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Conformation of Acyclic Vicinal Dinitriles and Diacids. Carbon-13 Nuclear Magnetic Resonance Correlations

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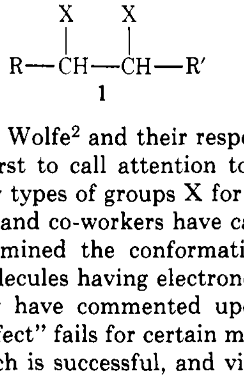
The conformations of certain acyclic dinitriles of the general structure RCH(CN)CH(CN)R′ were studied using ^1H NMR techniques in conjunction with dipole moment techniques. The conformation of the dinitriles was markedly solvent sensitive. Under conditions in which the carbons bearing CN become less conformationally pure, an R′ = benzyl group attains a greater conformational purity. The relative stabilities of the isomeric dinitriles were determined (the threo isomer was usually the more stable). The diacids analogous in structure to the dinitriles were considerably more conformationally pure. In deuteriochloroform, the conformation of the diacids was very sensitive to 1,8-bis(dimethylamino)naphthalene. ^{13}C coupling constants were determined for various compounds for certain CN or CH_3 groups; other groups gave indistinct or difficultly interpreted splitting patterns. The ^{13}C data for methyl groups were generally in accord with other data with regard to conformation.

The nature of the interaction of two electronegative groups X (as in structure 1) has received considerable attention. Lowe[1] and Wolfe[2] and their respective co-workers were among the first to call attention to the widespread preference of many types of groups X for a gauche conformation.[3] Abraham and co-workers have calculated and experimentally determined the conformational preferences for a variety of molecules having electronegative groups.[4,5] Phillips and Wray have commented upon the fact that Wolfe's "gauche effect" fails for certain molecules in which Abraham's approach is successful, and vice versa.[3-6] Phillips and Wray have correlated the tendency for a molecule to have gauche X groups with the total electronegativity of the two groups. In one case, Kagarise and co-workers have shown that bond angle changes are an important consideration.[6c] Furthermore, it seems fairly clear that certain polar groups, e.g., carbonyl groups, do not necessarily prefer a gauche conformation. Zefirov and co-workers have shown that second-row periodic chart atoms have a much lower tendency to be near one another in space than first-row atoms.[7] Rouvier and co-workers showed that cyano and amino groups prefer a trans orientation by a small amount.[8] Chen and Lin have shown that 3-methoxypropionitrile is more stable in the gauche conformation.[9]



$$R{-}\overset{\overset{\displaystyle X}{|}}{C}H{-}\overset{\overset{\displaystyle X}{|}}{C}H{-}R'$$

1

Eliel and Kaloustian attributed the tendency for oxygen containing groups X to be near one another in space to van der Waals attractions.[10] Later, Eliel discussed the conformation of 1,3-dioxanes having other electronegative groups X in terms of the interesting idea of mutual solvation.[11]

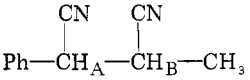
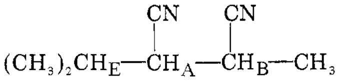
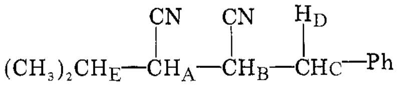
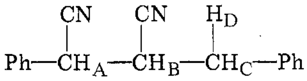
Pople et al. have advanced a hyperconjugative explanation to account for the tendency of vicinal fluoride groups to be gauche, but they consider the interaction of the fluoride groups themselves to be repulsive.[12] Apparently Hoffman entertains similar ideas.[13] On the other hand, Epiotis considers the interaction of gauche fluoride groups to be attractive.[14] The interaction of the lone pairs on the two X's forms bonding and antibonding combinations of energy levels. The destabilizing effect of the antibonding combination is reduced owing to charge transfer from this orbital into an antibonding orbital of the ethanic skeleton. Since the destabilizing interaction is thus reduced, whereas the bonding interaction is unaffected, the net interaction of the two fluorides is attractive, according to Epiotis.

Neither the Pople hyperconjugation argument nor the Epiotis argument appears to be sufficient to explain the tendency for the two chlorine groups in 2,2′-dichlorobiphenyls to lie in virtual contact with one another.[15] Thus, the question remains whether some new all-encompassing explanation should be sought to explain all cases, or whether the biphenyls are an unrelated situation.

More recently, Abraham has reproduced the conformational preferences of a series of fluorocarbons using a conventional molecular mechanics program.[16] It was stated that no special explanations were necessary to account for the conformational preferences of the fluoride groups.

