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

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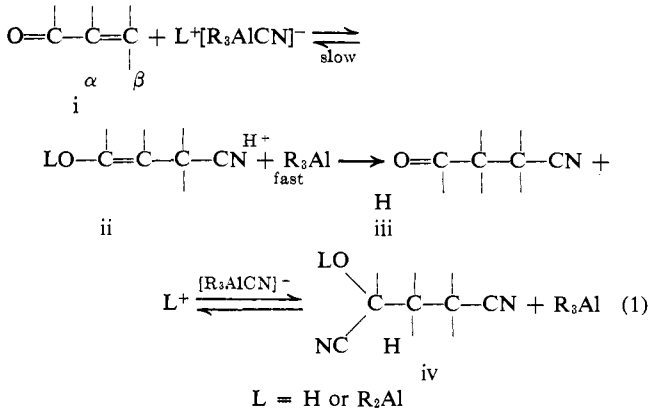
Abstract: Stereochemistry of hydrocyanation of various polycyclic α,β-unsaturated ketones in both thermodynamically and kinetically controlled processes is discussed. Some fundamental studies on stereochemistry using $\Delta^{4(10)}$-octalin-3-one (**5**) and the 9-methyl analog **6** revealed that (1) 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.

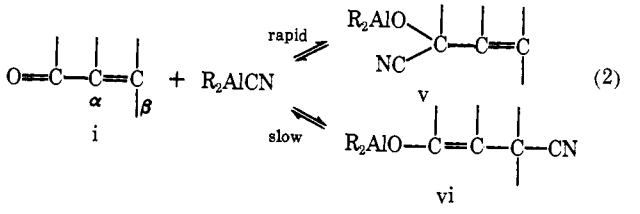
In the foregoing paper,[1a] we described new hydrocyanation methods using a combination of an alkylaluminum (R_3Al; R = alkyl or halogen, at least one of R_3 is alkyl) and hydrogen cyanide (HCN) (method A) or an alkylaluminum cyanide (R_2AlCN) (method B). The following mechanisms as expressed by eq 1 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).

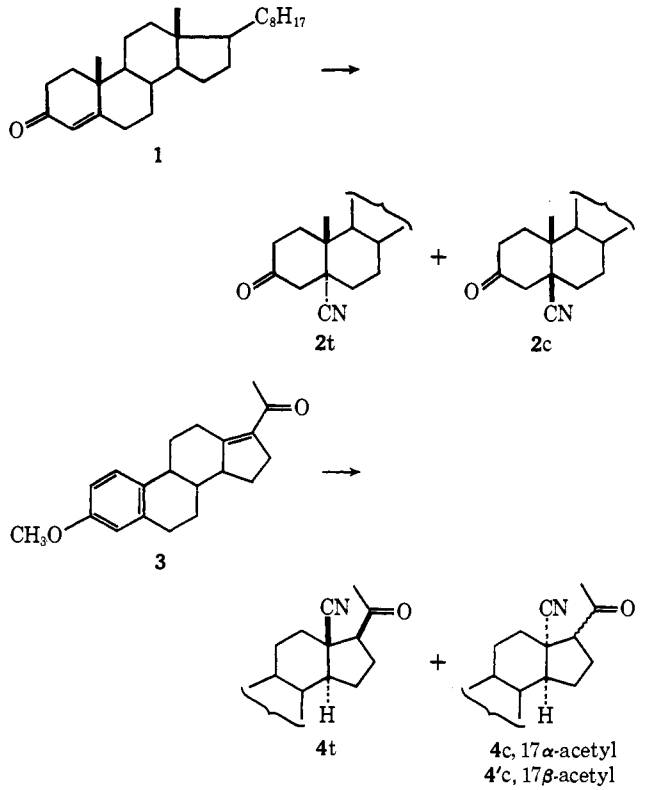
Method A



Method B



cess, method B hydrocyanation is reversible and, therefore, can be controlled both kinetically and thermodynamically. These distinct features of method A and method B hydrocyanations should give rise to different stereochemical results in conjugate hydrocyanation of α,β-unsaturated ketones. In fact, as pointed out in the previous papers,[1a,c] in hydrocyanation of cholestenone (**1**) and *dl*-18-nor-17-acetyl-1,3,5(10),13(17)-estratetraene (**3**) the kinetic and thermodynamic trans/cis ratios of products are surprisingly different. Thus,



while the kinetic ratios of **2t**[2] to **2c**[2] and **4t** to **4c** (+ **4'c**) are 1.2–0.8 and 2.2, respectively, the ratios decrease to 0.1 and 0.85 under thermodynamically controlled conditions (method B hydrocyanation in benzene and with a prolonged reaction time). This observation is remarkedly important from a stereochemical viewpoint and led us to examine the stereochemistry of the new hydrocyanations more fundamentally.

On the other hand, we also described[1c] the broad application of the new hydrocyanation methods to a number of cyclic α,β-unsaturated ketones of structurally different types, and the results obtained from these examples led us to two other important stereochemical observations regarding kinetically controlled conjugate hydrocyanation. First, an axial addition principle is borne out in all the examples and, secondly, a relationship exists between the trans/cis product ratio and the type of the polycyclic α-enones in kinetic angular cyanation by both methods A and B. These stereochemical observations are also important from a synthetic point of view.

The present paper deals with these stereochemical aspects of conjugate hydrocyanation by the new methods.[3] In the first section, we describe some fundamental studies on the stereochemical course of the conjugate hydrocyanations under kinetically and thermodynamically controlled conditions using elementary bicyclic α,β-unsaturated ketones, namely $\Delta^{4(10)}$-octalin-3-one (**5**) and its 9-methyl derivative **6**, and in the second section, we discuss the relation between the trans/cis product ratios and types of α-enone structures under kinetically controlled conjugate hydrocyanation. Some stereochemical results and the interpretation[4] of conjugate hydrocyanation by our earlier method[5] using potassium cyanide and ammonium chloride in dimethylformamide (KCN–NH_4Cl in DMF; method C) are also presented for comparison with those obtained by the new methods.

Results and Discussion

A. Stereochemistry of Thermodynamic and Kinetic Conjugate Hydrocyanation of $\Delta^{4(10)}$-Octalin-3-one and 9-Methyl-$\Delta^{4(10)}$-octalin-3-one. Thermodynamic and Kinetic Product Ratios. Based upon the suggested mechanisms[1b] (*cf.* eq 1 and 2), the reaction paths for conjugate hydrocyanation of $\Delta^{4(10)}$-octalin-3-one (**5**) and its 9-methyl analog **6** according to methods A and B can be expressed by eq 3. In method A hydrocyanation of octalinone **5**, the trans/cis ratio of the initially formed cyano enolate **7** (**7t**/**7c**) should correspond to the total trans/cis ratio of the secondary products **9** and **11** (**9t**/**9c** plus **11t**/**11c**), since the dinitrile **11** is derived from **9** without any configurational alteration at C_{10}. The total trans/cis ratio can be obtained by determining the trans/cis ratio of the cyano ketones **9t** and **9c** formed after alkali quenching, since **11** can be converted quantitatively to **9** by this treatment. Now, this ratio may

(2) Hereafter, t and c are used for trans- and cis-fused cyano ketones.

(3) Stereochemical results of angular cyanation by the new methods have already been interpreted by us in certain individual cases: (a) W. Nagata, I. Kikkawa, and M. Fujimoto, *Chem. Pharm. Bull.*, **11**, 226 (1963); (b) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Amer. Chem. Soc.*, **89**, 1483 (1967).

(4) Some stereochemical interpretations regarding the earlier hydrocyanation method have been reported by other authors also in limited cases: (a) E. Toromanoff, *Bull. Soc. Chim. Fr.*, 708 (1962); (b) W. L Meyer and N. G. Schnautz, *J. Org. Chem.*, **27**, 2011 (1962); (c) W. L. Meyer and K. K. Maheshwari *Tetrahedron Lett.*, 2175 (1964); (d) E. Wenkert and D. P. Strike, *J. Amer. Chem. Soc.*, **86**, 2044 (1964).

(5) W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *J. Org. Chem.*, **26**, 2413 (1961).

