN), 1740 (ester C=O), and 1723 cm^{-1} (C=O); CD (*c* 0.55, CH_3OH) $[\theta]^{23}_{335}$ 0, $[\theta]^{23}_{290}$ +2837, $[\theta]^{23}_{235}$ 0.

Anal. Calcd for $C_{30}H_{47}O_3N$: C, 76.71; H, 10.09; N, 2.98. Found: C, 76.52; H, 10.01; N, 2.87.

An analytical sample of the *cis*-nitrile **26ac** had mp 148–149.5°; $[\alpha]^{23}D$ +45° (*c* 0.73, CH_3OH); ir 2249 (CN), 1742 (ester C=O), and 1719 cm^{-1} (C=O); CD (*c* 0.73, CH_3OH) $[\theta]^{23}_{315}$ 0, $[\theta]^{23}_{284}$ −450, $[\theta]^{23}_{242}$ −37.

Anal. Calcd for $C_{30}H_{47}O_3N$: C, 76.71; H, 10.09; N, 2.98. Found: C, 76.46; H, 9.93; N, 2.82.

Reaction of 6β-Acetoxycholest-4-en-3-one (25b) with Et_2AlCN. To a solution of 0.310 g (0.7 mmol) of the enone **25b**[32] in 5 ml of toluene was added 2.8 ml of a 1.2 *M* solution of Et_2AlCN in benzene. After being kept at room temperature for 6 hr, the reaction mixture was worked up as described above. Repeated recrystallization of the product from methanol gave 31.4 mg of 6β-acetoxy-3-oxo-5α-cholestane-5-carbonitrile (**26bt**), mp 175–176°. The residue from the mother liquor was chromatographed. Elution with petroleum ether–benzene (2:1 and 1:1) afforded 8.9 mg of crude **26bt**, mp 155°. Further elution gave 44.8 mg of the *cis*-cyano ketone **26bc**, mp 143–146° (from ethanol). Preparative tlc of mixed fractions gave 1.8 mg of **26bt**, mp 162–171°, and 25.0 mg of **26bc**, mp 136–143°. The total yield of the *trans*-cyano ketone **26bt** was 14.6% and that of the cis epimer was 24.2%.

An analytical sample of the *trans*-cyano ketone **26bt** (mp 175–176°) showed the following properties: $[\alpha]^{23}D$ −18° (*c* 0.83, CH_3OH); ir 2240 (CN), 1746 (ester C=O), and 1721 cm^{-1} (C=O); CD (*c* 0.062, CH_3OH) $[\theta]^{23}_{327}$ 0, $[\theta]^{23}_{289}$ +3606, $[\theta]^{23}_{240}$ +373, $[\theta]^{23}_{212}$ +2524.

Anal. Calcd for $C_{30}H_{47}O_3N$: C, 76.71; H, 10.09; N, 2.98. Found: C, 76.56; H, 10.18; N, 2.92.

The *cis*-cyano ketone **26bc** (mp 143–146°) showed the following properties: $[\alpha]^{23}D$ +8.5° (*c* 0.63, CH_3OH); ir 2240 (CN), 1746 OAc), 1726 cm^{-1} (C=O); CD (*c* 0.313, CH_3OH) $[\theta]^{23}_{305}$ 0, $[\theta]^{23}_{285}$ −255, $[\theta]^{23}_{240}$ 0, $[\theta]^{23}_{215}$ +1824.

Anal. Calcd for $C_{30}H_{47}O_3N$: C, 76.71; H, 10.09; N, 2.98. Found: C, 76.69; H, 10.30; N, 2.90.

Reaction of 3,17-Dioxoandrost-4-ene-1α-carbonitrile (27) with Et_2AlCN. The enone **27** (0.301 g, 0.966 mmol) in 4.5 ml of THF was treated with 4 ml of a 1.2 *M* solution of Et_2AlCN in toluene at room temperature for 2.5 hr. The usual work-up and repeated recrystallization of the product from methanol gave 22.4 mg (6.9%) of 3,17-dioxo-5α-androstane-1α,5-dicarbonitrile (**28t**), mp 280–287° (dec). Preparative tlc of the mother liquor afforded an additional 16.5 mg (5.0%) of **28t**, mp 278–285 dec, and 167 mg (51.1%) of the cis epimer **28c**, mp 220–223° (from methanol).

The *trans*-nitrile **28t** had the following properties: $[\alpha]^{21}D$ +85° (*c* 0.45, dioxane); ir 2248 (CN), 1739, and 1715 cm^{-1} (C=O); CD (*c* 0.22, dioxane) $[\theta]^{21}_{330}$ 0, $[\theta]^{21}_{298}$ +6410, $[\theta]^{21}_{250}$ 0; nmr δ 0.90 (s, 3, 18-CH_3) and 1.22 ppm (s, 3, 19-CH_3).

Anal. Calcd for $C_{21}H_{26}O_2N_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.12; H, 7.76; N, 8.12.

An analytical sample of the *cis*-nitrile **28c** had mp 221–222.5°; $[\alpha]^{24}D$ +53.6° (*c* 0.593); ir 2245 (CN) and 1737 cm^{-1} (C=O); CD (*c* 0.035, dioxane) $[\theta]^{24}_{335}$ 0, $[\theta]^{24}_{303}$ +8780, $[\theta]^{24}_{270}$ +2520, $[\theta]^{24}_{250}$ +3890, $[\theta]^{24}_{231}$ 0, $[\theta]^{24}_{220}$ −8560; nmr δ 0.90 (s, 3, 18-CH_3) and 1.61 ppm (s, 3, 19-CH_3).

Anal. Calcd for $C_{21}H_{26}O_2N_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.12; H, 7.76; N, 8.12.

Reaction of Cholest-5-en-7-one (29a) with HCN–$AlEt_3$. The enone **29a**[33] (0.491 g, 1.28 mmol) in 5 ml of THF was allowed to react with a reagent solution consisting of 3.8 mmol of HCN, 6.4 mmol of $AlEt_3$, and 5 ml of THF at room temperature for 4.5 hr. The usual work-up and recrystallization of the product from ethanol gave 0.483 g (92.8%) of 7-oxo-5α-cholestane-5-carbonitrile (**30a**), mp 141–143°. An analytical sample had mp 142–144°; $[\alpha]^{23}D$ −62° (*c* 1.07); ir 2243 (CN) and 1712 cm^{-1} (C=O); ORD (*c* 0.21, CH_3OH) $[\alpha]^{24}_{700}$ −47°, $[\alpha]^{24}_{314}$ −585° (trough), $[\alpha]^{24}_{274}$ +94° (peak), $[\alpha]^{24}_{240}$ −311°.

(32) L. F. Fieser, *J. Amer. Chem. Soc.*, **75**, 4377 (1953); *cf.* C. P. Balant and M. Ehrenstein, *J. Org. Chem.*, 17, 1587 (1952).

(33) A. Nickon and J. F. Bagli, *J. Amer. Chem. Soc.*, **83**, 1498 (1961).

Anal. Calcd for $C_{28}H_{45}ON$: C, 81.69; H, 11.02; N, 3.40. Found: C, 81.88; H, 11.07; N, 3.54.

Reaction of 3β-Acetoxycholest-5-en-7-one (29b) with HCN–AlEt$_3$. The enone **29b** (5.76 g, 0.013 mol) was treated with HCN–AlEt$_3$ as described in Recommended Procedure for Method-A Hydrocyanation. Recrystallization of the product (6.15 g) from benzene–pentane afforded 5.655 g (92.5%) of 3β-acetoxy-7-oxo-5α-cholestane-5-carbonitrile (**30b**), mp 194–195°; $[\alpha]^{23}D$ −36° (*c* 1.07); ir 2217 (CN), 1738 (ester C=O), and 1719 cm^{-1} (C=O).

Anal. Calcd for $C_{30}H_{47}O_3N$: C, 76.71; H, 10.09; N, 2.98. Found: C, 76.14; H, 9.97; N, 3.52.

Reaction of 3β-Hydroxycholest-5-en-7-one (29c) with KCN–NH$_4$Cl. A mixture of 0.500 g (1.25 mmol) of the enone **29c**, 0.147 g (2.5 mmol) of KCN, 0.091 g (1.9 mmol) of NH_4Cl, 20 ml of dimethylformamide, and 2 ml of water was heated at 100° for 23.5 hr. The same amounts of KCN, NH_4Cl, and water as described above and 10 ml of dimethylformamide were added. The heating at 100° was continued for 9.5 hr, and then the mixture was refluxed for 16.5 hr, evaporated to remove the bulk of the solvent, mixed with ice water, and extracted with ether. The product (0.52 g) was chromatographed. Elution with benzene–chloroform (4:1) afforded 82 mg of the unchanged **29c**. Further elution gave 0.232 g (43.4%) of 3β-hydroxy-7-oxo-5α-cholestane-5-carbonitrile (**30c**), mp 179–181° (from acetone–ether); $[\alpha]^{16}D$ −50° (*c* 1.06); ir (Nujol) 3300 (br, OH), 2220 (CN), and 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{28}H_{45}O_2N$: C, 78.63; H, 10.61; N, 3.28. Found: C, 78.00; H, 10.60; N, 3.27.