The purpose of this work was to study the conformational preferences in molecules having vicinal cyanide groups, in which the nonbonded pairs central to the Epiotis argument are lacking (although formation of bonding and antibonding combinations are still possible through interaction of the *bonded* π electrons).[17] In the cyanides, the position of highest electron density is closer to nitrogen, and not carbon. While we have no firm data, our impression is that

Table I
100-MHz ^1H NMR Data for 2–9

Compd	Solvent	Coupling constants, Hz[c]				Chemical shifts, ppm[c]					
		J_{AE}	J_{AB}	J_{BC}	J_{BD}	H_A	H_B	H_C	H_D	H_E	CH_3
 $\mathrm{Ph{-}CH_A(CN){-}CH_B(CN){-}CH_3}$											
erythro-**2**	$CDCl_3$		7.4			4.07	3.13				1.52
	Pyridine		7.2			4.83	3.68				1.38
	Me_2SO		7.2			4.78	3.70				1.30
threo-**3**	$CDCl_3$		5.5			4.05	3.13				1.52
	Pyridine		5.8			4.73	3.65				1.46
	Me_2SO		5.8			4.77	3.70				1.40
 $\mathrm{(CH_3)_2CH_E{-}CH_A(CN){-}CH_B(CN){-}CH_3}$											
erythro-**4**	$CHCl_3$	4.2	10.6			2.74	2.93			2.25	1.15, 1.19, 1.58
	Pyridine	4.8	9.2			3.09	3.24			~2.1	0.98, 1.01, 1.41
	Me_2SO	7.0	8.7			3.25	3.33			~2.0	1.03, 1.03, 1.39
threo-**5**	$CDCl_3$	8.2	5.2			2.48	3.02			2.15	1.12, 1.23, 1.5
	Pyridine	7.8	5.2			2.79	3.25			~2.0	0.96, 1.08, 1.3
	Me_2SO	7.4	5.5			3.02	3.34			1.96	1.02, 1.08, 1.3
 $\mathrm{(CH_3)_2CH_E{-}CH_A(CN){-}CH_B(CN){-}CH_C(H_D){-}Ph}$											
erythro-**6**	$CDCl_3$	~4	~11	*d*	*d*	~2.7	~2.5	~2.5	~2.5	2.26	
	Pyridine	4.5	9.9	4.3	9.7	3.22	3.68	3.35	3.11	2.25	
	Me_2SO	4.7	9.2	4.6	10.6	3.32	3.66	3.16	2.94	2.14	
threo-**7**	$CHCl_3$	8.8	4.2	~8	~8.8	2.34	2.98	3.23	3.06	2.14	
	Pyridine	8.2	4.8	6.9	8.9	2.94	3.63	3.31	3.19	2.14	
	Me_2SO	7.6	4.7	5.9	10.3	3.02	3.55	3.08	2.96	2.04	
 $\mathrm{Ph{-}CH_A(CN){-}CH_B(CN){-}CH_C(H_D){-}Ph}$											
erythro-**8**	$CDCl_3$		8.1	~5.2[d]	~8.8[d]	3.98	3.31	3.13	3.09		
	Pyridine		7.5	5.0	10.4	4.87	4.09	3.20	3.03		
	Me_2SO		7.2	4.8	11.1	4.81	4.07	3.06	2.75		
threo-**9**	$CDCl_3$[b]		5.0	*a*	*a*	4.24	3.37	3.16	3.15		
	Pyridine		5.4	*a*	*a*	4.87	3.97	3.29	3.29		
	Me_2SO		5.6	5.6	11.1	4.87	3.89	3.13	2.96		

[a] May be "deceptively simple". [b] Some CH_3CN added to separate the resonances of B from C and D. [c] These solutions were usually 5.0% w/v. In the one case tested (*threo*-7), J_{AB} diminished by ca. 0.2 Hz in moving from a 5% to a 20% solution. [d] Nearly superposed resonances prevent obtainment of accurate values.

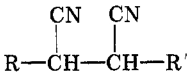
the interaction of the electrons in the two vicinal cyanides would be smaller than in the fluorides, owing to greater separation of the nitrogens from one another. Several workers have commented upon the presumed attractive nature of gauche CN groups. In a recent intensive study, Bodot and co-workers considered the interaction to be weakly attractive.[18] Peterson showed, however, that the interaction was strong enough to affect relative isomer stability.[19]

In this study, we hoped to compare ^{13}C techniques for conformational analysis to the more widely used ^1H and dipole moment techniques,[20-24] since the cyanide group is particularly convenient for study by ^{13}C NMR. A secondary objective of this work was to study the conformational preferences of the benzyl group. The type of compounds of interest is indicated in structure 1 (X = CN; R or R′ = alkyl, aryl, or benzyl). The ^1H NMR data are listed in Table I. The conformations of these compounds will be interpreted in terms of the conformers shown in Scheme I, in which the dihedral angles are arbitrarily shown as 60°. As before, J_{AB} values of 10–13 Hz are taken as indicative of predominately trans hydrogens, whereas J_{AB} values of 1–3 Hz are taken as indicative of gauche hydrogens.[25] Intermediate values usually indicate weighted means of these conformations. In Scheme I, the notation E_T signifies the conformer of the erythro diastereomer having trans hydrogens, etc.

Magnitude of the Dipole Moments. Comparison to NMR Results. In succinonitrile, the dipole moment of the conformer having gauche CN functions is 5.6 D, owing to the partial reinforcement of the individual CN group vectors.[20] The conformer having trans CN groups will have a resultant moment of near 0 D (however, owing to librational effects the actual moment will probably be larger, ca. 0.3 D).[20]