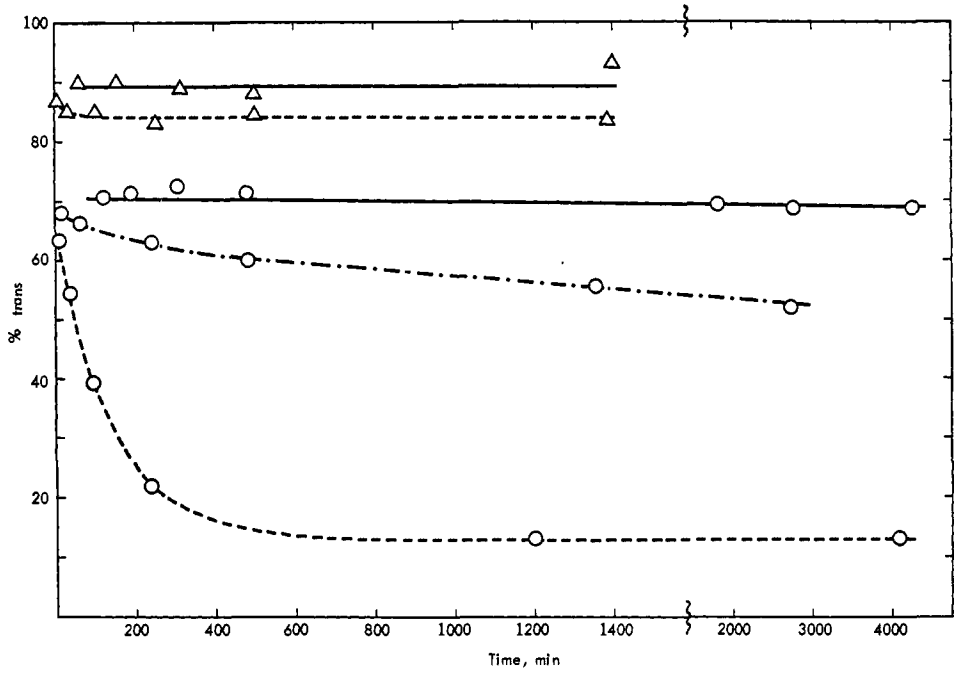
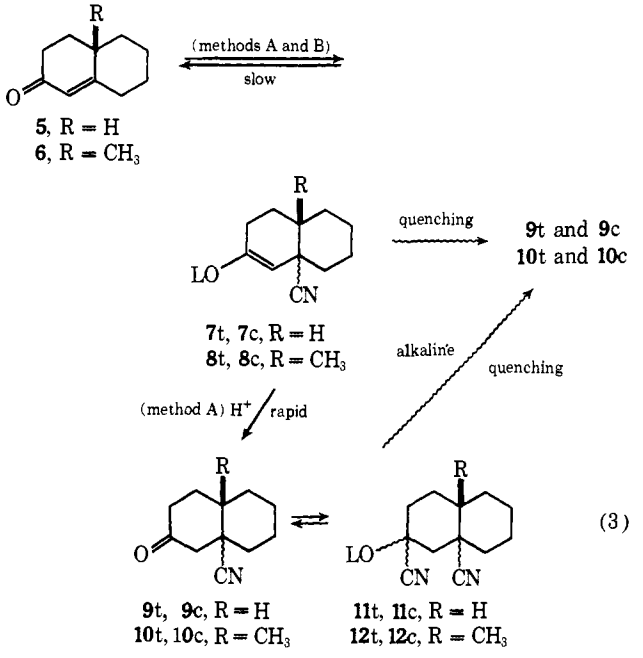


Figure 1. Plot of the percentages of the trans isomers as a function of time in conjugate hydrocyanation of $\Delta^{4(10)}$-octalin-3-one (**5**) and 9-methyl-$\Delta^{4(10)}$-octalin-3-one (**6**) (0.1 *M*) with HCN-$AlEt_3$ (each 0.3 *M*) or Et_2AlCN (0.3 *M*) at 25°: —△—, **5**-HCN-$AlEt_3$ in THF; - -△- -, **5**-Et_2AlCN in benzene; —○—, **6**-HCN-$AlEt_3$ in THF; - -○- -, **6**-Et_2AlCN in benzene; - -○- —, **6**-Et_2AlCN in THF.



represent the kinetic product ratio, since the slow reverse reaction from **7** to **5** at the initial step is interrupted by irreversible protonation as shown in eq 3. On the other hand, in method B hydrocyanation, there is no such interruption. Therefore, an ultimate equilibration may be expected between the *trans*- to *cis*-cyano enolates **7t** and **7c** in an appropriate solvent and a thermodynamic mixture of the *trans*- and *cis*-cyano ketones **9t** and **9c** would, thus, be formed after prolonged reaction time and work-up. The situation is the same with the 9-methyloctalinone (**6**).

In order to prove this possibility, alteration of the trans–cis product distribution (per cent trans) as a function of time in both method A and B hydrocyanations of **5** and **6** was examined. The reactions were carried out in THF and benzene (for method B) at 25° and the products were analyzed by glc. The results show that while there is no alteration in the trans/cis ratio in method A hydrocyanation of **5** and **6**, the ratio is markedly decreased with increasing reaction time in method B hydrocyanation as expected. This is illustrated in Figure 1. The figure also shows that the ratio alters more rapidly in benzene than in THF and becomes constant within about 4 hr for **5** and 10 hr for **6** in the former solvent. Clearly, the trans–cis equilibrium is reached within these reaction times and the final ratio represents the thermodynamic trans/cis ratio in each. Moreover, the ratio in the initial stage of method B hydrocyanation, where the forward reaction is completed, is almost the same as that in method A hydrocyanation in each example, implying that even in method B hydrocyanation the initial ratio represents a kinetic trans/cis ratio, since in most cases the reverse reaction is slow compared with the forward reaction. Thus, we obtained the per cent kinetic and thermodynamic ratios of *ca.* 8 (89/11) and 5.3 (84/16), respectively, for **5**, and *ca.* 2.3 (70/30) and 0.15 (13/87), respectively, for **6**.[6]

Stereochemical Reaction Pathways. Next, we were interested in interpreting these kinetic and thermodynamic product ratios by means of estimated free-energy differences between the probable trans and cis transition states and between the trans and cis final products. Here, the final products mean the cyano enolates **7** and **8** formed before quenching in the method B hydrocyanation. Such an interpretation would be rather qualitative because of rough approximations and large assumptions involved in the energy estimation (see later); nevertheless it may serve for better understanding of the stereochemical course of the present new hydrocyanation reactions.

(6) Very recently, another example of a dramatic reversal of trans and cis predominance in method A and B hydrocyanations was reported: R. E. Ireland and S. C. Welch, *J. Amer. Chem. Soc.*, **92**, 7232 (1970).

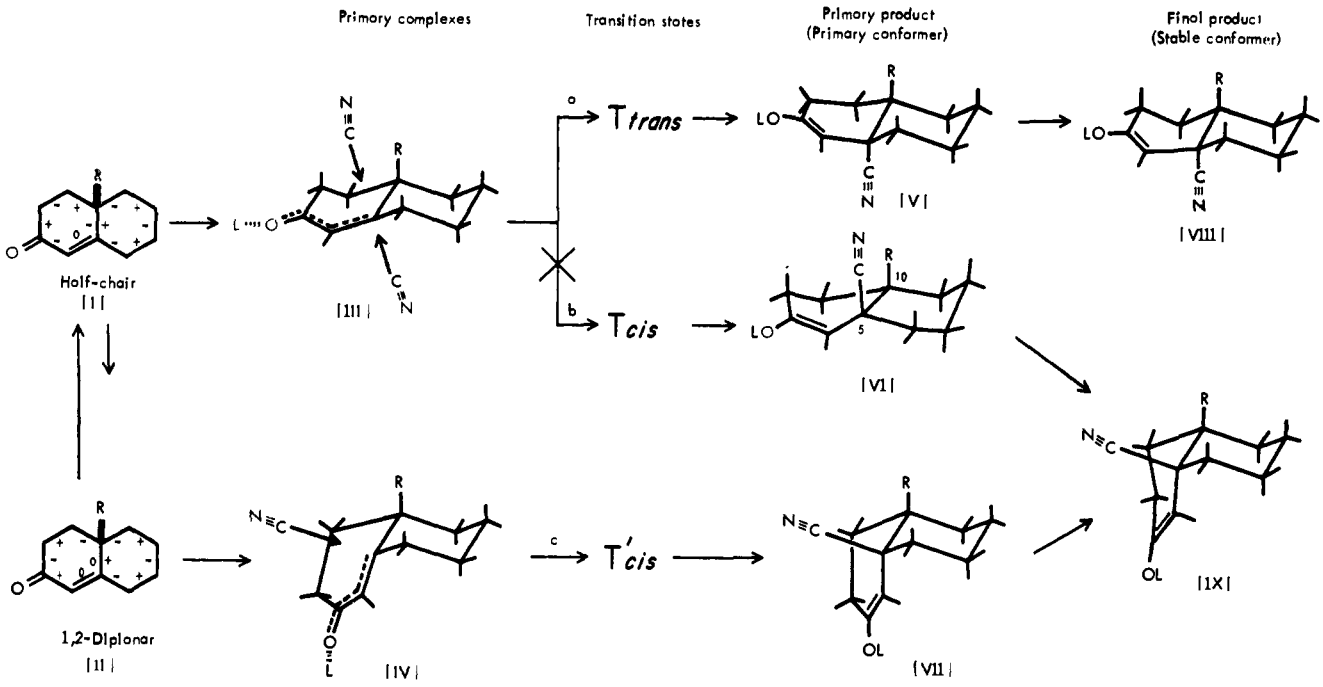
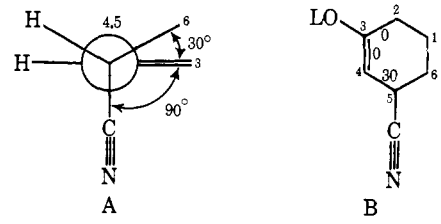