Reaction of 3β,20β-Diacetoxy-5α-pregn-9(11)-en-12-one (35) with Et$_2$AlCN. The enone **35**[34] (1.291 g, 3.1 mmol) in 26 ml of benzene was treated with 9.5 ml of a 1.7 *M* solution of Et_2AlCN in toluene at room temperature for 3 hr. The reaction mixture was poured into 2 *N* NaOH–ice and extracted with dichloromethane. The product was acetylated to convert the partly formed 20β-hydroxyl derivative. Recrystallization of the acetylation product from ethanol gave 0.415 g of 3β,20β-diacetoxy-12-oxo-5α-pregnane-9-carbonitrile (**36**), mp 240–243°. The residue from the mother liquor was chromatographed. Elution with petroleum ether–benzene (up to 1:1) gave 0.423 g of fractions containing the unchanged **35**. Further elution afforded 0.360 g of the *trans*-cyano ketone **36**, mp 232–237°. The enone-containing fraction (0.423 g) was hydrocyanated again in the same way as described above. Recrystallization of the second product (0.514 g) gave 0.162 g of **36**, mp 240–243°, and chromatography of the residue from the mother liquor afforded 0.108 g of the cyano ketone **36**, mp 239–242°. The total yield of the cyano ketone **36** is 76.7%. The sample of mp 240–243° showed the following data: $[\alpha]^{24}D$ +107° (*c* 1.06); ir 2231 (CN) and 1727 cm^{-1} (C=O and ester C=O); CD (*c* 0.0624, CH_3OH) $[\theta]^{24}_{338}$ 0, $[\theta]^{24}_{290}$ +4205, $[\theta]^{24}_{242}$ +324, $[\theta]^{24}_{215}$ +4653.

Anal. Calcd for $C_{26}H_{37}O_5N$: C, 70.40; H, 8.41; N, 3.16. Found: C, 70.24; H, 8.53; N, 3.14.

Reaction of B-Norandrost-4-ene-3,17-dione (41a) with Et$_2$AlCN. To a solution of 0.272 g (1 mmol) of the enone **41a** in 2.6 ml of THF was added 8.4 ml of a 0.59 *M* solution of Et_2AlCN in benzene. After being kept at room temperature for 2 hr, the reaction mixture was poured into 2 *N* NaOH–ice and extracted with ether. Recrystallization of the product from dichloromethane–ether afforded 0.253 g (84.5%) of 3,17-dioxo-B-nor-5β-androstane-5-carbonitrile (**42a**), mp 166–168°. An analytical sample had mp 168–169°; $[\alpha]^{23}D$ +74° (*c* 1.04); ir 2235 (CN) and 1732 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{23}O_2N$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.22; H, 8.51; N, 4.45.

Reaction of 6β-Methyl-B-norandrost-4-ene-3,17-dione (41b) with Et$_2$AlCN. The enone **41b** (0.100 g, 0.35 mmol) in 1 ml of THF was treated with 3 ml of a 0.59 *M* solution of Et_2AlCN in benzene. The same work-up as described above afforded 88 mg (80%) of 3,17-dioxo-6β-methyl-B-nor-5β-androstane-5-carbonitrile (**42b**), mp 181–184° (from dichloromethane–ether). An analytical sample had mp 184–185°; $[\alpha]^{23}D$ +118° (*c* 1.06); ir 2239 (CN) and 1730 cm^{-1} (C=O).

Anal. Calcd for $C_{20}H_{27}O_2N$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.76; H, 8.61; N, 4.58.

Reaction of 6β-Ethyl-B-norandrost-4-ene-3,17-dione (41c) with Et$_2$AlCN. To a solution of 0.100 g (0.333 mmol) of the enone **41c** in 3 ml of THF was added 1.0 ml of a 1.63 *M* solution of Et_2AlCN in toluene. The mixture was heated at 70° for 1 hr in a sealed tube, poured into 2 *N* NaOH–ice, and extracted with ether. Preparative tlc of the product gave 14.1 mg (13%) of 3,17-dioxo-6β-ethyl-B-nor-5β-androstane-5-carbonitrile (**42c**), mp 183–185° (from dichloromethane–ether). An analytical sample had mp 184–186°; ir 2242 (CN) and 1730 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{29}O_2N$: C, 77.02; H, 8.93; N, 4.28. Found: C, 77.13; H, 8.72; N, 4.23.

Reaction of B-Norandrost-4-en-3-one (41d) with Et$_2$AlCN. The enone **41d** (0.100 g, 0.387 mmol) in 0.8 ml of THF was allowed to react with 1.2 ml of a 1.63 *M* solution of Et_2AlCN in toluene at room temperature for 2 hr. The same work-up as described above afforded 80.0 mg (72.4%) of 3-oxo-B-nor-5β-androstane-5-carbonitrile (**42d**), mp 143–144° (from ether). An analytical sample had mp 144–144.5°; $[\alpha]^{23}D$ −11° (*c* 1.00); ir 2220 (CN) and 1726 cm^{-1} (C=O); CD (*c* 0.069, CH_3OH) $[\theta]^{23}_{330}$ 0, $[\theta]^{23}_{295}$ −5293, $[\theta]^{23}_{290}$ −5392, $[\theta]^{23}_{240}$ −437.

Anal. Calcd for $C_{19}H_{27}ON$: C, 79.95; H, 9.54; N, 4.91. Found: C, 80.22; H, 9.54; N, 5.03.

Reaction of 6β-Methyl-B-norandrost-4-en-3-one (41e) with Et$_2$AlCN. The enone **41e** (0.108 g, 0.396 mmol) in 1.2 ml of THF was treated with 1.2 ml of a 1.63 *M* solution of Et_2AlCN in toluene at room temperature for 2.5 hr. The same work-up as described above gave 64.0 (54%) of 6β-methyl-3-oxo-B-nor-5β-androstane-5-carbonitrile (**42e**), mp 122–124° (from ether–pentane). An analytical sample had mp 124–125°; $[\alpha]^{23}D$ +31° (*c* 1.00); ir 2220 (CN) and 1723 cm^{-1} (C=O); CD (*c* 0.070, CH_3OH) $[\theta]^{23}_{320}$ 0, $[\theta]^{23}_{295}$ −4568, $[\theta]^{23}_{243}$ 0.

Anal. Calcd for $C_{20}H_{29}ON$: C, 80.22; H, 9.76; N, 4.68. Found: C, 80.43; H, 9.47; N, 4.71.

Reaction of *dl*-3-Methoxy-1,3,5(10),13(17)-gonatetraen-16-one (43) with HCN–AlEt$_3$. To a solution of 0.750 g (2.8 mmol) of the enone **43**[35] in 15 ml of THF was added a reagent solution consisting of 5.6 mmol of HCN, 8.4 mmol of $AlEt_3$, and 5 ml of THF. After being kept at room temperature for 3.5 hr, the reaction mixture was poured into 2 *N* NaOH–ice and extracted with benzene. Fractional recrystallization of the product (0.848 g) from acetone–ether gave 0.533 g (64.5%) of *dl*-3-methoxy-16-oxo-13-iso-19-norestra-1,3,5(10)-triene-18-nitrile (**44***c*), mp 141–143°, and the trans epimer **44***t*, mp 218–223°.

The *cis*-cyano ketone **44***c* showed ir absorptions at 2247 (ε 30.7) (CN), 1753 (C=O), 1603, and 1580 cm^{-1} (Ar).

Anal. Calcd for $C_{19}H_{21}O_2N$: C, 77.26; H, 7.17; N, 4.74. Found: C, 76.92; H, 7.17; N, 4.77.

The *trans*-cyano ketone **44***t* showed ir absorptions at 2245 (ε 26.3) (CN), 1755 (C=O), 1613, and 1578 cm^{-1} (Ar).

Anal. Calcd for $C_{19}H_{21}O_2N$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.03; H, 7.23; N, 4.82.

The CN intensity (ε) of the ketal of the *cis*-nitrile, mp 135–137°, was 35.4 and that of the ketal of the *trans*-nitrile, mp 191–193°, was 23.2. The determination was made to confirm the cis and trans assignment to the cyano ketones, **44***c* and *t*, whose CN intensity difference was small.

Reaction of *dl*-3β-Hydroxy-18-nor-5α-pregn-13(17)-en-20-one (47) with Et$_2$AlCN. The enone **47** (1.00 g, 3.31 mmol) in 50 ml of dichloromethane was treated with 12.8 ml of a 1.3 *M* solution of Et_2AlCN in benzene at room temperature for 20 min. The reaction mixture was poured into 2 *N* NaOH–ice and extracted with dichloromethane. Recrystallization of the product from acetone–ether gave 0.642 g (59.1%) of *dl*-3β-hydroxy-20-oxo-5α-pregnane-18-nitrile (**48***t*), mp 169–170°, identical with an authentic sample of **48***t*.[36] The residue (0.5 g) from the mother liquor containing the unchanged **47** was hydrocyanated again in the same way as described above. Recrystallization of the second product afforded an additional 0.189 g (17.4%) of the *trans*-nitrile **48***t*, mp 171–173°. The residue from the mother liquor was chromatographed. Elution with petroleum ether–benzene and benzene gave 27 mg (2.9%) of a cyano ketone **48***c*, mp 178–179°, which was tentatively assigned a cis structure.