In the case of *erythro*-2 (R = Ph; R′ = CH_3; structure

Table II
Dipole Moment and Equilibration Data of the Isomeric Dinitriles

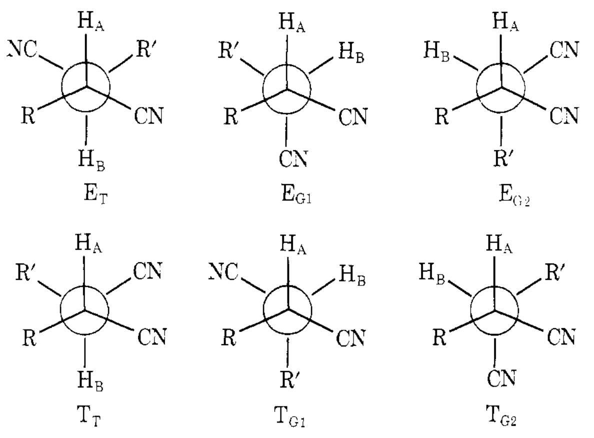


$$R{-}\underset{|}{\overset{CN}{CH}}{-}\underset{|}{\overset{CN}{CH}}{-}R'$$

Compd	R	R′	μ_{obsd}	μ_G	μ_T	% E_T or % T_{G1}		Equilibrium % erythro[b]
erythro-2	Ph	CH_3	3.7	5.75–5.0	1.0	53 ± 7		41
threo-3	Ph	CH_3					(35)[a]	41
erythro-4	*i*-C_3H_7	CH_3	2.2	5.8	0.3	86 ± 2		50
threo-5	*i*-C_3H_7	CH_3	5.3	5.8–5.6	0.4		18 ± 4	50
erythro-6	*i*-C_3H_7	CH_2Ph	1.6	5.8–5.6	0.5	92 ± 4		42
threo-7	*i*-C_3H_7	CH_2Ph	5.3	5.7–5.6	0.3		12 ± 2	42
erythro-8	Ph	CH_2Ph	3.3	5.6–5.0	0.7	63 ± 5		40
threo-9	Ph	CH_2Ph	4.3	5.6–4.9	0.9		32 ± 10	40

[a] Estimated from NMR data. [b] % erythro of an erythro–threo mixture produced by $NaOCH_3$ catalyzed equilibration of the individual diastereomers (average of duplicate runs); confidence level ±3%.

Scheme I



given in Table I), the observed dipole moment is 3.7 D (Table II), indicating a sizable population of conformers with gauche CN groups (E_{G1} and/or E_{G2}). The NMR J_{AB} value in $CDCl_3$ (7.6 Hz) is indicative of a sizable population of conformers having gauche hydrogens (also E_{G1} and/or E_{G2}). The theoretical maximum dipole moment should be adjusted to account for the varying effect of the R and R′ groups. The dipole vector for Ph is directed toward Ph, and its magnitude is 0.8 D.[20] The vector for CH_3 is directed from CH_3 toward the ethanic backbone, and its magnitude is smaller, 0.3 D. Calculations, taking into consideration the angles these subsidiary dipoles make with the CN dipoles, give 5.75 D as the moment expected for E_{G1}, and 5.0 D for E_{G2}. The fraction of molecules having trans CN groups, N_T (which is the population of E_T), may be calculated from eq. 1[20] using both extreme values for the magnitude of the dipole of conformers having gauche CN's, and averaging the results.

$$N_T = \frac{\mu_G^2 - \mu_{obsd}^2}{\mu_G^2 - \mu_T^2} \qquad (1)$$

Thus, the weight of E_T for *erythro*-2 is 0.53 ± 0.07, in agreement with the NMR data which suggests about 50% E_T.

For *erythro*-4 (R = *i*-C_3H_7; R′ = CH_3), a much larger J_{AB} value is observed in $CDCl_3$ (10.6 Hz) indicative of a very strong preference for E_T. Correspondingly, the dipole moment (2.2 D) for 4 is much smaller than for 2 since the CN groups are trans in the predominant conformer, E_T. Either E_{G1} or E_{G2} would have the same moment, 5.8 D. Using eq 1, the weight of E_T is calculated to be 0.86.

For *erythro*-6 (R = *i*-C_3H_7; R′ = $PhCH_2$), the dipole moments for the various conformers are approximated as indicated in Table II. Conformer E_T is calculated to have a weight of 0.92 ± 0.04. The J_{AB} value, ca. 11 Hz, is in agreement with the high predominance of E_T. For *erythro*-8 (R = Ph and R′ = $PhCH_2$), the weight of E_T is much lower (0.63 ± 0.05), also in agreement with NMR data. Thus, compounds having R = Ph show a much smaller preference for E_T than compounds having alkyl or benzyl substituents. The error limits indicated above may be somewhat low, since the above analysis utilizes dihedral angles of 60°, which is an idealized value, seldom present.

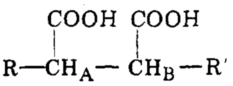
An exact identification of the limiting NMR coupling constant for pure trans protons (J_T) or pure gauche protons (J_G) is not possible. However, using the weights of the individual conformers determined from dipole moment data, and using the theoretical prediction[26] that the ratio of J_T to J_G is 5.5, the calculated values for J_T and J_G may be checked for consistency. For 8, J_T is calculated to be 11.8 ± 0.7 Hz, and J_G 2.1 ± 0.2 Hz (8 has the highest uncertainty); for 2, J_T = 12.0, and J_G = 2.2 Hz; for 4, J_T = 12.2, and J_G = 2.2 Hz; and for 6, J_T = 11.8 and J_G = 2.1 Hz. The consistency of J_T and J_G suggests that the geometry of the trans or gauche conformers in 2, 4, 6, and 8 is not grossly different.