Figure 2. Stereochemical pathways leading to trans- and cis-fused 10-cyano-3-decalone (R = H) (**9**) and 9-methyl-10-cyano-3-decalone (R = CH_3) (**10**); L represents an enone-activating species (see text).

Prior to the energy estimation, we postulated the following stereochemical pathways for conjugate hydrocyanation of **5** and **6** based upon well-accepted stereochemical principles, *i.e.*, (1) maximum orbital overlap (stereoelectronic control)[7] and (2) least motion principle.[7f,8] As illustrated in Figure 2, octalinones **5** and **6** exist as two low-energy conformers with ring A half-chair [I] and 1,2-diplanar [II] conformations, with [I] predominating.[7f,9] The hydrocyanating species attacks [I] and [II] perpendicularly to the plane defined by the C_3, C_4, and C_5 trigonal carbons (steroid numbering) either from the α or β side to give the primary complexes[7f] [III] and [IV], which represent the intermediate states where the interaction between the cyanide orbital and C_5 π orbital begins and the original ring A conformation deforms slightly so as to satisfy the maximum orbital overlap. The α side attack of [II] may be discounted in view of the steric hindrance. Following the progress of the reaction, these primary complexes are transformed by way of the transition states T_{trans}, T_{cis}, and T_{cis}' to the primary products [V], [VI], and [VII], respectively. Here, the primary product is defined as follows: (1) the carbon–carbon bond formation is accomplished at this stage; (2) as a result of maintenance of the maximum orbital overlap as well as the least motion principle, the conformation of the molecule, particularly that of ring A, deforms considerably, the whole conformation being designated as the primary conformation. The maximum orbital overlap requires disposition of the C_5–CN bond at right angles to the C_3–C_4 double bond and a dihedral angle of 30° around the C_4–C_5 bond as is well accepted



(projection A). For a minimum increase of energy in the transition state, change of the interatomic distance and angle should be minimum during the reaction (the least motion principle), this requiring no flipping of the ring A conformation (no change in the signs of the dihedral angles). These requirements result in the 1,2-diplanar ring A conformation of the lowest energy[10] as shown in conformation B. While the ring A of the primary products [V] and [VII] can take this conformation, this is not possible in [VI]. A probable ring A conformation in [VI] is a 1,3-diplanar form of higher energy with a 0° dihedral angle around the C_5–C_{10} bond, which gives rise to flattening of the ring B conformation and eclipsing of the CN and R groups. Thus, the primary product [VI] possesses very high energy and, therefore, route b ([III] → T_{cis} → [VI]) may be eliminated. The primary products [V] and [VII] are finally transformed to the final trans and cis products [VIII] and [IX] with stable conformations. Thus, the product developing process involves routes a and c leading to the trans and cis final products, respectively, under kinetic conditions. In the thermodynamic method B hydrocyanation the overall steps shown in Figure 2 are reversible. In the following, we attempt to estimate the energy difference between the trans and cis final products and between the two tran-

(7) (a) E. J. Corey, *Experientia*, **9**, 329 (1953); (b) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **78**, 6269 (1956); (c) J. Valls and E. Toromanoff, *Bull. Soc. Chim. Fr.*, 758 (1961); (d) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 307–317; (e) L. Velluz, J. Valls, and G. Nomine, *Angew. Chem., Int. Ed. Engl.*, 4, 181 (1965); (f) E. Toromanoff, *Top. Stereochem.*, 2, 157 (1969).

(8) (a) F. O. Rice and E. Teller, *J. Chem. Phys.*, **6**, 489 (1938); **7**, 199 (1939); (b) J. Hine, *J. Org. Chem.*, 31, 1236 (1966); (c) E. Toromanoff, *Bull. Soc. Chim. Fr.*, 3357 (1966).

(9) The signs of the dihedral angles are given as defined by Bucourt and Hainaut.[10]

(10) R. Bucourt and D. Hainaut, *Bull. Soc. Chim. Fr.*, 1366 (1965).

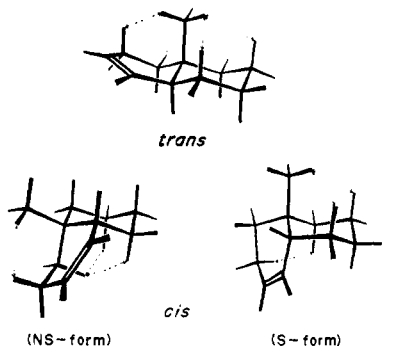
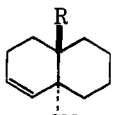


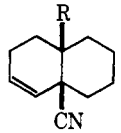
Figure 3. Illustration for *trans*- and *cis*-9-methyl-Δ^3-octalins (**16t** and **16c**).

sition states T_{trans} and T_{cis}' in order to prove the postulated stereochemical pathways.

Estimation of Energy Differences and Comparison with the Observed Values. From the foregoing discussion, it is clear that the trans to cis product ratio is related to the energy difference between *trans*- and *cis*-enolates[VIII] and [IX] in the thermodynamic method B hydrocyanation, *i.e.*, the energy difference between **7t** and **7c** for octalinone hydrocyanation and **8t** and **8c** for methyloctalinone hydrocyanation. Since the diethylaluminoxy group at C_3 may hardly affect the present estimation of the relative strain energies, one may select the desdiethylaluminoxy analogs **13t**, **13c**, **14t**, and **14c** for the energy estimation in place of **7t**,



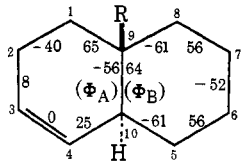
13t, R = H
14t, R = CH_3



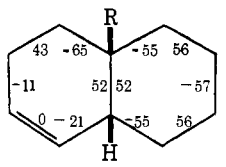
13c, R = H
14c, R = CH_3

7c, **8t**, and **8c**. Because of the lack of reasonable nonbonded interaction functions for the cyano group, the trigonal carbon, and the methyl group, it seemed impossible to calculate *a priori* the total strain energy of the cyanooctalins. Therefore, we estimated the total strain energies *semiempirically* by summing up the ring strain energies ($E_P + E_B$) calculated *a priori* for the parent octalin ring systems and the nonbonded interaction energies (E_N) evaluated on the basis of the known conformational energies of the substituents (*A* values) obtained *empirically*.

The ring-strain energies for **13** and **14** are obtained in the following way. Bucourt and Hainaut[10] gave the conformations Ct and Cc of minimum deformation

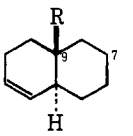


Ct, R = H or CH_3

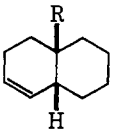


Cc, R = H or CH_3

energies for the parent octalin systems **15t** and **15c**, respectively. On the basis of these conformations, we obtained the ring strain energies of 2.6 and 2.1 kcal/mol for **15t** and **15c** by calculation according to the method of the same authors.[10] We used these values as the ring strain energies of the cyanooctalins **13t** and **13c** without any alteration, since the cyano group of a small conformational energy[11] is not considered to affect the basic ring conformations.