Reaction of 6-Acetyl-B-norandrost-5-en-3β-ol (49) with Et$_2$AlCN. The enone **49** (0.398 g, 1.32 mmol) in 4 ml of benzene was allowed to react with 4 ml of a 1.65 *M* solution of Et_2AlCN in toluene at room temperature for 30 min. The reaction mixture was poured into 2 *N* NaOH–ice and extracted with ether–dichloromethane (3:1). Recrystallization of the product from ether–pentane gave 0.248 g of 6β-acetyl-3β-hydroxy-5α-B-norandrostane-5-carbonitrile (**50**), mp 128–131°. The residue from the mother liquor in 3 ml of benzene was hydrocyanated again with 1.3 mmol of Et_2AlCN as described above. Recrystallization of the second product afforded 0.126 g of **50**, mp 127–129°. Preparative tlc of the mother liquor

(34) C. R. Engel, *Can. J. Chem.*, **40**, 921 (1962).

(35) W. Nagata and I. Kikkawa, to be submitted for publication.

Table VI. Reaction Conditions and Apparent Pseudo-First-Order Rate Constant K for Conjugate Hydrocyanation of Enones with Et_2AlCN in THF

Example no.	Enone	Concentration, M Enone	Concentration, M Et_2AlCN*	Temp, °C	$K \times 10^{-4}$, sec^{-1}	$K \times 10^{-4}$ for **23a**,[a] sec^{-1}	Relative rate[b]
7	**29a**	0.005	0.030	10	1.5	5.9	0.26
8	**25a**	0.005	0.030	20	2.2	18	0.12
9	**25b**	0.005	0.030	20	0.3	18	0.016
10	**41a**	0.005	0.030	15	1.3	10	0.13
1	**1**	0.005	0.045	0	22	2.3	10
2	**19**	0.005	0.045	0	3.9	2.3	1.7
3	**7**	0.005	0.030	15	0.53	10	0.053
4	**33b**	0.005	0.095	0	0.47	2.8	0.17
5	**31a**	0.068	0.136	0	7.7	4.3	1.8

[a] Rate constant for conjugate addition of cholestenone (**23a**) under the specified conditions. [b] The rate for reaction of cholestenone is taken to be unity.

gave 27 mg of **50**, mp 129–132°. The total yield of the *trans*-cyano ketone **50** is 93%. A pure sample had mp 131–134°; $[\alpha]^{25}D$ −87° (*c* 0.46); ir 3605, 3480 (OH), 2215 (CN), and 1715 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{31}O_2N$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.48; H, 9.44; N, 3.90.

Hydrocyanation of Mesityl Oxide (51a). A. With HCN–$AlEt_3$. To a solution of 3.93 g (0.04 mol) of the enone **51a** in 4 ml of THF was added a reagent solution consisting of 0.12 mol of $AlEt_3$, 0.08 mol of HCN, and 44 ml of THF. After being kept at room temperature for 3.5 hr, the reaction mixture was gradually poured into 200 ml of cold 4 *N* HCl saturated with sodium chloride and extracted with chloroform (washing with saturated sodium chloride) to give 7.06 g of an oily product. A mixture of the product, 60 ml of dichloromethane, and 30 ml of 2 *N* NaOH was vigorously stirred for 15 min. Separation of the organic layer and extraction of the aqueous layer with chloroform (washing with saturated sodium chloride) gave 5.5 g of an oil, which was distilled at a reduced pressure to afford 4.41 g (88.0%) of 2-methyl-4-oxopentane-2-carbonitrile (**52a**), bp 61° (1.1 mm); ir 2236 (CN) and 1729 cm^{-1} (C=O).

Anal. Calcd for $C_7H_{11}ON$: C, 67.13; H, 8.86; N, 11.19. Found: C, 67.43; H, 8.89; N, 11.02.

2,4-Dinitrophenylhydrazone had mp 108.5–109° (from dichloromethane–methanol); ir 3327 (NH), 2235 (CN), 1621 (C=N), and 1598 cm^{-1} (aromatic).

Anal. Calcd for $C_{13}H_{13}O_4N_5$: C, 51.14; H, 4.95; N, 22.94. Found: C, 51.14; H, 4.81; N, 22.89.

Hydrocyanation of Cyclohexenone (51b). A. With HCN–$AlEt_3$. To 6.03 g (0.0628 mol) of cyclohexenone (**51b**) in 50 ml of ether was added at −15° a reagent solution prepared by adding a solution of 0.18 mol of HCN in 56 ml of ether to a solution of 0.30 mol of $AlEt_3$ in 200 ml of ether with ice cooling. The mixture was kept overnight (22 hr) at −15°, poured into 2 *N* HCl–ice and extracted with dichloromethane. The extracts were washed with 8.5% sodium carbonate and water, dried, and evaporated at atmospheric pressure to give 7.9 g of an oil, which was distilled to afford 6.16 g (79.6%) of 3-oxocyclohexane-1-carbonitrile (**52b**), bp 126–129 (7 mm) [lit.[36] bp 149–150° (17 mm)]. Its semicarbazone had mp 169–172° (lit.[36] mp 177–178°).

B. With Et_2AlCN. To a solution of 11.4 g (0.119 mol) of cyclohexenone (**51b**) in 200 ml of hexane was added 320 ml of a 1.1 *M* solution of Et_2AlCN in benzene–hexane (3:1) with cooling at −15°. After being kept at −15° for 30 min, the reaction mixture was poured into 2 *N* HCl–ice and extracted with dichloromethane. The extracts were washed with cold 2 *N* NaOH and water, dried, and evaporated at atmospheric pressure. Distillation of the product gave 1.50 g (13.2%) of the unchanged **51b**, bp 58–63° (16 mm), and 8.29 g (56.7%) of the cyano ketone **52b**, bp 145–146° (16 mm).

Reaction of 3β-Acetoxypregna-5,16-dien-20-one (53a) with HCN–$AlEt_3$. To a solution of 0.372 g (1 mmol) of the enone **53a** in 4 ml of THF was added a reagent solution consisting of 2 mmol of HCN, 3 mmol of $AlEt_3$, and 2.5 ml of THF. After being kept at room temperature for 2.5 hr, the mixture was poured into 2 *N* NaOH–ice and extracted with ether. Recrystallization of the product from acetone–ether gave 0.206 g (51.6%) of 3β-acetoxy-20-oxopregn-5-ene-16α-carbonitrile (**54a**), mp 192–194° (lit.[4b] mp 196–198°). The residue from the mother liquor was chromatographed. Elution with petroleum ether–benzene (1:1–1:4) afforded 70 mg (17.6%) of the nitrile **54a**, mp 192–196°.

Reaction of 3β,21-Diacetoxypregna-5,16-dien-20-one (53b) with HCN–$AlEt_3$. The enone **53b** (3.32 g, 0.008 mol) in 5 ml of THF was treated with a reagent solution consisting of 0.032 mol of HCN, 0.04 mol of $AlEt_3$, and 31 ml of THF at room temperature for 7 hr. The reaction mixture was poured into 2 *N* NaOH–ice and extracted with chloroform. The product was acetylated to convert a partly formed 20-hydroxy compound into its 20-acetate. Recrystallization of the acetylation product from dichloromethane–acetone gave 2.030 g (71.5%) of 3,21-diacetoxy-20-oxopregn-5-ene-16α-carbonitrile (**54b**), mp 197–198° (lit.[4b] mp 195–197°).

Reaction of 5α-Cholest-1-en-3-one (55) with HCN–$AlEt_3$. The enone **55**[37] containing a small amount of 5α-cholestan-3-one (1.00 g, 2.6 mmol) in 7 ml of THF was allowed to react with a reagent solution consisting of 7.8 mmol of HCN, 10.4 mmol of $AlEt_3$, and 11 ml of THF at room temperature for 1.3 hr. The reaction mixture was poured into 2 *N* NaOH–ice and extracted with ether. Recrystallization of the product (1.05 g) from acetone–methanol gave 0.678 g of 3-oxo-5α-cholestane-1α-carbonitrile (**56**), mp 168–170° (lit.[37] mp 164°). The residue from the mother liquor was chromatographed. Elution with petroleum ether–benzene (9:1 and 4:1) afforded 88 mg of 5α-cholestan-3-one. Further elution gave an additional 0.201 g of the nitrile **56**. The total yield of **56** based on the enone portion was 90%.