For the threo isomers, the dipole moment data also may be used to calculate the weight of the conformers having trans CN groups (T_{G1}). These data are indicated in Table II. In order to roughly differentiate between T_T and T_{G2}, the average values for J_T and J_G roughly determined for the erythro isomers were used in a set of simultaneous equations using the weight of T_{G1} determined by dipole moment studies. The weights of T_T, T_{G1}, and T_{G2} are found to be 0.4, 0.2, and 0.4 for 5; 0.3, 0.1, and 0.6 for 7; and 0.4, 0.3, and 0.3 for 9, with confidence limits of ca. ±0.1.[27] The conformer having trans CN groups (T_{G1}) is most frequently the minor conformer. However, none of these threo isomers show really strong conformational preferences.

Equilibration Studies. Equilibrium was approached from erythro and from threo extremities using methoxide as catalyst. The results are tabulated in Table II. In all cases except 3, the threo isomer predominated at equilibrium.[19,28] It is noteworthy that the threo isomers usually contain a greater weight of the conformers having gauche CN groups.

Solvent Effects on Conformation. A change to solvents of increased polarity results in sharply reduced J_{AB} values for the erythro isomers 4, 6, and 8. *erythro*-2, which is already highly conformationally mixed, undergoes only a small change. As others have noted,[3,4,11,18,29] polar solvents are able to support conformers having large dipole mo-

Table III
100-MHz ^1H NMR Coupling Constants (J_{AB}, Hz) of the Isomeric Diacids



$R{-}CH_A(COOH){-}CH_B(COOH){-}R'$

Compd	R	R′	CDCl$_3$ solvent: Free acid	CDCl$_3$ solvent: DAN[d]	CDCl$_3$ solvent: AP[e]	D$_2$O solvent: DAN[a,b]	D$_2$O solvent: AP[c]	D$_2$O solvent: NH$_4^+$[f] (pH 8)	D$_2$O solvent: Na$^+$[g] (pH 9)	D$_2$O solvent: Ba^{2+}[h] (pH 11)
erythro-**12**	Ph	CH$_3$	11.3	6.2	10.3	12.0	10.8	10.1	11.1	~10.7[a]
threo-**13**	Ph	CH$_3$	10.6	3.5	6.6	10.2	11.5	11.5	11.5	11.6
erythro-**14**	*i*-C$_3$H$_7$	CH$_3$	8.4	3.8	4.6	9.0	10.9	9.2	10.8	*a*
erythro-**16**	Ph	CH$_2$Ph	11.0[i]						11.2[i]	
threo-**17**	Ph	CH$_2$Ph	11.2[i]	~3	5.2				11.2[i]	11.4

[a] Insolubility was a severe problem. [b] Excess DAN [1,8-bis(dimethylamino)naphthalene] present. [c] Excess AP (2-aminopyridine) present. [d] One equivalent of DAN present. [e] One equivalent of AP present. [f] The diammonium salts were prepared and dissolved in D$_2$O. [g] Anhydrous Na$_2$CO$_3$ added to acid until pH ~9. [h] BaO added to pH ~11; the solution was filtered before use. [i] Very similar to the data of Opara and Read, ref 38f.

ments better than nonpolar solvents, since dipole–dipole repulsion is reduced by solvation of the individual dipoles. Thus, conformers such as E_{G1} become more important in polar solvents. The threo isomers appear to undergo a slight change in J_{AB} to higher values indicative of a slightly greater preference for T_T. This conformer permits a closer contact of CN with solvent.

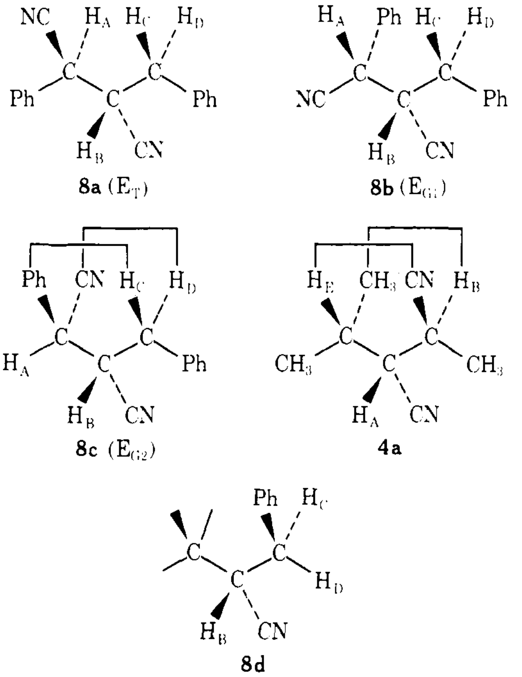
Conformation of the Benzyl Group. In earlier work, and in several compounds of this study, whenever part of a molecule assumes greater conformational purity (through a change in solvent or temperature), other parts of the molecule do the same.[30] For example, in *erythro*-**4**, the magnitude of J_{AB} (10.6 Hz) is near maximum, and the magnitude of J_{AE} (4.2 Hz) is near minimum. Cooling the sample to −57° results in a further increase in J_{AB} (10.9 Hz) and a decrease in J_{AE} (3.6 Hz).[31]