15t, R = H
16t, R = CH_3

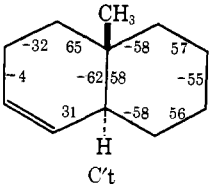


15c, R = H
16c, R = CH_3

Similarly, one may calculate the ring strain energies of the 9-methyl-10-cyanooctalins **14t** and **14c** on the basis of ring conformations of **16t** and **16c** of minimum deformation energies. However, these conformations were not available in the literature, so we attempted to derive them in the following way. It seemed that while conformation Cc given to **15c** may be applicable also to **16c** with some alteration of the bond angles, conformation Ct given to **15t** is not, since introduction of a methyl group at C_9 gives rise to a severe nonbonded interaction between the methyl and 5β hydrogen in the *trans*-octalin system, as pointed out by many authors.[10,12] This interaction is clear from the interatomic distances (Table I and Figure 3) in the conformations Ct and Cc. The close proximity of the methyl hydrogen to the 5β hydrogen (1.79 Å) clearly arises from the large Φ_B (64°) in Ct, which exceeds the normal value of 58° by 6°. With this conformation, one cannot apply the standard conformational energies of the substituents (*A* values) and, therefore, an attempt was made to modify the conformation so as to keep a reasonable interatomic distance between the angular methyl and the 5β hydrogen. As a result, we derived conformation C′t as a probable conformation of **16t**,

Table I. Calculated Interatomic Distances (Å) in *trans*- and *cis*-9-Methyl-Δ^3-octalins (**16t** and **16c**), Having the Conformations Ct, Cc, and C′t as the Basic Ring Systems

Atoms	**16t** (Ct)	**16c** (Cc) S form	**16c** (Cc) NS form	**16t** (C′t)
Methyl H ↔ 2β-H	2.23		2.16	2.43
Methyl H ↔ 5β-H	1.79	2.01		1.94
Methyl H ↔ 7β-H	1.93	2.04		1.97
1αH ↔ 8α-H		2.08		
1αH ↔ 7α-H			1.95	
1αH ↔ 5α-H			2.09	



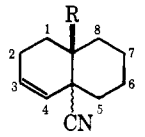
C′t

in which Φ_B and the interatomic distance between the methyl and the 5β hydrogen are normal as shown in Table I. Based on the conformations of C′t and Cc, we then estimated[10] the approximate ring strain ener-

(11) J. A. Hirsch, *Top. Stereochem.*, **1**, 197 (1967).
(12) (a) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **77**, 2505 (1955); (b) R. B. Turner, W. R. Meador, and R. E. Winkler, *ibid.*, **79**, 4122 (1957).

gies ($E_P + E_B$) for **16t** and **16c** as 3.3 and 2.0[13a] kcal/mol, respectively. The total strain energies ($E_P + E_B + E_N$) for **13t**, **13c**, **14t**, and **14c** were then calculated by adding the known nonbonded interaction energies[11] giving 2.9, 3.9, 6.5, and 5.3 kcal/mol, respectively, as summarized in Table II.[13b] The calculated differences in the total strain energies ($\Delta E_{trans-cis}$) of −1.0 (84.5% trans and 15.5% cis) and 1.2 kcal/mol (12% trans and 88% cis) thus obtained for the 10-cyanooctalins **13t** and **13c** and the 9-methyl-10-cyanooctalins **14t** and **14c**, respectively, are in good accordance with the free-energy differences of −0.91 (82.5% trans and 17.5% cis) and 1.16 kcal/mol (12.6% trans and 87.4% cis) observed for the thermodynamic hydrocyanation of **5** and **6** according to method B in benzene. The accordance is better than we expected and verifies the postulated enolate structures **7** and **8** of the final products from the stereochemical point of view. It is suggested that with other substrates a trans/cis ratio at equilibrium can be predicted semiquantitatively, provided similar estimation of the total strain energy difference between the trans and cis final products is possible. The free-energy difference of 1.28 kcal/mol (10.4% trans and 89.6% cis) observed for the thermodynamic hydrocyanation of cholestenone **1** (see above) is reasonable in view of the structural similarity to the 9-methyloctalinone (**5**).

Table II. Evaluation of the Total Strain Energies (kcal/mol) for *trans*- and *cis*-10-Cyano-Δ^3-octalins (**13t** and **13c**) and *trans*- and *cis*-9-Methyl-10-cyano-Δ^3-octalins (**14t** and **14c**)

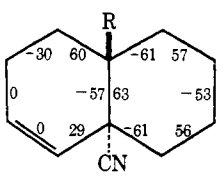


13, R = H
14, R = CH_3

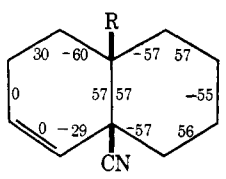
Energy term	13t	13c S form	13c NS form	14t	14c S form	14c NS form
Ring strain ($E_P + E_B$)	2.6	2.1	2.1	3.3	2.0	2.0
Nonbonded interaction (E_N)[a]						
CH_3–5β-H,7β-H				1.7	1.7	
CH_3–Δ^3,2β-H				1.2[b]		1.2[b]
1α-H–5α-H,7α-H			1.7			1.7
8α-H–Δ^3,2α-H		1.2[b]			1.2[b]	
Δ^3–6α-H		0.4[c]			0.4[c]	
α-CN-6α-H,8α-H	0.2			0.2		
β-CN-6β-H,8β-H			0.2			0.2
α-CN–1α-H	0.1			0.1		
β-CN–1β-H		0.1			0.1	
β-CN–CH_3					0.1	0.1
Total	2.9	3.8	4.0	6.5	5.5	5.2
		3.9			5.3	
Difference (trans − cis)		−1.0			1.2	

[a] Reference 11. [b] See E. R. Talaty and G. A. Russell, *J. Amer. Chem. Soc.*, **87**, 4867 (1965); B. Rickborn and S.-Y. Lwo, *J. Org. Chem.*, **30**, 2212 (1965). [c] Reference 11, p 114.

Next, we turn to an interpretation of the kinetic trans/cis product ratio based upon the postulated product developing process (Figure 2). Clearly, the kinetic product ratio is determined by a free-energy difference between the transition states T_{trans} and T_{cis}'. However, as one cannot at present estimate this difference, we replaced it by an energy difference between the primary products [V] and [VII] on the following grounds. As pointed out by Toromanoff,[7f] primary products are energetically close to transition states and, moreover, in the present hydrocyanation the transition state seems to be more nearly like primary product than the primary complex, since, as shown later, the kinetic hydrocyanation of the tricyclic enone **29** (Table V, type Ia) and $\Delta^{8(9)}$-11-oxo steroid **45** (Table V, type III) gives exclusively the trans products **30t** and **44t** and this fact can be better accounted for by the assumption that the transition state is similar to the primary product. This assumption indicates further that in the transition state C_{10} has a considerable degree of tetragonal character and that the conformation of the primary product is rather important for the energy estimation. We therefore carried out energy estimation of the primary products [V] and [VII] on the basis of their



[V]



[VII]

probable conformations shown below, these being derived[10] from conformation B defined by maximum orbital overlap principle. The estimated ring strain energies and the nonbonded interaction energies[15] taken roughly as the same as those in the energy estimation of **13** and **14** (see Table II) are summarized in Table III.

Table III. Estimated Total Strain Energies of Primary Products (kcal/mol)

Energy term	[V] R = H	[V] R = CH_3	[VII] R = H	[VII] R = CH_3
Ring strain[a] ($E_P + E_B$)	3.0	3.1	2.9	2.9
Nonbonded (E_N)	0.3	3.2 ± α[b]	1.7	3.5
Total	3.3	6.3 ± α	4.6	6.4

[a] Estimated from the data given in ref 10. [b] Extra energy due to proximity of the methyl to the 5β and 7β hydrogens.

The energy estimation shows the trans primary product [V] is 1.3 kcal/mol more stable than the *cis*-[VII] in the reaction of **5** (R = H) and comparably stable in

(13) (a) The ring strain energies ($E_P + E_B$) of **15c** and **16c** are different, though the same conformation Cc is used. This difference results from different E_B equations for tertiary (R = H) and quaternary (R = CH_3) 9-carbon atoms. (b) The cis isomers may exist as a conformational mixture of the steroidal (S) and the nonsteroidal (NS) forms and should have an advantage in entropy of mixing (calcd, *ca.* 0.4 kcal/mol). However, this advantage is not taken into account in the present estimation, the reason being based upon the fact that the experimental entropy difference between *cis*- and *trans*-decalins was found to be 0.55–0 eu/mol[14] which is far smaller than the calculated value of 1.38 eu/mol.