Reaction of 3,17-Dioxo-5β-androst-1-ene-5-carbonitrile (57) with Et_2AlCN. The enone **57** (0.105 g, 0.338 mmol) in 1.5 ml of THF was treated with 1 ml of a 1.7 *M* solution of Et_2AlCN in toluene at room temperature for 5 hr. The mixture was poured into 2 *N* HCl–ice and extracted with dichloromethane. Recrystallization of the product from methanol gave 89.7 mg (78.2%) of 3,17-dioxo-5β-androstane-1β,5-dicarbonitrile (**58**), mp 265–268° dec; $[\alpha]^{21}D$ +79° (*c* 0.71); ir 2256 (CN) and 1738 cm^{-1} (C=O); nmr δ 0.91 (s, 3, 18-CH_3) and 1.63 ppm (s, 3, 19-CH_3).

Anal. Calcd for $C_{21}H_{26}O_2N_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.25; H, 7.58; N, 8.36.

Relative Reactivities for Conjugate Hydrocyanation of Various α,β-Unsaturated Ketones with Et_2AlCN. Kinetic runs were carried out in the same way as described in the previous paper.[1c] The relative reactivity of an enone was estimated by comparing the apparent pseudo-first-order rate constant K of the enone with that of cholest-4-en-3-one (**23a**) under the same conditions. Table VI lists kinetic conditions and data.

Preparation of the Tricyclic $\Delta^{1(10a)}$-2-Ketones 5a and b. A mixture of 3 g of 2-methoxy-5,6,7,8,9,10-hexahydrophenanthren-7-one (**61**), 25 ml of anhydrous ethanol, 15 ml of dry dioxane, and 45 ml of dry ether was added dropwise to a stirred solution of 6 g of lithium in 180 ml of liquid ammonia at −50 to −60°. After the stirring was continued for 5 min, 35 ml of methanol was added, and the ammonia was evaporated off at room temperature. The residual mixture was mixed with 50 ml of water and extracted with ether. Crystallization of an oily product from acetone–pentane gave 1.984 g of crystals, mp 120–122°. A mixture of the crystals, 80 ml of methanol, and 40 ml of 5 *N* HCl was refluxed for 15 min, evaporated, mixed with water, and extracted with ether. Crystallization of the product from acetone–pentane gave 1.60 g (52% from **61**)

(36) D. K. Banerjee, J. Dutta, and G. Bagavant, *Proc. Indian Acad. Sci., Sect. A*, **46**, 80 (1957); *Chem. Abstr.*, **52**, 3701 (1958).

(37) S. Julia, H. Linares, and P. Simon, *Bull. Soc. Chim. Fr.*, 2471 (1963).

of the hydroxy enone **5b**, mp 140–141°; ir 3470 (br, OH), 1675 (C=O), and 1622 cm^{-1} (C=C); uv max 240 mμ (ε 18,100).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.23; H, 9.16.

Acetylation of **5b** afforded the acetoxy enone **5a**, mp 117–118°.

Preparation of the Tricyclic $\Delta^{4(4a)}$-3-Ketone (11). A. Reaction of 6,6-Ethylenedioxy-3-methoxy-5,6,7,8,9,10-hexahydrophenanthrene (62) with Sodium in Liquid Ammonia. A solution of 0.94 g of the ketal **62** in 30 ml of aniline is added to a stirred solution of 1.2 g of sodium in 300 ml of liquid ammonia at −50 to −60°. The stirring was continued for 1.5 hr at the same temperature, and NH_4Cl was added to stop the reaction. The ammonia was evaporated off at room temperature, and the residual mixture was poured into ice water and extracted with ether. The product (1.02 g) was chromatographed. Fractions (0.95 g) eluted with petroleum ether to benzene were heated with 20 ml of 70% acetic acid at 100° for 30 min. The mixture was evaporated, mixed with water, and extracted with ether. Preparative tlc [cyclohexane–ether (4:1), four developments] of the product (0.785 g) gave 0.448 g (50.8%) of 3-methoxy-4bα,5,6,7,8,8aβ,9,10-octahydrophenanthren-6-one (**63a**), mp 95–99° (from ether–pentane), and 0.216 g (25.6%) of the cis epimer **63b**, mp 121–122° (from ether–pentane).

B. Hydrogenation of the Olefin 62. A solution of 0.264 g of the olefinic ketal **62** in 10 ml of dry ethanol was hydrogenated over 25 mg of 10% palladium-on-carbon for 4 hr. The catalyst was filtered off, and the filtrate was evaporated. Crystallization of the residue from methanol gave 0.177 g of crystals, mp 87–88°, which was heated with 10 ml of 70% acetic acid at 100° for 30 min. The mixture was evaporated, mixed with water, and extracted with ether. Crystallization of the product (0.142 g) from ether–pentane afforded crystals, mp 119–120°, identical with the *cis*-ketone **63b** obtained above.

C. Birch Reduction of the Aromatic *trans*-Ketone 63a. A mixture of 0.480 g of compound **63a**, 15 ml of dry ether, and 5 ml of dry ethanol was added dropwise to a stirred solution of 1.2 g of lithium in 50 ml of liquid ammonia at −50 to −60°. After the stirring was continued for 1 hr, 20 ml of ethanol was added, and the ammonia was evaporated off at room temperature. The resulting mixture was poured into ice water and extracted with dichloromethane. The product (0.51 g) in 30 ml of methanol was mixed with 7.5 ml of 4 *N* HCl. After being kept at room temperature for 40 hr under nitrogen, the reaction mixture was poured into ice water and extracted with dichloromethane. The product was purified by preparative tlc and recrystallization from dichloromethane–ether to give 0.282 g (61.4%) of the hydroxy enone (OH instead of OAc in formula **11**), mp 141–143°. Acetylation of this compound afforded the 6β-acetoxy-$\Delta^{4(4a)}$-3-ketone **11**, mp 85–86° (from ether–pentane); ir 1731 (ester C=O), 1670 (C=O), and 1617 cm^{-1} (C=C); uv_{max} 239 mμ (ε 16,300).

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.34; H, 8.50.

Preparation of the B-Nor-Δ^4-3-oxo Steroids 41a–e. A. B-Norandrost-4-ene-3,17-dione (41a). A mixture of 25.0 g of 3β,17β-diacetoxy-5-hydroxy-B-nor-5β-androstane-6β-carboxaldehyde (**64a**),[12] 1 l. of dichloromethane, 7.6 g of ethylene glycol, and 0.31 g of *p*-toluenesulfonic acid was slowly distilled with stirring, while the distillate was recycled after being dried with silica gel. After 80 min, the reaction mixture was concentrated, cooled, poured into 2 *N* sodium carbonate, and extracted with dichloromethane to give 33 g of the acetal of **64a**. A mixture of the acetal, 500 ml of methanol, and 100 ml of 2 *N* potassium carbonate was refluxed for 3.5 hr. The usual work-up and recrystallization of the product from dichloromethane–ether afforded 21.93 g (97.3% from **64a**) of 6β-ethylenedioxymethyl-B-nor-5β-androstane-3β,5,17β-triol, mp 120–121°. A solution of 21.75 g of the triol in 500 ml of pyridine was added dropwise to a mixture of 21.75 g of chromium trioxide and 430 ml of pyridine with stirring and ice cooling. After being kept at room temperature for 17 hr, the reaction mixture was cooled, mixed with 1 l. of dichloromethane, and filtered. The precipitate was washed with two 500-ml portions of dichloromethane. The filtrate and the washings were combined, mixed with 4 l. of ether, and filtered. The filtrate was poured into ice water and worked up in the usual way to give 16.4 g of the product, which was chromatographed on 100 g of alumina. Elution with benzene–dichloromethane (4:1) gave 11.21 g (52.2%) of 6β-ethylenedioxymethyl-5-hydroxy-B-nor-5β-androstane-3,17-dione (**65a**), mp 146–149° (from dichloromethane–ether). An analytical sample had mp 155–157°; $[\alpha]^{26}D$ +3.8° (*c* 1.04); ir 3535 (OH), 1728, and 1719 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.41; H, 8.42.

A mixture of 0.317 g of the ketol **65a**, 32 ml of ethylene glycol, and 1.6 ml of 50% potassium hydroxide was heated at 150° for 50 min with stirring while nitrogen was bubbled through the mixture. The reaction mixture was cooled, poured into ice water, and extracted. Crystallization of the product from dichloromethane–ether gave 0.167 g (70.2%) of B-norandrost-4-ene-3,17-dione (**41a**), mp 139–141°. Recrystallization from acetone afforded a pure sample, mp 142–143°; $[\alpha]^{24}D$ +63° (*c* 1.09); uv_{max} 241 mμ (ε 15,800) (lit.[11a] mp 142–143°; $[\alpha]^{26}D$ +61° (*c* 1.16); uv_{max} 240 mμ (ε 15,200)).