Similar unified changes occur on solvent variation. Thus, for *erythro*-**4**, J_{AB} varies from 10.6 (CDCl$_3$) to 8.7 Hz (Me$_2$SO) whereas J_{AE} changes from 5.2 (CDCl$_3$) to 7.0 Hz (Me$_2$SO). The origin of these variations in J_{AB} and J_{AE} in opposite directions has been discussed earlier in terms of minimization of 1,3 interactions between large groups (cf. **4a**).[30,32] A similar variation might have been expected for J_{BC} and J_{BD} of the benzyl group in compounds **6–9**.[33] The extended conformational diagrams in Scheme II illustrate the conformational possibilities for **8**. As the polarity of the solvent is increased (see Table I), J_{AB} for **8** moves toward the averaged value of 7 Hz, showing that E_{G1} and possibly E_{G2} become present in sizable concentrations. *However, as conformational purity diminishes at the carbons bearing CN, the conformational purity of the benzyl group appears to increase.* A change in J_{BD} from 5.2 (CDCl$_3$) to 4.8 Hz (Me$_2$SO), coupled with a change in J_{BD} from ca. 8.8 (CDCl$_3$) to 11.1 Hz (Me$_2$SO), is observed. Thus, conformations of the benzyl group as in **8d** (Scheme II) appear to become increasingly excluded. The rather incomplete data for *erythro*-**6** and *threo*-**7** suggest similar behavior.

Although an explanation similar to Brown's "windshield wiper" is possible in which rotational changes at the carbons bearing CN would tend to exclude certain regions of space from the phenyl group of benzyl,[34] it is difficult to believe that rotation about one C–C bond of a propane skeleton could be that much faster than rotation about a less sterically hindered C–C bond.

Although no certain explanation seems readily evident, we suggest that the effect of the solvent molecules as they aggregate near the CN functions may tend to restrict the benzyl group.[29] It is noteworthy that a large change in chemical shift of H_A and H_B occurs in moving to polar solvents, whereas the chemical shifts of H_C and H_D change but slightly.

Scheme II



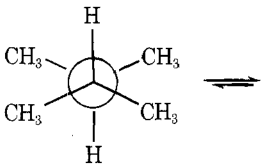
To the extent that conformers such as **8c** become more important in polar solvents, the benzyl group would be forced to occupy the position shown (and not that shown in **8d**) in order to minimize 1,3 interactions.

With regard to effective size, the benzyl group appears rather similar to methyl (compare compounds **2** and **8** and compounds **4** and **6**), rather than phenyl owing to the nature of the carbon attached to the ethanic skeleton.

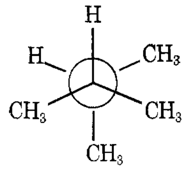
Conformation of the Diacids. Table III lists the NMR data for certain diacids of similar structure to the dinitriles discussed earlier. It is evident that a considerably higher degree of conformational purity is present in the diacids. Specifically, E_T and T_T are now strongly favored.[35] The data also show that compounds having R or R′ = Ph now have a higher degree of conformational purity than R or R′ = alkyl.

The strong preference and E_T or T_T is quite common for compounds having carbonyl groups,[30b] and other sp^2-hybridized groups such as phenyl[30] or groups such as halogen,[23,35] sulfoxide,[36] sulfone,[37] phosphine oxide,[37] and others.[38] Generally, the preference for the conformer having trans vicinal hydrogens (E_T or T_T), termed type II behavior, is found for compounds having few alkyl groups attached to the ethanic backbone. Compounds with R and R′ = alkyl frequently show a preference for the conformer with trans alkyl groups (E_T or T_{G2}).[39] This behavior, termed type I, minimizes the quite large repulsion between the alkyl groups.[40] Both type I and type II behavior may be overridden if substantial attractive interactions occur between various substituents, such as intramolecular hydrogen bonding.[41]

Many subtle changes in molecular geometry occur between different compounds, and between different conformers of the same compounds. Crystal structures and other absolute methods are slowly clarifying these changes. For example, Allinger and co-workers showed that the conformer with gauche hydrogens in 2,3-dimethylbutane is preferred owing to a widening of the dihedral angle between geminal methyl groups.[6c] Thus, the interaction between vicinal methyl groups is worsened in **10a**, leading to a preference for **10b**.[42]

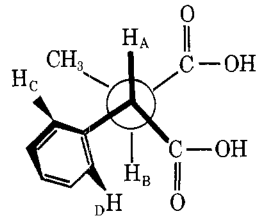


10a

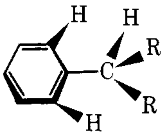


10b

However, in studies of a considerable number of tetrasubstituted ethanes, no general tendency for gauche hydrogens was noted. A large number of compounds, such as the diacids **12**, **13**, **16**, and **17**, prefer trans hydrogens.[38] We tentatively suggest that an angle contraction between geminal groups may be present as in structure **11a**. The highly polarizable π electron clouds on phenyl and carboxyl may not result in the degree of repulsion found in geminal methyl groups in 2,3-dimethylbutane. The contracted dihedral angle would reduce the repulsion between vicinal COOH–COOH or Ph–CH_3 groups. The diminished dihedral angle would require that the smallest group possible, namely hydrogen, be situated between Ph and COOH. This, in turn, would result in trans vicinal hydrogens.