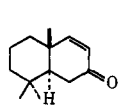
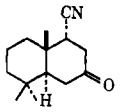
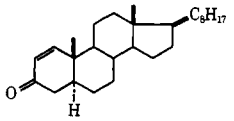
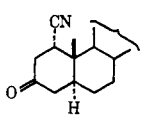
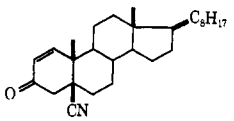
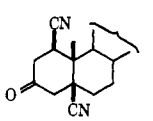
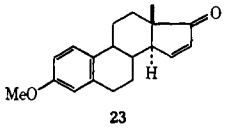
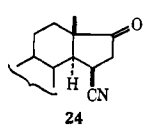
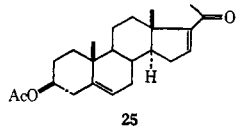
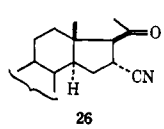
(14) (a) N. L. Allinger and J. L. Coke, *J. Amer. Chem. Soc.*, **81**, 4080 (1959); (b) J. P. McCullough, H. L. Finke, J. F. Messerly, S. S. Todd, T. C. Kincheloe and G. Waddington, *J. Phys. Chem.*, **61**, 1105 (1957).

(15) Only the steroidal form is possible in the cis primary product [VII] and, therefore, only the corresponding nonbonded interaction energies were taken into account.

the reaction of the 9-methyl homolog **6** (R = CH_3). The experimental data show the trans products, **9t** and **10t**, are favored by 1.2 (89% trans and 11% cis) and 0.5 kcal/mol (70% trans and 30% cis), respectively, indicating that accordance with the estimated values is less satisfactory for the 9-methyl homolog **6**. However, one can reasonably assume that a slight conformational change giving some trigonal character to C_{10} considerably reduces the ring strain and, more particularly, removes the extra energy (α in Table III) due to the close proximity of the methyl to the 5β and 7β hydrogens in the trans primary product [V] (R = CH_3). Thus, the estimated energy differences between the trans and the cis transition states become >1.3 (R = H) and >0.1 (R = CH_3) kcal/mol in favor of the trans, showing considerable accordance with the experimental energy differences after making allowance for the rough approximation to the transition state and the low reliability of energy estimation for the primary products. In this way, it is possible to understand at least the trend of the less predominant formation of the trans product with 9-methyloctalinone (**6**) compared with the nonmethylated octalinone **5** in the kinetic hydrocyanation.

From the above argument, the stereochemical course in the product-developing process postulated in the foregoing part (Figure 2) now becomes plausible. Moreover, it should be emphasized that the method of approximating the energy difference between the trans and cis transition states to that between the corresponding trans and cis primary products is very useful, even if qualitative, for interpretation or prediction of the stereochemical results of the kinetic conjugate hydrocyanation of a number of polycyclic conjugated enones as shown in the next section.

Table IV. Stereochemical Results in Conjugate Hydrocyanation of Representative Polycyclic α,β-Unsaturated Ketones (Nonangular Cyanation)

Enone[a]	Product	Method[b]	Yield,[c] %	Ref
 17	 18	C	76	*d*
 19	 20	A	90	
		C′	70	*e*
 21	 22	B	78	
 23	 24	C″	93	*f*
 25	 26	A	69	
		C″	67	*g*

[a] The undesignated configurations of hydrogens at C_8, C_9, and C_{14} in tetracyclic compounds are the same as those in steroids. [b] A, HCN-$AlEt_3$ in THF, room temperature; B, Et_2AlCN-aprotic solvent, below room temperature; C, KCN-NH_4Cl in DMF-H_2O, 100°, or MeOH-H_2O, reflux; C′, acetone cyanohydrin in THF-MeOH, reflux; C″, NaCN or KCN-protic solvent, reflux. [c] Isolated yields unless otherwise stated. [d] Reference 4d. [e] Reference 17a. [f] Reference 17b. [g] Reference 17c.

Table V. Stereochemical Results in Conjugate Hydrocyanation of Representative Polycyclic α,β-Unsaturated Ketones (Angular Cyanation)

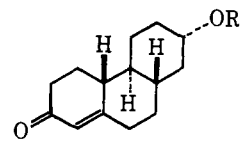
Type	Enone[a]	Product	Method[b]	Yields,[c] % Trans	Yields,[c] % Cis	Ref
Ia	**5**	**9**	A	89[e]	11[e]	
			A	72	4	
			C[d]	45	22	
Ia	**27**	**28**	A	85[e]	15[e]	
			A	65	10	
			C	43	32	
Ia	**29**	**30**	A	72	0	
			C	14	0	
Ia	**31**	**32**	A	67	18	
			C	48	25	19b
Ia	**33**	**34**	A	55[f]	0	
Ib	**35**	**36**	A	63[e]	37[e]	
			A	50	30	
Ib	**37**	**38**	A	25	40	19c
			C	21	49	19c
II	**6**	**10**	A	71[e]	29[e]	
			C	57[e]	43[e]	
II	**1**	**2**	A	49	42	
			C	33	51	
II	**39**	**40**	A	76	8	
			C	53	15	
III	**41**	**42**	A	93	0	
			C	43	0	
III	**43**	**44**	B	77	0	
III	**45**	**46**	A	65–78	0	
			B	84	0	
III	**47**	**48**	C″	80–85	0	19a
IV	**49**	**50**	C	29	50	19d
IV	**3**	**4**	A	67	9	
			B[g]	69[e]	31[e]	
			C	22	57	
IV	**51**	**52**	A	80	0	
			B[h]	77	3	
IV	**53**	**54**	B	93	0	
V	**55**	**56**	B	0	80–85	
V	**57**	**58**	A	16	65	

[a–c] See footnotes *a–c* of Table IV. [d] Carried out at room temperature. [e] Estimated from glc. [f] Overall yield in three-step reaction. [g] Reaction time = 3 min. [h] Reaction time = 20 min.

B. Stereoselectivity–Structure Relation in the Kinetic[16] Hydrocyanation of α,β-Unsaturated Ketones. Nonangular Cyanation. In Table IV are summarized several stereochemical results obtained by our[1c] and other research groups[4d,17] on the conjugate hydrocyanation of cyclic α,β-unsaturated ketones, in which the β carbon does not occupy a bridgehead position of polycyclic systems (nonangular cyanation). The cyano groups introduced in these compounds are exclusively oriented in an axial or a quasiaxial conformation, as is expected from the above discussion. In the hydrocyanation of cholest-1-en-3-one (**19**), for in-

(16) Although process B is by nature a thermodynamically controlled one, the reaction can be regarded practically as kinetically controlled, particularly when THF is used as solvent, since in most cases the hydrocyanation is completed very early before it enters into equilibration. The situation is clear from Figure 1.