B. B-Norandrost-4-en-3-one (41d). In the same way as described above, 3β-acetoxy-5-hydroxy-B-nor-5β-androstane-6β-carboxaldehyde (**64b**)[3j] (prepared from androst-5-en-3β-ol 3-acetate by the method of Tanabe and Morisawa[11b]) was converted *via* the ketol **65b** (mp 135–136° (from methanol); $[\alpha]^{22}D$ −76° (*c* 1.04). *Anal.* Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.13; H, 9.17) into B-norandrost-4-en-3-one (**41d**), mp 47–48° (from pentane); $[\alpha]^{22}D$ −33° (*c* 0.99); ir 1655 cm^{-1} (C=O); uv_{max} 242 mμ (ε 15,100).

Anal. Calcd for $C_{18}H_{26}O$: C, 83.66; H, 10.14. Found: C, 83.75; H, 10.32.

C. 6β-Methyl-B-norandrost-4-ene-3,17-dione (41b). A mixture of 2.00 g of the aldehyde **64a**, 20 ml of hydrazine hydrate, and 6 g of potassium hydroxide was gradually heated to 210° while a distillate was collected. After being kept at 210° for 2 hr, the mixture was cooled, poured into ice water, and extracted with dichloromethane–methanol (9:1). To a stirred mixture of the product (1.45 g), 44 ml of acetone, 15 ml of *tert*-butyl alcohol, and 8 ml of water was added 3.25 g of *N*-bromoacetamide. After being stirred at room temperature for 1 hr, the reaction mixture was cooled to 10°, mixed with 70 ml of 5% sodium bisulfite, poured into ice water, and extracted with dichloromethane. Recrystallization of the product from dichloromethane–ether gave 0.828 g (57.7%) of 5-hydroxy-6β-methyl-B-nor-5β-androstane-3,17-dione (**66a**), mp 170–177°, whose ir spectrum is identical with that of an authentic sample.[12] Dry hydrogen chloride gas was bubbled through a solution of 0.700 g of the ketol **66a** in 70 ml of dry, ethanol-free chloroform for 25 min with ice cooling. The mixture was poured into ice cold 5% sodium bicarbonate solution and extracted with dichloromethane. Recrystallization of the product from dichloromethane–ether afforded 0.551 g (83.6%) of the enone **41b**, mp 135–136.5°; $[\alpha]^{24}D$ +89° (*c* 0.49); uv_{max} 243 mμ (ε 15,200) (lit.[35] mp 133.5–134°; $[\alpha]^{29}D$ +91°; uv_{max} 240 mμ (ε 15,900)).

D. 6β-Methyl-B-norandrost-4-en-3-one (41e). In the same way as described in C, the enone **41e** was obtained as an oil from the aldehyde **64b** *via* the ketol **66b** (mp 191–194° (from dichloromethane–methanol); $[\alpha]^{23}D$ −32° (*c* 1.02). *Anal.* Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.24; H, 10.24).

E. 6β-Ethyl-B-norandrost-4-ene-3,17-dione (41c). To a suspension of 3.88 g (4.6 mmol) of triphenylphosphine–methyl bromide in 24 ml of dry ether was added 0.929 g (3.5 mmol) of potassium *tert*-butoxide over 12 min, with stirring and ice cooling under nitrogen. The stirring and cooling were continued for 2.3 hr. To the resulting mixture was added dropwise a solution of 0.960 g (2.36 mmol) of the aldehyde **64a** in 12 ml of dry THF over 7 min. After being stirred at 0° for 3 hr under nitrogen, the reaction mixture was poured into ice water and extracted with ether–dichloromethane (4:1). The residue (2.36 g) from the extracts was heated at reflux with 8 ml of 2 *N* potassium carbonate and 14 ml of methanol for 2 hr. The mixture was worked up in the usual way. The crude product (2.16 g) was heated with 4.6 ml of dry pyridine and 1.07 g of succinic anhydride at 87° for 5.5 hr. The resulting mixture was poured into 2 *N* potassium carbonate–ice and extracted with ether–dichloromethane (3:1). The extracts were washed twice with 2 *N* potassium carbonate. The alkaline layer and the washings were collected, made acid with 4 *N* HCl under cooling, and extracted with ether–dichloromethane (3:1) to give 1.165 g of the disuccinate of the olefin **67**. A mixture of the disuccinate, 16 ml of methanol, and 5.5 ml of 3 *N* potassium hydroxide was heated at reflux for 1.5 hr, and then worked up in the usual way to give 0.720 g of 6β-vinyl-B-nor-5β-androstane-3β,5,17β-triol (**67**) as an oil. The olefin **67** (0.720 g) in 15 ml of ethyl acetate was hydrogenated over 84 mg of platinum dioxide for 30 min. The catalyst was filtered off, and the filtrate was evaporated. Recrystallization of the residue from ether afforded 0.595 g (78.2%) of 6β-ethyl-B-nor-5β-androstane-3β,5,17β-triol, mp 151–152°; $[\alpha]^{24}D$ +51° (*c* 1.08) (*Anal.* Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.59; H, 10.87). The triol (0.548 g) in 10 ml of acetone was treated with 0.65 ml of

Jones reagent at room temperature for 5 min. The mixture was poured into ice water and extracted with ether. Recrystallization of the product from dichloromethane–ether gave 0.428 g (79.1%) of 6β-ethyl-5-hydroxy-B-nor-5β-androstane-3,17-dione (**68**), mp 137–138°; $[\alpha]^{24}D$ +30° (*c* 1.07); ir 3610 (OH), 1735, and 1722 cm^{-1} (C=O).

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.70; H, 9.66.

To a solution of 0.411 g of the ketol **68** in 2 ml of dichloromethane containing 0.6 ml of dry pyridine was added 0.13 ml of thionyl chloride in 0.4 ml of dichloromethane at −60°. After being kept at −60° for 80 sec, the reaction mixture was poured into ice water and extracted with ether. Recrystallization of the product from dichloromethane–ether gave 0.325 g (83.7%) of 6β-ethyl-B-norandrost-4-ene-3,17-dione (**41c**), mp 151–153°. An analytical sample of **41c** had mp 153.5–155°; $[\alpha]^{24}D$ +86° (*c* 1.08); ir 1739 (C=O) and 1656 cm^{-1} (C=C); uv_{max} 243 mμ (ε 15,100).

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.08; H, 9.37.

Preparation of 6-Acetyl-B-norandrost-5-en-3β-ol (49). To a solution of 10.01 g of the hydroxy aldehyde **64b** in 1.2 l. of methanol was added dropwise a solution of 35.0 g of potassium carbonate in 250 ml of water at 22°. After being kept at room temperature for 19 hr, the reaction mixture was concentrated *in vacuo* below 40°, and extracted with dichloromethane. Recrystallization of the product from ether–petroleum ether gave 6.37 g (76.6%) of 3β-hydroxy-B-norandrost-5-ene-6-carboxaldehyde (**69**), mp 143.5–147.5°; $[\alpha]^{25}D$ −103° (*c* 0.52); ir 3600, 3450 (OH), 2750, 1673 (CHO), and 1601 cm^{-1} (C=C); uv_{max} 257 mμ (ε 12,800).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.28; H, 9.74.

A solution of 6.347 g (0.022 mol) of the enal **69** in 143 ml of dry benzene was added to a solution of methylmagnesium iodide, prepared from 1.67 g of magnesium, 18.74 g of methyl iodide, and 32 ml of ether. After being refluxed for 1 hr, the reaction mixture was cooled, poured into a mixture of 47 g of ammonium chloride and 2 l. of ice water, and extracted with dichloromethane. The thus obtained crude methylhydrin **70** (6.55 g) in 79 ml of dry dioxane was mixed with 5.94 g of DDQ. The resulting mixture was kept at 23° for 2 days and at 25–30° for 16 hr, and filtered. The precipitate was washed with three 100-ml portions of dichloromethane. The filtrate and the washings were combined and evaporated *in vacuo* below 40°. The residue (6.5 g) was chromatographed. Fractions eluted with benzene to dichloromethane–methanol (99.5:0.5) were recrystallized from ether–pentane to give 3.405 g (51.2%) of the enone **49**, mp 102–105°. Elution with dichloromethane–methanol (97:3) afforded 1.12 g of the unchanged **70** which was treated again with DDQ in the same way as described above to give an additional 0.271 g (4.1%) of **49**, mp 99–103°. An analytical sample of the enone **49** had mp 105–107°; $[\alpha]^{25}D$ −157° (*c* 0.49); ir 3600, 3450 (OH), 1672 (C=O), and 1616 cm^{-1} (C=C); uv_{max} 251 mμ (ε 6100).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.32; H, 10.00.

Determination of Hydrolysis Rates for 2-Oxo-7α-tetrahydropyranyloxy-1,2,3,4,4aβ,5,6,7,8,8aβ,9,10,10a-tetradecahydrophenanthrene-10a-carbonitriles (71*t* and *c*). A mixture of 0.500 g of the *trans*-nitrile **6b***t*, 0.508 g of dihydropyran, 8 ml of THF, and 1 drop of concentrated HCl was refluxed for 5 hr, cooled, poured into water, and extracted with chloroform. The extracts were washed with 5% sodium bicarbonate and water, dried, and evaporated. Recrystallization of the residue from acetone–ether gave 0.597 g of the *trans*-cyano ether **71***t*, mp 138–148°.