11a



11b

The frequent involvement of phenyl in type II behavior may be due to a second factor, which is the result of the distinctive shape of phenyl. One ortho hydrogen of phenyl is eclipsed with one geminal substituent (probably another hydrogen); the other ortho hydrogen bisects the angle between the R groups as shown in **11b**.[43] In **11a**, if H_C is eclipsed with H_A, H_D extends toward the center of the ethanic skeleton and impinges upon one of the vicinal substituents. The least unfavorable interaction would occur with H_B. Again the result is a preference for a conformer having trans hydrogens H_A and H_B.

The cyanides **2–9** do not easily fit into type I or type II behavior patterns. The anomalous behavior is very likely the result of the weak attraction between cyanides, and due to the fairly small size of cyanide. However, compounds **4** and **6** strongly prefer E_T. Thus, the repulsion of the alkyl groups overcomes any attractive interaction of the two cyanides.[44]

A phenyl group and an alkyl group will tolerate a gauche orientation much more readily than two alkyl groups. Thus, **2** and **8** show a much higher population of the conformers with gauche CN functions (E_G) as indicated by the smaller J_{AB} values and dipole moments. The attraction of the cyanides may release the compound from any angle contractions associated with type II behavior, and the small size of cyanide may permit the ortho hydrogen of phenyl to be eclipsed with cyanide rather than H_A (cf. **11b**).

For the threo isomers, the optimum arrangement presumably should be trans alkyl groups and gauche cyanides as found in T_{G2}. This conformer is indeed highly populated for **7**, which has the largest alkyl groups. However, the reason for the general lack of conformational purity in other compounds remains obscure.

Effect of Ionization upon Conformation. In Table III, it is seen that the dianions of *erythro*-**12** and *threo*-**13** in D_2O have approximately the same conformational preference as the free acids in $CDCl_3$, namely for E_T or T_T.[45] The divalent cation, barium, does not draw the carboxylate anions together in the erythro isomer, since a decrease in J_{AB} was not observed in the presence of this cation. The concentration of di–di ion pairs is sizable at the concentrations of substrate utilized, but the separation of the barium cation from the organic dianion would be on the order of 8–14 Å.[46] Thus, several water molecules may separate the cation from the anion, and both the attraction between the cation and dianion and the repulsion between the carboxylates is reduced.

The most dramatic change observed recently in our laboratory occurred upon addition of 1,8-bis(dimethylamino)naphthalene (DAN) to solutions of the diacids in $CDCl_3$. For *erythro*-**12**, the J_{AB} value diminished from 11.3 to 6.2 Hz upon addition of 1 equiv of DAN (an additional though smaller decrease was observed upon addition of excess DAN). For *threo*-**13**, a decrease in J_{AB} from 10.6 to 3.5 Hz was observed.

The exact state of ionization of these diacids in the presence of DAN remains uncertain. To test whether hydrogen bonding, and not ionization, might be the cause of these strong changes in J_{AB}, 2-aminopyridine (AP) was utilized in parallel experiments. A small decrease in J_{AB} was observed for **12**, but sizable decreases were observed for **13**, **14**, and **17**. The pyridine derivative, AP, is a bifunctional hydrogen bond acceptor, but it is not sufficiently basic to cause ionization. On the other hand, DAN, although bifunctional, is not expected to be a good double hydrogen bond acceptor, because of steric hindrance to proper orientation of the lone pairs. DAN (proton sponge) is, of course, a strong base.[47]

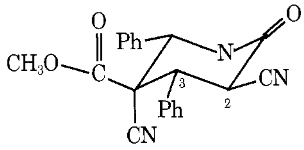
We tentatively suggest that the monoanion is formed to a significant extent in the DAN solutions. Intramolecular hydrogen bonding is believed to hold the COOH and COO^- in a gauche conformation in the monoanion. In the AP solutions, hydrogen bonding to the bifunctional base also would lead to gauche carboxyl functions. In aqueous solutions, neither DAN or AP has a large effect upon the conformation of **12** or **13**, since water is the primary agent for solvation or hydrogen bonding.

The threo isomers also undergo pronounced changes upon addition of DAN or AP, even though the preferred conformation in $CDCl_3$ (T_T) already has gauche carboxyl groups. The reason for the change of conformation (probably to T_{G2}) is not immediately obvious. Possibly the intramolecular hydrogen bonding between carboxyl functions releases the molecule from the angle deformations (as in structure **11**) that gave rise to the preference for T_T.

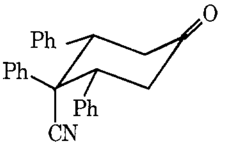
^{13}C NMR Data. The ^{13}C chemical shifts for the compounds of this study are shown in Table IV. The chemical shifts show the expected changes as structure is varied, and these will not be considered further.

It was possible to determine ^{13}C–H coupling constants between certain types of carbons and vicinal hydrogens. Perlin and co-workers have indicated that a Karplus type of relationship exists for the dihedral angle between ^{13}C and a vicinal hydrogen and the magnitude of the coupling constant $^3J_{CH}$.[48] For trans nuclei, ^3J was found to be ca. 8 Hz, whereas for gauche nuclei, ^3J was ca. 1 Hz. These values were considered to be quite sensitive to such internal factors as strain, electronegativity, etc., as indeed was shown by the earlier work of Karabatsos and co-workers.[48d] For carbonyl-hydrogen coupling constants, $^3J_T \sim 13$, $^3J_G \sim 2$ Hz.[48f]

In order to apply ^3J values to problems in conformation, it is necessary to observe these values for compounds of near conformational purity having functional groups similar to **2–9** and **12–17**. Compounds **18** and **19** were used to partially satisfy this objective.