(17) (a) S. Julia, H. Linares, and P. Simon, *Bull. Soc. Chim. Fr.*, 2471 (1963); (b) E. W. Cantrall, R. Littel, and S. Bernstein, *J. Org. Chem.*, **29**, 64 (1964); (c) J. Romo, *Tetrahedron*, **3**, 37 (1958).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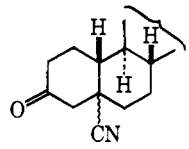
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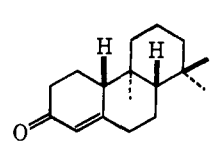
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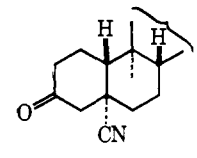
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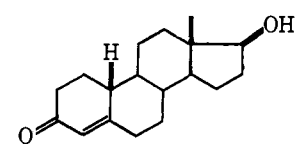
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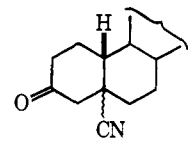
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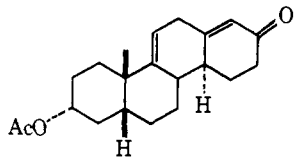
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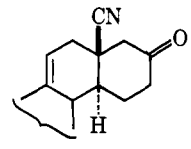
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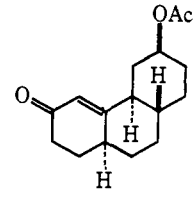
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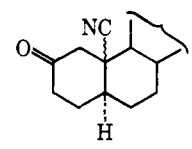
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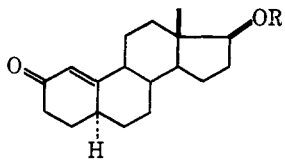
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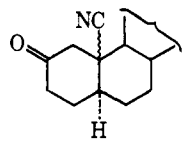
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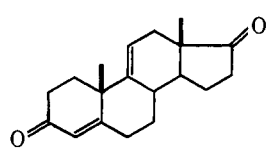
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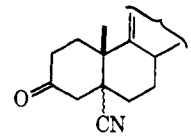
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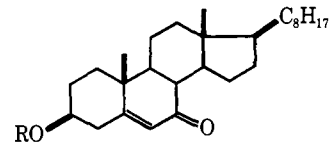
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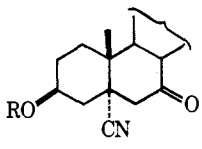
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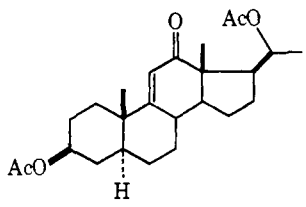
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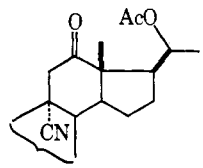
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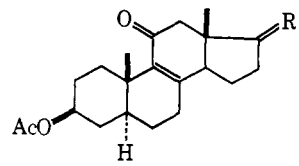
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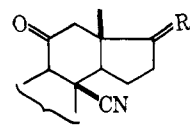
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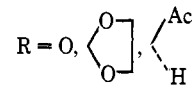

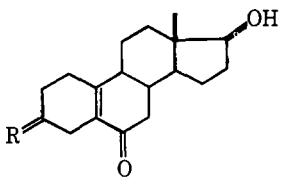
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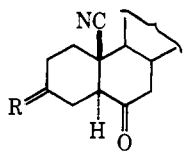
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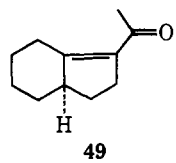
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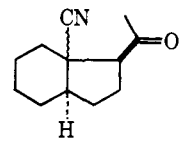
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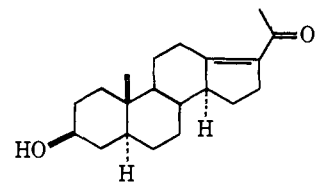
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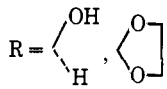

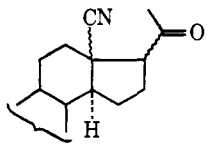
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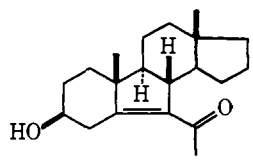
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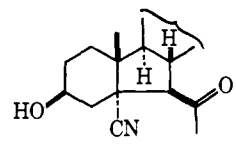
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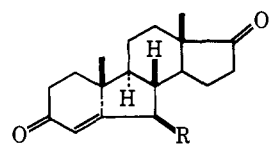
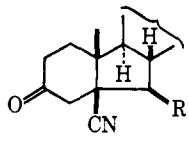
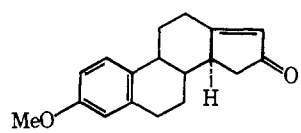

55, R = H, CH_3


56, R = H, CH_3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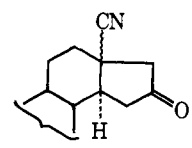

58

stance, possible conformations of the axial and the equatorial primary products are the 1,2-diplanar [X] and the 1,3-diplanar form [XI], respectively. The latter conformation, corresponding to the conformation [VI] in Figure 2, involves an insufficient orbital overlap and, moreover, this 1,3-diplanar conformation is destabilized by *ca.* 5 kcal/mol[10] compared with the 1,2-diplanar form. The axial cyano ketone **20** is thus

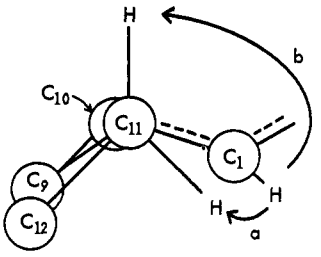
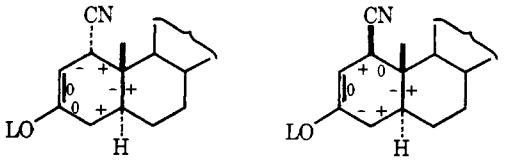


Figure 4. Movement of the hydrogen (C_1) accompanied with the conformational changes of A ring from the ground state to the primary products in hydrocyanation of **35**. Arrow a indicates the movement to the trans primary product and arrow b that to the cis primary product.



[X] [XI]

formed exclusively. Molecular model inspection shows that only the 15β-cyano primary product is probable in the D-ring hydrocyanation of **23**. Exclusive formation of the 16α-cyano ketone **26** is accounted for by the fact that while a severe CN–CH_3 interaction exists in the 16β-cyano primary product, the 16α-cyano primary product is free from such an interaction. It may be noteworthy that the observed axial addition is not limited to the nonangular hydrocyanation but commonly valid to the angular hydrocyanation discussed below.

Angular Cyanation. In Table V, we summarize the stereochemical results[1a,c,3a,18] in kinetic hydrocyanation of representative polycyclic α-enones, in which the β carbon occupies a bridgehead position (angular cyanation). The several results obtained in other laboratories[19] are also included. We have found that relations exist between the trans/cis product ratios and the α-enone structures. Accordingly, the data are classified into five types and the following generalizations may be deduced. (1) Hydrocyanation of terminal-ring enones of six-membered polycyclic compounds (type I and II compounds) usually leads to a mixture of trans- and cis-fused products, the trans/cis ratio depending on the enone structure and the reagent species. Type I compounds, having no angular methyl group in the terminal enone ring, give by method A (HCN–$AlEt_3$ in THF) a higher ratio of *trans*-cyano ketones than do type II compounds having an angular methyl group. The structure–selectivity relationship is discussed in detail later. With the same substrate, the use of an alkali metal cyanide in a polar solvent, as method C (KCN–NH_4Cl in DMF–H_2O), favors the formation of the cis isomer as compared with the reaction by method A. (2) Hydrocyanation of polycyclic enones having the enone function in a trans-fused intermediate ring (type III compounds) gives only *trans*-cyano ketones, irrespective of the kind of reagent, as exemplified by hydrocyanation of steroidal ring B or C enones. (3) Hydrocyanation of acetylhydrindenes (type IV compounds) affords a mixture of trans and cis products, the trans isomer predominating greatly in methods A and B,[16] and the cis in method C. Exclusive formation of the trans isomer in hydrocyanation of **53** corresponds to the situation with type III compounds. (4) Hydrindenones (type V compounds) predominantly or exclusively give cis products. In the following, we discuss these selectivity–structure relations in detail on the basis of the view that the energy difference between the trans and cis transition states may be approximated to that between the corresponding products, as discussed in the foregoing section.

Type I and II Compounds. Type Ia compounds predominantly afford trans products by method A hydrocyanation and this fact can be easily understood by structural analogy with $\Delta^{4(10)}$-octalin-3-one (**5**) and by the argument given in the foregoing section. The trend of the decreasing trans/cis ratio with an increasing number of trans-fused rings is ascribable to the increasing conformational rigidity raising the energy barrier in the trans transition state to a greater extent than in the cis. Conspicuously the *trans*-cyano ketone **30** is formed exclusively in hydrocyanation of the tricyclic enone **29** as referred to previously and this fact is explainable by inspecting the conformations of the trans and cis primary products, the syn-axial 9α-methyl–C_4-methine interaction (steroid numbering) in the latter being more serious than the syn-axial 9α-methyl–5α-cyano interaction in the former. Presence of a double bond para to the enone ring reduces the ring strain energy and the nonbonded interaction in the primary product as expected and, consequently, formation of the trans product becomes almost exclusive as exemplified by hydrocyanation of **33**.