Anal. Calcd for $C_{20}H_{29}O_3N$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.55; H, 8.77; N, 3.96.

In the same way, 0.500 g of the *cis*-nitrile **6b***c* was converted into 0.559 g of the *cis*-cyano ether **71***c*, mp 130–148°.

Anal. Calcd for $C_{20}H_{29}O_3N$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.70; H, 8.96; N, 4.38.

A kinetic run was carried out by adding 400 mg of a substrate (**71***t* or *c*) to a mixture of 1 ml of 2 *N* NaOH and 99 ml of 95% ethanol maintained at 54.7 ± 0.2°, withdrawing an aliquot at appropriate intervals, pouring it into cold 2 *N* HCl, extracting the mixture with chloroform, and measuring the ir C≡N intensity of the product in chloroform to determine the amount of the unchanged nitrile. The pseudo-first-order reaction rates for hydrolysis of the *trans*- and *cis*-cyano ketones **71***t* and *c* were determined to be 3.0×10^{-5} and 2.6×10^{-4} sec^{-1}, respectively.

Epimerization of 3,17-Bisethylenedioxy-5β-androstane-1β,5-dicarbonitrile (72a). A mixture of 20 mg of the 1β,5β-dicyano ketone **58**, 0.027 ml of ethylene glycol, 1.3 mg of *p*-toluenesulfonic acid, and 3 ml of dry benzene was distilled slowly while dry benzene was added to keep the total volume of the mixture constant. After 3 hr, the mixture was poured into 5% sodium bicarbonate–ice, and extracted with dichloromethane to give 22.1 mg of the crude ketal **72a**. A mixture of 18.0 mg of the 1β,5β-dicyano ketal **72a**, 28 mg of potassium *tert*-butoxide, and 7 ml of *tert*-butyl alcohol was kept at 30° for 2 hr, poured into ice water, and extracted with dichloromethane. Preparative tlc of the product afforded 5.3 mg of the 1α,5β-dicyano ketal **72b**, mp 227–228°, identical with an authentic sample of **72b** (see below), and 1 mg of the crude unchanged **72a**.

3,17-Bisethylenedioxy-5β-androstane-1α,5-dicarbonitrile (72b). The 1α,5β-dicyano ketone **28***c* (20 mg) was ketalized in the same way as described above to give 13.1 mg (52%) of the 1α,5β-dicyano ketal **72b**, mp 219.5–221°. An analytical sample had mp 225–227°; $[\alpha]^{26}D$ −35° (*c* 0.34); ir (KBr disk) 2238 cm^{-1} (CN).

Anal. Calcd for $C_{25}H_{34}O_4N_2$: C, 70.29; H, 8.03; N, 6.57. Found: C, 70.37; H, 7.97; N, 6.74.

Conversion of 3β-Hydroxy-7-oxo-5α-cholestane-5-carbonitrile (30*c*) into 3β-Hydroxy-5α-cholestane-5-carbonitrile (74). A mixture of 0.170 g of the cyano ketone **30***c*, 0.8 ml of boron trifluoride ethereate, and 0.8 ml of ethanedithiol was kept at room temperature for 1.5 hr. The mixture was poured into ice water and extracted with ether. The extracts were washed with 5% potassium hydroxide and water, dried, and evaporated. Recrystallization of the residue from methanol gave 0.167 g of the thioketal **73**, mp 240–242°; $[\alpha]^{19}D$ +13° (*c* 1.05); ir 3280 (br, OH) and 2225 cm^{-1} (CN).

Anal. Calcd for $C_{30}H_{49}ONS_2$: C, 71.53; H, 9.83, N, 2.78; S, 12.70. Found: C, 71.54; H, 9.79; N, 2.92; S, 12.57.

A mixture of 0.200 g of the thioketal **73**, 2 g of Raney nickel, and 40 ml of 95% ethanol was refluxed for 6.5 hr. The nickel was filtered off, and the filtrate was evaporated. Crystallization of the residue from ether–pentane gave 28 mg of crystals, mp 148–152°. Chromatography of the residue from the mother liquor afforded additional crystals, mp 157–159°. Both crops of crystals were identified with an authentic sample of 3β-hydroxy-5α-cholestane-5-carbonitrile (**74**).[2b]

Conversion of the 5α-Cyano-6β-acetyl-B-nor Steroid 50 into 6β-(1-Ethylenedithio)ethyl-3α-hydroxy-B-nor-5α-androstane-5-carboimidic Acid 3,5-Lactone (78). A. 6β-(1-Ethylenedithio)-ethyl-3β-hydroxy-B-nor-5α-androstane-5-carbonitrile (75). To a solution of 0.978 g of the cyano ketone **50** in 8 ml of dichloromethane were added 4 ml of ethanedithiol and 4 ml of boron trifluoride etherate. The resulting mixture was refluxed for 25 hr, cooled, poured into ice water, and extracted with ether. The extracts were washed with 2 *N* sodium hydroxide and water, dried, and evaporated. Recrystallization of the residue from ether–petroleum ether gave 0.972 g (81%) of the thioketal **75**, mp 222–225°. An analytical sample had mp 226.5–229°; $[\alpha]^{22}D$ +4° (*c* 1.02); ir 3610, 3460 (OH), and 2210 cm^{-1} (CN).

Anal. Calcd for $C_{23}H_{35}ONS_2$: C, 68.10; H, 8.70; N, 3.45; S, 15.80. Found. C, 68.14; H, 8.89; N, 3.53; S, 15.82.

B. 6β-(1-Ethylenedithio)ethyl-3-oxo-B-nor-5α-androstane-5-carbonitrile (76). A mixture of 0.406 g of the 3-hydroxy thioketal **75**, 2 ml of cyclohexanone, 0.117 g of aluminum isopropoxide, and 10 ml of toluene was heated for 5 hr while 7 ml of a distillate was collected. The reaction mixture was cooled, poured into 2 *N* HCl–ice, and extracted with ether–dichloromethane (3:1). Crystallization of the product from acetone–ethanol gave 0.208 g (51.4%) of the ketone **76**, mp 245–248°; $[\alpha]^{23}D$ +20° (*c* 0.52); ir 2225 (CN) and 1708 cm^{-1} (C=O); CD (*c* 0.005) $[\theta]^{23}_{333}$ 0, $[\theta]^{23}_{290}$ +1763, $[\theta]^{23}_{268}$ +2030, $[\theta]^{23}_{259}$ 0, $[\theta]^{23}_{245}$ −5413, $[\theta]^{23}_{232}$ 0, $[\theta]^{23}_{222}$ +3739.

Anal. Calcd for $C_{23}H_{33}ONS_2$: C, 68.44; H, 8.24; N, 3.47; S, 15.89. Found: C, 68.65; H, 8.21; N, 3.37; S, 16.03.

C. Imino Lactone 78. Lithium tri-*tert*-butyoxyaluminum hydride (0.198 g) was added to 49.1 mg of the ketone **76** in 3 ml of THF. After being stirred at room temperature for 4 hr, the mixture was poured into 2 *N* HCl–ice and extracted with ether–dichloromethane (3:1). The ir spectrum and tlc of the crystalline product (52 mg) indicated that it consisted of small amounts of the 3β-hydroxy derivative **75** and the imino lactone **78** and a major amount of the 3α-hydroxy derivative **77**. A mixture of the crude product, 30 mg of *p*-toluenesulfonic acid, and 7 ml of benzene was stirred at room temperature for 2.8 hr, poured into 2 *N* sodium carbonate–ice, and extracted with ether–dichloromethane (3:1). The ir spectrum and tlc of the product showed that it consisted of a small amount of the 3β-ol **75** and a major amount of the imino lactone **78**. The product was chromatographed. Elution with benzene to benzene–dichloromethane (2:1) gave 38.4 mg (77.8%) of the imino lactone **78**, mp 162–167° (from methanol). Further elution af-

forded 4.3 mg (8.7%) of the 3β-ol **75**, mp 223–225°. An analytical sample of **78** had mp 165.5–167°; $[\alpha]^{22}D$ +31° (*c* 1.02); ir 3370 (NH) and 1670 cm^{-1} (C=N).

Anal. Calcd for $C_{23}H_{35}ONS_2$: C, 68.10; H, 8.70; N, 3.45; S, 15.80. Found: C, 67.79; H, 8.78; N, 3.29; S, 15.39.

3β-Hydroxy-6β-(1-hydroxyethyl)-B-nor-5α-androstane-5-carbonitriles (79a and b). To a solution of 0.304 g of the cyano ketone **50** was added 2.0 g of lithium tri-*tert*-butoxyaluminum hydride. The mixture was refluxed for 1 hr, cooled, poured into 2 *N* HCl–ice, and extracted with dichloromethane. Recrystallization of the product from ether–petroleum ether gave 0.251 g (82%) of mixed crystals, mp 183–184°. A 0.15 g portion of the crystals was subjected to preparative tlc. Recrystallization of a less polar fraction (77 mg) from ether–petroleum ether afforded 55.8 mg of the 6a-hydroxy derivative **79a**, mp 187–188.5°; $[\alpha]^{24}D$ −25° (*c* 0.99); ir 3610, 3460 (OH), and 2228 cm^{-1} (CN).