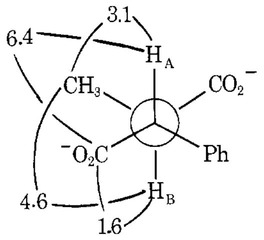
18



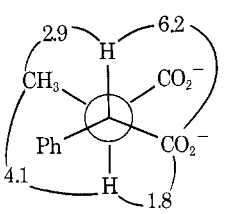
19

In studies on **18** and **19** and a number of similar compounds coupling constants from trans (diaxial) cyanide and hydrogen groups were 9.2 ± 0.5 Hz. In **18**, the equatorial cyanide at C-2 showed a coupling constant to H-3 of 1.7 Hz. This value should be reasonably characteristic of gauche nuclei.

The diacids **12** and **13** showed very high J_{AB} values in ^{1}H spectra, and these molecules are also close to conformational purity. Observation of the ^{13}C spectrum of the methyl group in **12** and **13** (disodium salts in D_2O) showed splittings of 3.1 and 4.6, and 2.9 and 4.1 Hz, respectively, in addition to the larger splitting due to the directly bound hydrogens ($^1J_{CH} = 128$ Hz). These values are considered good to ±0.4 Hz. The smaller splitting (~3 Hz) is believed to be due to $^3J_{CH}$, and the larger due to $^2J_{CH}$ (this assignment was made on the basis of consistency with other results from our laboratory). The small ^3J is in qualitative agreement with the large J_{AB} in requiring a very high population of conformers E_T and T_T as shown in structure **12** and **13**.



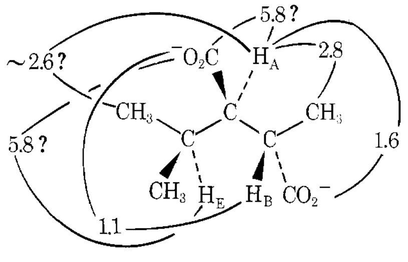
12



13

For **12** and **13**, it was also possible to obtain sharp spectra for certain carboxyl groups. In **12**, the carboxyl nearest methyl was poorly resolved, but the carboxyl nearest Ph was a double doublet from which assignments of $^2J = 6.4$ and $^3J = 1.4$ Hz were made (**18** gave similar values). The latter is in agreement with the preference for E_T since gauche COOH and H_B nuclei would be in evidence.

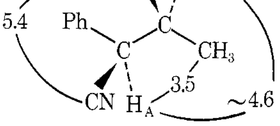
In **14**, a double-triplet splitting pattern was observed for one carboxyl, most likely the carboxyl nearest isopropyl. This carboxyl must have one two-bond coupling and two three-bond couplings. The proton spectrum indicates a predominance of E_T (redrawn in **14a**).



14a

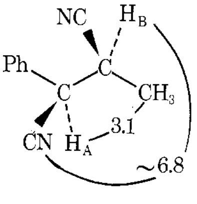
In agreement with **14a**, the coupling constant between methyl and H_A was found to be 2.8 Hz, indicative of gauche nuclei. For the carboxyl one possible assignment is $^3J_{CO-H_B} = 1.1$, $^3J_{CO-H_E} \sim 5.8$, and $^2J_{CO-H_A} \sim 5.8$ Hz. The coupling to H_B is consistent with conformer **14a**, but the coupling to H_E seems much too low.[48f] A similar double-triplet pattern was noted for compounds **4–6** (i.e., through observation of one CN in each compound). It is difficult to believe that $^3J_{CH}$ would be equivalent to $^2J_{CH}$ in so many compounds, and we have reservations about the implications from these double triplets. Computer simulation of the spectra showed that larger or smaller coupling constants resulted in splittings of nearly the proper magnitude in the simulated spectra, however.

For the dinitriles **2–5**, the J_{AB} values indicated a greater mixture of conformers than for the diacids. In *erythro*-**2**, the weight of E_T is roughly 0.5. It was of interest to see how closely the carbon couplings agree with this population and the conformational weights in other structures. In **2**, the cyanide couplings, $^3J_{CH-H_B} = 5.4$ and $^3J_{CN-H_A} \simeq 4.6$ Hz, do indeed indicate considerable conformation averaging. If the weight of E_T is taken as 0.5 and using a set of simultaneous equations with $^3J_T = 9$ Hz, the weights of E_{G1} and E_{G2} are roughly 0.2 and 0.3. Observing the methyl group of **2**, $^3J_{CH_3-H_A}$ is 3.5 Hz, which is consistent with the low population of E_{G2}.



2a (E_T shown)

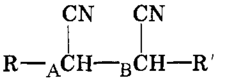
For *threo*-**3**, $^3J_{CN-H_B} \simeq 6.8$ and $^3J_{CH_3-H_A} = 3.1$ Hz. These data are consistent with sizable populations of T_T and T_{G2} but a very low population of T_{G1}.