In hydrocyanation of type Ib compounds, an obvious decrease of the trans/cis ratio is seen as compared with the ratio observed in type Ia compounds. This decrease of the trans product formation may be accounted for by the greater energy increase in the trans transition state due to greater steric interaction between the C_1-methine and C_{11}-methylene (steroid numbering) as shown by the projection through the C_{11}–C_{10} axis (Figure 4). This effect may become more prominent in the more rigid tetracyclic enone **37**, which gives the *cis*-cyano ketone **38**c predominantly, according to the result obtained by Fishman and Torigoe.[19c]

Decrease in predominant formation of the trans product with type II compounds is easily understandable from the discussion made in the forgoing section (A). The trend of decreasing the trans/cis ratio with increasing trans-fused rings is also observed and the presence of a double bond in the neighborhood increases the trans product as a result of disappearance of one syn-axial CN–H interaction in the trans primary product as exemplified by hydrocyanation of **39**.

Type III Compounds. Conspicuously, trans products are formed exclusively with this type of compound, in which the enone function is located in an intermediate ring of trans-fused polycyclic systems. The result can be readily interpreted by the above discussed assumption. In this case, route c leading to the cis

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(19) (a) J. Fishman and H. Guzik, *Tetrahedron Lett.*, 1483 (1966); (b) J. Fishman and M. Torigoe, *Steroids*, **5**, 599 (1965); (c) M. Torigoe and J. Fishman, *Tetrahedron Lett.*, 1251 (1963); *Tetrahedron*, 21, 3669 (1965); (d) W. L. Meyer and J. F. Wolfe, *J. Org. Chem.* **29**, 170 (1964).

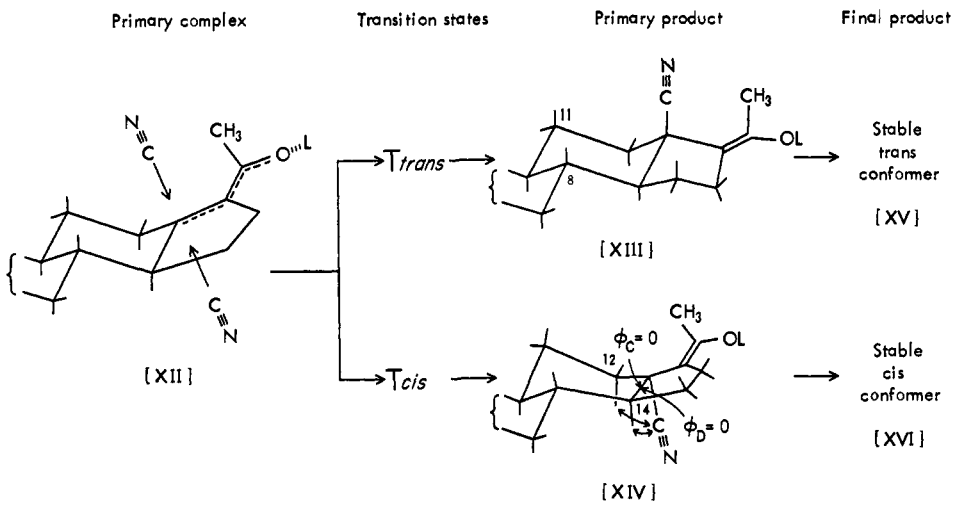
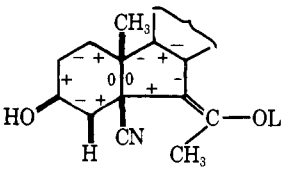


Figure 5. Stereochemical pathways for hydrocyanation of $\Delta^{13(17)}$-20-keto steroids.

product is ruled out, since the intermediate cyclohexenone ring cannot take the 1,2-diplanar form [II] in Figure 2 and a remaining route leading to a cis product (route b) requires a 1,3-diplanar [VI] or a 1,4-diplanar conformation for the primary product, a very high energy in the cis transition state being thus apparent.

Type IV Compounds. Hydrocyanation of acetylhydrindene derivatives belonging to this type gives predominantly the trans products with the present new method, as stated in the introductory section. This fact is remarkable in view of our steroid total syntheses[18,20] and, therefore, worthy of discussion in detail. The stereochemical pathway during the product-developing process in hydrocyanation of **3** and **51** is illustrated in Figure 5. As the reaction progresses, the initial primary complex [XII] changes its conformation significantly in the cis transition state T_{cis} but only slightly in the trans transition state T_{trans}. This situation can be seen from the conformations of the cis and trans primary products [XIV] and [XIII], respectively. In the former conformation, ring C changes from a chair to a monoplanar form with $\Phi_C = \Phi_D = 0$, this form giving rise to a large strain energy surmounting that[21,22] produced by the trans fusion of the cyclopentane D ring to the cyclohexane C ring in the trans primary product [XIII], since the energy of a monoplanar form exceeds that of a normal chair form by *ca.* 13 kcal/mol[10] and, moreover, the additional two eclipsed CN–H interactions (CN–12αH and –14αH) in [XIV] may bring about a greater strain than do the two syn-axial CN–H interactions in [XIII]. The predominant formation of the trans products **4t** and **52t** can thus be interpreted. An analogous explanation is also valid for the case of 6-acetyl-*B*-norsteroid **53**, which gives exclusively the *trans*-cyano ketone **54** in high yield by method B hydrocyanation. In the conformation of the cis primary product [XVII], the strain energy produced by the ring A monoplanar form and two eclipsed CH_3–CN and CN–4βH interactions may exceed greatly that imposed by the trans fusion of the cyclopentane ring B to the two cyclohexane A and C rings in the trans primary product. Thus, the cis primary product [XVII] is destabilized greatly. It should be noticed that the selectivity in hydrocyanation of this type of compound is sensitive to reagent species, as is clear from the results in method C hydrocyanation of **49** and **3**, which give predominantly the *cis*-cyano ketones **50c** and **4c** as described in the introductory section.



[XVII]

Type V Compounds. Compounds of this type include hydrindenone derivatives, which give predominantly or exclusively the *cis*-cyano ketones in contrast to the acetylhydrindene derivatives of type IV. In hydrocyanation of *B*-norandrost-4-en-3,17-dione (**55**), the cis primary product may take, unlike 9-methyloctalinone (**6**), a conformation with a 1,3-diplanar ring A form, corresponding to [VI] in Figure 2, since the 1,2-diplanar conformation of **55** is very unstable. This conformation with a 1,3-diplanar form of ring A ($\Phi_A = 0$) becomes possible, when ring B is a five-membered ring, because of the small dihedral angle Φ_B. On the contrary, in a conformation of a trans primary product corresponding to [V] in Figure 2, a large ring strain will be imposed at the A–B ring juncture, since the dihedral angle Φ_B should be greater than the normal value in this conformation (*cf.* conformation [V]) in an opposing fashion to the smaller dihedral angle of the cyclopentane B ring. The lower ring strain in the cis transition state may thus be responsible for the exclusive formation of the *cis*-cyano ketone **56**. The stereochemical result in hydrocyanation of **57** can be accounted for analogously. However, in this case the cyclopentane D ring is terminal and, therefore, the ring strain imposed in the trans primary product may be smaller than in the above case, giving some amount (16%) of the trans product **58t**.

Stereochemistry of Method C Hydrocyanation. In cases where hydrocyanation of polycyclic enones gives a mixture of *trans*- and *cis*-cyano ketones, the stereoselectivity to give the trans isomer is always lower in method

(20) W. Nagata, T. Terasawa, and T. Aoki, *Tetrahedron Lett.*, 865 (1963).
(21) H. O. House and G. H. Rusmusson, *J. Org. Chem.*, **28**, 31 (1963).
(22) Reference 7d, p 230.

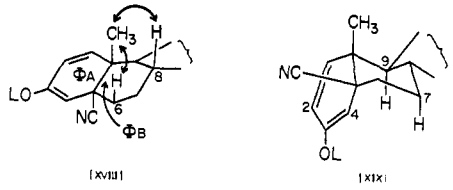
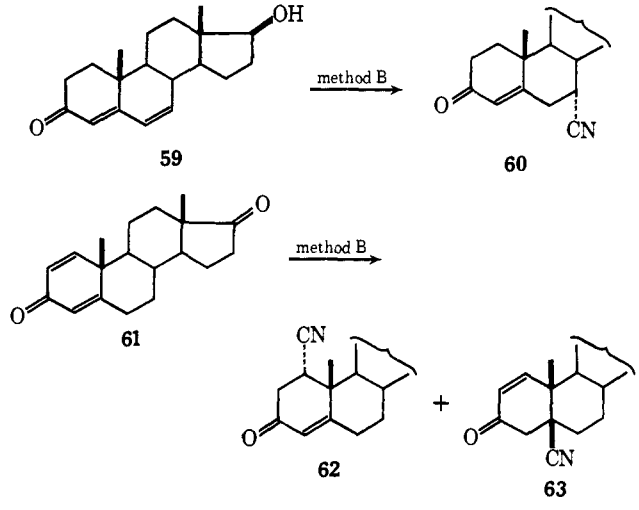


Figure 6. Primary products in hydrocyanation of **61**.