Anal. Calcd for $C_{21}H_{33}O_2N$: C, 76.09; H, 10.03; N, 4.23. Found: C, 76.10; H, 10.12; N, 4.04.

Recrystallization of a more polar fraction (56 mg) gave 50.3 mg of the epimeric alcohol **79b**, mp 196.5–197°; $[\alpha]^{24}D$ −16° (*c* 1.03); ir 3590, 3350 (OH), and 2228 cm^{-1} (CN).

Anal. Calcd for $C_{21}H_{33}O_2N$: C, 76.09; H, 10.03; N, 4.23. Found: C, 76.06; H, 10.12; N, 4.03.

Acid Treatment of the 6a-Hydroxy Derivatives 79a and b. A mixture of 9.0 mg of **79a**, 7.3 mg of *p*-toluenesulfonic acid, and 4 ml of benzene was refluxed for 1.5 hr, cooled, poured into 2 *N* sodium carbonate–ice, and extracted with dichloromethane. Recrystallization of the residue from the extracts gave 6.0 mg (67%) of the unchanged alcohol **79a**. The epimeric alcohol **79b** (9.7 mg) was treated in the same way to recover 9.0 mg (93%) of the unchanged material **79b**.

Reaction of 17β-Hydroxyandrosta-4,6-dien-3-one (80a) with Et_2AlCN. To a solution of 1.089 g (3.81 mmol) of the 4,6-dienone **80a** in 20 ml of THF was added 12 ml of a 1.63 *M* solution of Et_2AlCN in toluene. After being kept at room temperature for 45 min, the reaction mixture was poured into 2 *N* NaOH–ice and extracted with dichloromethane. Recrystallization of the product from methanol gave 0.881 g of 17β-hydroxy-3-oxoandrost-4-ene-7α-carbonitrile (**81a**), mp 289–292°, identical with an authentic sample of **81a**.[19a] The residue (0.31 g) from the mother liquor was chromatographed. Elution with benzene–dichloromethane (4:1 and 2:1) afforded 41 mg of **81a**, mp 284–286°. Fractions (0.24 g) eluted with benzene–dichloromethane (9:1) were treated with Et_2AlCN in the same way as described above. Recrystallization of the second product gave an additional 0.149 g of the nitrile **81a**, mp 282–286°. The hydrocyanation was repeated on the residue (85 mg) from the mother liquor to afford 31 mg of **81a**, mp 279–284°. The total yield of the 7α-cyano compound **81a** was 92.2%.

Reaction of Androsta-1,4-diene-3,17-dione (83) with Et_2AlCN. The 1,4-dienone **83** (1.01 g, 3.55 mmol) in 14 ml of THF was treated with 11 ml of a 1.63 *M* solution of Et_2AlCN in toluene at room temperature for 15 min. The usual work-up and crystallization of the product from ethanol gave 0.222 g of 3,17-dioxoandrost-4-ene-1α-carbonitrile (**27**), mp 204–207°/218–223°. The residue (0.9 g) from the mother liquor was chromatographed on 100 g of Kieselgel G nach Stahl with benzene–ethyl acetate (1:9) to afford 0.192 g of 3,17-dioxo-5β-androst-1-ene-5-carbonitrile (**57**), mp 227–230° (from ethanol), and 0.163 g of the 1α-cyano enone **27**, mp 207–210°/220–222°. The column chromatography was repeated on the residue (0.45 g) from the mother liquors to give 80 mg of **57**, mp 210–222°, and 0.134 g of **27**, mp 206–208°/220–222°. The residue from the mother liquors was subjected to preparative tlc to afford 66 mg of **57**, mp 210–220°, and 51 mg of **27**, mp 208–210° (221–225°). The total yield of the 1α-cyano compound **27** was 51.6%, and that of the 5β-cyano compound **57** was 30.4%.

An analytical sample of the 1α-cyano-Δ^4-3-ketone **27** had mp 207–210°/222–225°; $[\alpha]^{24}D$ +193° (*c* 0.49); ir 2245 (CN), 1738 (17-C=O), 1678 (3-C=O), and 1618 (C=C); uv_{max} 242 mμ (ε 15,800); nmr δ 0.917 (s, 3, 18-CH_3), 1.317 (s, 3, 19-CH_3), 2.717 (d, 2, *J* = 4 Hz, 2-H), 3.233 (t, 1, *J* = 4 Hz, 1β-H), and 5.875 ppm (s, 1, $W_{1/2}$ = 2.5 Hz, 4-H).

Anal. Calcd for $C_{20}H_{25}O_2N$: C, 77.13; H, 8.09; N, 4.50. Found: C, 76.48; H, 8.23; N, 4.24.

An analytical sample of the 5β-cyano-Δ^1-3-ketone **57** had mp 227–231°; $[\alpha]^{24}D$ +140° (*c* 0.67); ir 2238 (CN), 1740 (17-C=O), 1688 (3-C=O), and 1617 cm^{-1} (C=C); uv_{max} 229 mμ (ε 7800); nmr δ 0.908 (s, 3, 18-CH_3), 1.492 (s, 3, 19-CH_3), 6.067 (d, 1, *J* = 10.5 Hz, 1-H), and 6.783 ppm (d, 1, *J* = 10.5 Hz, 2-H).

Anal. Calcd for $C_{20}H_{25}O_2N$: C, 77.13; H, 8.09; N, 4.50. Found: C, 77.04; H, 7.98; N, 4.30.

Hydrogenation of the 5β-Cyano-Δ^1-3-one 57. The enone **57** (50.3 mg) in 5 ml of ethyl acetate was hydrogenated over 23 mg of 10% palladium-on-carbon. The usual work-up gave 38 mg of crystals, mp 230–233° (from ethanol), which were identified with an authentic sample of the 5β-cyano-3-ketone **24cc** obtained earlier.

Preparation of 19-Nortestosterone Pyrrolidine Enamine (86) and its Perchlorate 87. A mixture of 1.1 g of 19-nortestosterone, 1.34 ml of pyrrolidine, and 50 ml of dry benzene was refluxed for 5 hr, slowly concentrated for 2.5 hr, and finally evaporated *in vacuo*. Recrystallization of the residue from ether gave 0.632 g (48.2%) of the enamine **86**, mp 147–150 dec; $[\alpha]^{21}D$ −171° (*c* 1.03); ir 3606 (OH), 1686, and 1601 cm^{-1} (NC=CC=C); uv_{max} 280 mμ (ε 18,900).

Anal. Calcd for $C_{22}H_{33}ON$: C, 80.68; H, 10.16; N, 4.28. Found: C, 80.45; H, 10.17; N, 4.09.

An additional 0.293 g (23.9%) of the enamine **86**, mp 139–143° dec, was obtained from the mother liquor.

To a mixture of 0.751 g of the enamine **86**, 15 ml of ether, and 6 ml of dichloromethane was added 0.5 ml of 60% perchloric acid. The precipitate was filtered off, washed with water, dried, and recrystallized from ethanol to give 0.418 g (42.6%) of the enamine perchlorate **87**, mp 215–217° dec; ir 3585 (OH) and 1620 cm^{-1} (N=CC=C); uv_{max} 277 mμ (ε 24,200).

Anal. Calcd for $C_{22}H_{34}O_5NCl$: C, 61.74; H, 8.01; N, 3.27; Cl, 8.29. Found: C, 61.61; H, 7.99; N, 3.20; Cl, 8.56.

An additional 0.234 g (23.9%) of the salt **87**, mp 204–206° dec, was obtained from the mother liquor.

Hydrocyanation of the Enamine 86. A. With HCN–$AlEt_3$. To 0.328 g (1 mmol) of the enamine **86** was added a reagent solution consisting of 3 mmol of HCN, 5 mmol of $AlEt_3$, and 5 ml of THF. After being allowed to stand at room temperature for 3 hr, the reaction mixture was poured into 2 *N* NaOH–ice and extracted with chloroform. To the residue from the extracts were added 5 ml of THF and 0.5 ml of 2 *N* HCl. The resulting mixture was kept at room temperature for 1 hr, poured into water, and extracted with chloroform. Recrystallization of the product from acetone gave 0.151 g of the *trans*-cyano ketone **18***t*, mp 236–239°. The residue from the mother liquor was chromatographed. Fractions eluted with benzene were crystallized from acetone to give 32 mg of the *trans*-cyano ketone **18***t*, mp 244–246°. The residue from the mother liquor was crystallized from ether to afforded 42 mg of the *cis*-cyano ketone **18***c*, mp 170–175°. Preparative tlc of the mother liquor yielded 3 mg of **18***t*, mp 228–232°, and 4 mg of **18***c*, mp 178–181°. The total yield of the *trans*-cyano ketone **18***t* is 62% and that of the *cis* isomer **18***c* is 15%.

B. With Et_2AlCN. The enamine **86** (0.270 g, 0.825 mmol) in 2 ml of benzene was treated with 2 ml of a 1.25 *M* solution of Et_2AlCN in benzene at room temperature for 1 hr. Work-up of the reaction mixture followed by acid treatment in the same way as described above afforded a crystalline product, which was recrystallized from acetone to give 76 mg (mp 250–252°) and 62 mg (mp 229–232°) of the *trans*-cyano ketone **18***t*. The residue (93 mg) from the mother liquor was chromatographed. Fractions (52 mg) eluted with benzene–dichloromethane (2:1) were crystallized from acetone to give 4 mg of **18***t*, mp 244–246°. The total yield of the *trans*-cyano ketone **18***t* was 57.4%. The residue (45 mg) from the mother liquor did not crystallize and tlc showed it consisted of a major amount of the cis isomer **18***c*, and small amounts of **18***t*, and impurities.

Reaction of the Enamine Perchlorate 87 with HCN–$AlEt_3$. To 0.377 g (0.884 mmol) of the perchlorate **87** in 3 ml of THF was added a reagent solution consisting of 2.7 mmol of HCN, 4.4 mol of $AlEt_3$, and 4.5 ml of THF. After being kept at room temperature for 3.7 hr, the reaction mixture underwent work-up, acid treatment, and separation in the same way as described above to give 109 mg (42.6%) of the *trans*-cyano ketone **18***t*, mp 250–251°, and 49 mg (19%) of the cis epimer **18***c*, mp 155–158°.

Reaction of 6-Methoxy-1-tetralone (89) with Et_2AlCN.[28] To a stirred solution of 6.15 g (0.035 mol) of the ketone **89** in 30 ml of toluene, placed in a two-necked flask and cooled at the specified temperature, was added 90 ml of a solution containing the specified amount of Et_2AlCN in toluene cooled to the same temperature, and the mixture was kept at this temperature for a given time. The operation should be carried out with vigorous exclusion of moisture. A stopper of the reaction flask was replaced by a glass tube having one end extending to the bottom of the flask and the other end mounted in a neck of a 2-l. flask, equipped with an efficient stirrer, containing a mixture of 250 ml of methanol and 150 ml of concentrated HCl cooled to −70°. The reaction mixture was added through the glass tube to the vigorously stirred acid mixture by

applying a positive nitrogen pressure to the reaction flask. The resulting acid mixture was stirred at −70° for 1 hr, poured into a mixture of 200 ml of concentrated HCl and 1 l. of ice water, and extracted with three 500-ml portions of dichloromethane. The extracts were washed once with water, dried, and evaporated *in vacuo* below 40°.[38] The residue, obtained as an oil (*ca.* 7.2 g) consisting of a major amount of the cyanohydrin **91** and a small amount of the unchanged **89**, was transferred to a 10-ml Claisen flask. Powdered potassium bisulfate (0.20 g) was added, and the flask was heated at 130° (5 mm) for 30 min. The pressure was then reduced to 0.2 mm and the temperature was raised to about 160° to collect all the distillate boiling usually at 130–145° (2 mm). Crystallization of the distillate (*ca.* 6.2 g) from ether–petroleum ether gave about 4 g of 6-methoxy-3,4-dihydronaphthalene-1-carbonitrile (**92**), mp 50–52°. The residue from the mother liquor was chromatographed. Elution with petroleum ether gave an additional crop of the nitrile **92**, and elution with benzene afforded the unchanged **89**. The conditions and results are shown in Table V.

(38) It was found later that addition of a small amount (20 mg) of *p*-toluenesulfonic acid monohydrate was preferable to prevent reconversion of the unstable cyanohydrin into the starting ketone. *Cf.* ref 28.

An analytical sample of **92** had mp 52.0–52.3°; ir 2230 (CN), 1620, 1572, and 1502 cm^{-1} (C=C and Ar); uv_{max} 205 mμ (ε 16,200), 215 (14,900), 231 (11,400), 291 (9820).

Anal. Calcd for $C_{12}H_{11}ON$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.55; H, 6.01; N, 7.74.

3ξ-Hydroxycholest-4-ene-3ξ-carbonitril (94). Cholestenone (**23a**) (2.00 g, 5.1 mmol) in 60 ml of THF was treated with 20 ml of a 1.3 *M* solution of Et_2AlCN in toluene in the same way as described above except that the reaction temperature was −60° and the reaction time was 15 min. The same work-up of the reaction mixture as described above and recrystallization of the product from ethanol afforded 1.439 g of the cyanohydrin **94**, mp 121–123° dec. A second crop (0.294 g), mp 123.5–125° dec, and a third crop (0.183 g), mp 130–137° dec, were obtained from the mother liquor. The total yield was 92%. An analytical sample prepared by recrystallization of the first crop had mp 118.0–121.5° dec; $[\alpha]^{22}D$ +147° (*c* 1.01); ir 3587, 3405 (OH), 2247 (CN), and 1656 cm^{-1} (C=C).

Anal. Calcd for $C_{28}H_{45}ON$: C, 81.69; H, 11.02; N, 3.40. Found: C, 81.83; H, 11.09; N, 3.29.

Acknowledgment. The authors wish to thank Dr. I. Kikkawa for performing hydrocyanation of compounds **5** and **43** and Mrs. T. Maeda, Messrs. T. Okumura, T. Aoki, K. Kawata, and M. Yamaguchi for technical assistance in part.

Hydrocyanation. VII. Stereochemistry of Conjugate Hydrocyanation of Cyclic α,β-Unsaturated Ketones

Wataru Nagata,* Mitsuru Yoshioka, and Tadao Terasawa

Contribution from the Shionogi Research Laboratory, Shionogi and Company, Ltd., Fukushima-ku, Osaka, Japan. *Received February 9, 1970*

Abstract: Stereochemistry of hydrocyanation of various polycyclic α,β-unsaturated ketones in both thermodynamically and kinetically controlled processes is discussed. Some fundamental studies on stereochemistry using $\Delta^{4(10)}$-octalin-3-one (**5**) and the 9-methyl analog **6** revealed that (1) while the method A hydrocyanation (R_3Al–HCN in THF) is kinetically controlled, the method B hydrocyanation (R_2AlCN) is thermodynamically controlled when the reaction is carried out in benzene for a prolonged reaction time; (2) the equilibration results in decrease of the trans isomers **9**t and **10**t. On the basis of a stereochemical pathway postulated for the new hydrocyanation (Figure **2**), the experimental thermodynamic trans/cis ratios are accounted for semiquantitatively by estimating the differences in the total strain energies of the enolates of the final products, **7**t and **7**c and **8**t and **8**c. The kinetic trans/cis ratios are also interpreted qualitatively by approximating the energy differences in the transition states to those of the trans and cis primary products (products resulting from stereoelectronic control). This treatment is based upon an assumption that the primary products are energetically close to the transition states. Analysis of the stereochemical results of kinetic hydrocyanation of a number of polycyclic α,β-unsaturated ketones with method A and method B reagents leads to the following stereochemical generalizations: (1) an axial addition principle is borne out in every example; (2) hydrocyanation of six-membered polycyclic terminal-ring enones (types I and II) gives a mixture of *trans*- and *cis*-nitriles in favor of the former in general; (3) only the trans isomer is produced from steroidal ring B or C enones (type III); (4) the reaction of acetylhydrindenes (type IV) gives a mixture of trans and cis isomers with the former greatly predominant; (5) hydrindenones (type V) predominantly or exclusively give *cis*-nitriles. These stereochemical observations are rationalized on the basis of the postulated stereochemical pathway. The use of an alkali metal cyanide in an aprotic solvent (method C) decreases the formation of the trans isomer. This effect is accounted for by solvation of the cyanide ion.

In the foregoing paper,[1a] we described new hydrocyanation methods using a combination of an alkylaluminum (R_3Al; R = alkyl or halogen, at least one of R_3 is alkyl) and hydrogen cyanide (HCN) (method A) or an alkylaluminum cyanide (R_2AlCN) (method B). The following mechanisms as expressed by eq 1 and 2 were suggested for the method A and method B hydrocyanations, respectively. In these mechanisms, it was pointed out that the steps involving necleophilic attack of $[R_3AlCN]^-$ and Et_2AlCN at the β carbon of an α-enone (the carbon–carbon bond forming step) to give the enolates ii and vi, respectively, are rate determining for conjugate hydrocyanation by methods A and B. Moreover, as is clear from the equations, while method A hydrocyanation is irreversible because of the presence of proton and, thus, represents a kinetic pro-

(1) (a) W. Nagata, M. Yoshioka, and S. Hirai, *J. Amer. Chem. Soc.*, 94, 4635 (1972); (b) W. Nagata, M. Yoshioka, and M. Murakami, *ibid.*, 94, 4644 (1972); (c) W. Nagata, M. Yoshioka, and M. Murakami, *ibid.*, 94, 4654 (1972).