C than in method A or B under kinetic conditions. The poor selectivity in method C would be ascribed to solvation of a polar solvent to the cyanide ion to increase the steric bulk of the cyanating species. Since the number of syn-axial cyano–hydrogen interactions is larger in the trans transition state than in the cis, the increase of the bulk of the cyanating species results in a decrease of formation of trans isomers. A possibility that the poor selectivity will be due to a thermodynamic nature of method C is excluded from the equilibration study carried out with the *trans*- and *cis*-5-cyano-3-oxo compounds **2t** and **2c**.

Stereochemistry in Hydrocyanation of Dienones. As described in a foregoing paper,[1c] the method B hydrocyanation of 17β-hydroxyandrosta-4,6-dien-3-one (**59**) gave 17β-hydroxy-3-oxoandrost-4-ene-7α-carbonitrile (**60**) in 92% yield, and the reaction of androsta-1,4-diene-3,17-dione (**61**) yielded 3,17-dioxoandrost-4-ene-1α-carbonitrile (**62**) and the 5β-cyano isomer **63**



in 52 and 30% yields, respectively. Formation of **60** and **62** is accounted for readily by the foregoing discussion on the axial addition principle. Exclusive formation of the *cis*-cyano ketone **63** is contrasted with the formation of both trans and cis isomers in hydrocyanation of the corresponding monoenone **1** (type II in Table V). The result can be explained as follows: the dihedral angle Φ_A in the trans primary product [XVIII] (Figure 6) should be smaller than that in the corresponding monoenone primary product [V] (*cf.* Figure 2) because of the flattened conformation of ring A, and accordingly the dihedral angle Φ_B should increase correspondingly. Since this large deformation brings about a large ring strain and severe syn-axial CH_3–6βH,8βH interactions, formation of the trans product is impossible. On the contrary, the ring strain is small in the cis primary product [XIX], and, because of a flat conformation of ring A, the interactions between ring A and 7α- and 9α-hydrogens are reduced. This argument accounts for the exclusive formation of the cis product **63**.

Conclusion

A stereochemical pathway of the new hydrocyanation is postulated as shown in Figure 2. The overall reaction is reversible in the thermodynamically controlled hydrocyanation. Some fundamental study on the stereochemistry of the new hydrocyanation with the $\Delta^{4(10)}$-octalin-3-one (**5**) and 9-methyl homolog **6** revealed that while method A hydrocyanation is kinetic, method B hydrocyanation is thermodynamic by nature. Reversibility of the reaction depends upon solvent species used and is rapid in benzene but very slow in THF. Therefore, method B hydrocyanation is practically kinetic in THF and also in benzene when the reaction is stopped as soon as the reaction completes. The thermodynamic trans to cis product ratios **9t** to **9c** and **10t** to **10c** are interpreted semiquantitatively by estimating total strain energies of the enolate forms of the final products **7t**, **7c**, **8t**, and **8c**. The kinetic trans to cis product ratios can also be interpreted qualitatively by approximating energy difference in the transition states to that of the trans and cis primary products. This treatment is based upon an assumption that the transition state is energetically close to the primary product. With respect to stereoselectivity giving the more unstable trans products predominantly, method A is more effective than method B; method C (KCN–NH_4Cl in DMF–H_2O) is inferior in this respect giving predominantly the cis product in most cases.

It was found that a relation exists between the trans to cis product ratio and an α-enone structure in kinetic hydrocyanation of polycyclic α,β-unsaturated ketones. According to this relation, the polycyclic α-enones can be classified into five types and some generalizations regarding their stereochemical outcomes have been deduced. These empirical but rationalized generalizations are important for prediction of the stereochemical outcome in the hydrocyanation of a polycyclic α-enone.

Experimental Section

For general indications see ref 1c.

Change of Trans/Cis Product Ratios as a Function of Time in Hydrocyanation of $\Delta^{4(10)}$-Octalin-3-one (5) and 9-Methyl-$\Delta^{4(10)}$-octalin-3-one (6). Method A and B hydrocyanations of enones **5** and **6** were carried out as described in the preceding paper[1b] using purified reagents and anhydrous solvents under argon. A 1.0-ml aliquot was withdrawn from a reaction solution at a given interval and added to 0.05 *N* hydrochloric acid–ethanol (7 ml) cooled at −50°. The resulting solution was poured into a mixture of 2 *N* sodium hydroxide (30 ml) and ice, and extracted with three 30-ml portions of methylene chloride. The extracts were washed with 2 *N* sodium hydroxide (twice) and water (twice), dried (sodium sulfate), and evaporated. The product was analyzed by glpc using a Shimazu gas chromatograph Model GC-1C equipped with a thermal conductivity detector.

trans- and *cis*-cyano ketones **9t** and **9c**[3a] had retention times of 18.0 and 16.5 min, respectively, on 3% QF-1 on Chromosorb W (3 m × 3 mm stainless steel column) at 160° with a nitrogen flow rate of 200 ml/min.

Retention times of 9-methylnitriles **10t** and **10c** were 16.0 and 11.5 min, respectively, on 5% PEG-6000 on Chromosorb W (3 m × 3 mm stainless steel column) at 170° with a nitrogen flow rate of 50 ml/min. The authentic samples of **10t** and **10c** were prepared by method C hydrocyanation of enone **6** as described below. To a solution of 493 mg (0.003 mol) of **6** in 9 ml of dimethylformamide was added a solution of 390 mg of potassium cyanide and 281 mg of ammonium chloride in 0.9 ml of water. The mixture was stirred at

room temperature for 21 hr and then poured into saturated sodium chloride solution. Extraction with methylene chloride followed by the usual work-up gave an oily product, which was shown to be a 57.4:42.6 mixture of the *trans*- and *cis*-cyano ketones **10**t and **10**c by glpc. Chromatography on alumina followed by fractional crystallization from methylene chloride–ether of the mixture gave 139 mg of *trans*-nitrile **10**t, mp 103–105°, and 130 mg of *cis*-nitrile **10**c, mp 127–130°. Repeated recrystallization raised the melting point of **10**t to 105–107° (lit.[23] 107–108°) and that of **10**c to 129.5–132° (lit.[23] 136–137°).

Attempted Equilibration of 3-Oxocholestane-5-carbonitriles 2t and 2c under Method C Conditions. A mixture of 206 mg (0.5 mmol) of **2**t, 4.0 ml of dimethylformamide, 32.7 mg (0.5 mmol) of potassium cyanide, 40.2 mg (0.75 mmol) of ammonium chloride, 28 mg (0.5 mmol) of potassium hydroxide, and 0.5 ml of water (the composition corresponds to that at the end of the reaction by method C) was heated for 17.2 hr at 102°. The reaction mixture was poured into water and extracted with ether–methylene chloride (1:1). The usual work-up gave 210 mg of a crystalline solid, which was recrystallized from ethanol to afford 146 mg of **2**t, mp 180.5–182°. An additional 14.2 mg of **2**t and 9.2 mg of **2**c were obtained by preparative tlc (silica gel) of the residue from the mother liquor. The overall yields of **2**t and **2**c were 93 and 5%, respectively. A similar experiment was carried out on compound **2**c and there were obtained 79% of crystalline **2**c together with 10% of crude **2**c and 4% of crystalline **2**t together with 6% of crude **2**t.

Conformational Analysis. The determination of the molecular geometry and the energy evaluation for the ring system were carried out according to the method of Bucourt and Hainaut.[10] Thus, most of the dihedral angles (ϕ_i), valency angles (θ_i), and angular strain energies ($E_P + E_B$) were taken or evaluated from the data and the equations cited in ref 10 reported by the French workers. The modified molecular geometry C′t for *trans*-9-methyl-Δ^3-octalin (**16**t) was consistently determined with the aid of a computer using Hendrickson's formula.[24]

Acknowledgment. The authors are grateful to Dr. M. Shiro for the kind cooperation in the calculation of molecular geometries and to Dr. K. Kuriyama for the valuable discussions on the conformational analyses. Thanks are also given to Mr. M. Murakami for his technical assistance.

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