3a (T_{G2} shown)

For *erythro*-**4**, a multiplet was found for one cyanide and a double triplet for the other. One possible assignment of the coupling constants is shown in the diagram (**4a**). In this case, the cyanide couplings are in good agreement with the conformation suggested from the proton spectra and dipole moment (ca. 86% E_T). Of the minor conformers, E_{G2} is ex-

Table IV
^{13}C Chemical Shifts

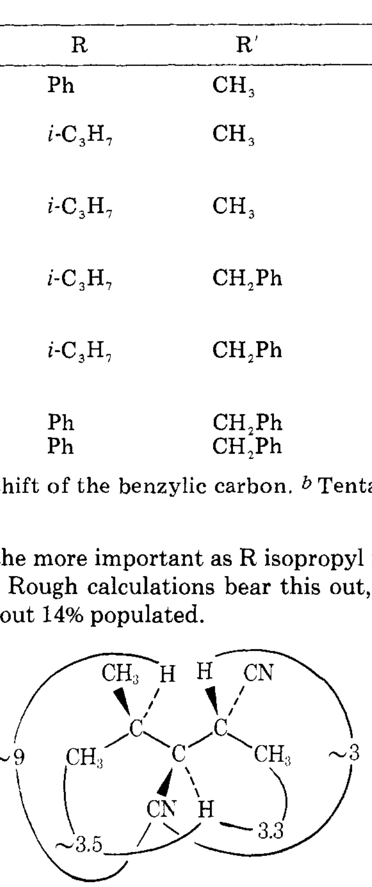


$$R{-}_{A}\overset{CN}{\overset{|}{C}}H{-}_{B}\overset{CN}{\overset{|}{C}}H{-}R'$$

Isomer	R	R'	δ_R	$\delta_{R'}$	δ_{CA}	δ_{CB}	δ_{CN}
erythro-2	Ph	CH$_3$		15.5	40.9	31.5	117.9, 118.1
threo-3				16.1	40.9	31.9	117.0, 118.5
erythro-4	*i*-C$_3$H$_7$	CH$_3$	CH 28.6 CH$_3$ 17.1 CH$_3$ 17.3	16.7	43.2	26.5	116.8, 119.1
threo-5	*i*-C$_3$H$_7$	CH$_3$	CH 29.3 CH$_3$ 19.9 CH$_3$ 20.2	16.9	43.3	26.5	117.3, 118.7
erythro-6	*i*-C$_3$H$_7$	CH$_2$Ph	CH$_3$ 28.6 CH$_3$ 17.1 CH$_3$ 21.3	36.4[a]	40.9	34.7	117.3, 117.8
threo-7	*i*-C$_3$H$_7$	CH$_2$Ph	CH 29.6 CH$_3$ 20.1 CH$_3$ 20.6	37.2[a]	40.9	34.3	
erythro-8	Ph	CH$_2$Ph		35.8[a]	39.6[b]	39.2[b]	117.1, 118.9
threo-9	Ph	CH$_2$Ph		36.6[a]	39.1	40.3	117.0, 118.5

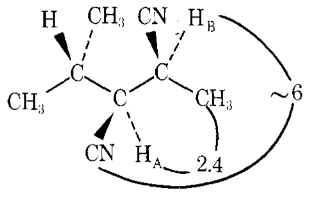
[a] Chemical shift of the benzylic carbon. [b] Tentative assignment.

pected to be the more important as R isopropyl is very hindered in E_{G1}. Rough calculations bear this out, suggesting that E_{G2} is about 14% populated.



4a

In *threo*-**5**, the coupling constants $^3J_{CN\text{-}H_B} \simeq 6$ and $^3J_{CH_3\text{-}H_A} = 2.4$ Hz were determined. These data are in agreement with the data of Table II, which indicate that the weight of T_{G1} (which has trans CH$_3$ and H$_A$ groups) is quite small (~20%).



5a (T$_{G2}$ shown)

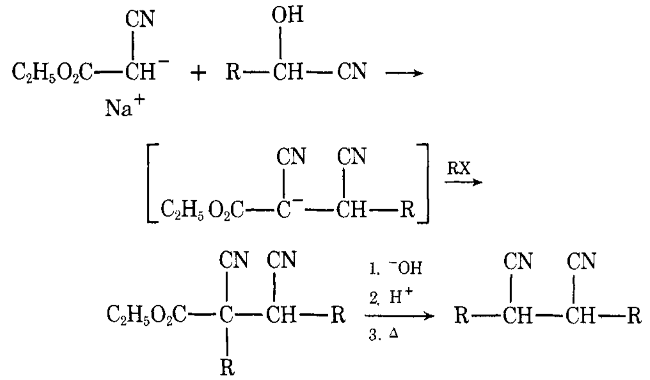
In conclusion we would point out that ^{13}C coupling constants involving methyl groups are in good qualitative agreement with conformational preferences derived from ^{1}H and dipole moment data. Some reservations have been indicated above about ^{13}C couplings involving cyanide or COOH, but agreement is satisfactory in many cases with other lines of evidence. As greater understanding of ^{13}C-H coupling constants is attained, these data should become as important as H-H couplings as a conformational probe. The ^{13}C couplings have an added advantage that a number of different carbons in a given molecule may be studied in contrast to the more limited proton couplings.

The conformational weights derived from ^{1}H and dipole moment data can be accommodated with trans and gauche $^3J_{CN\text{-}H}$ couplings of 9–9.5 and 2–3 Hz, respectively, and by $^3J_{CH_3\text{-}H}$ couplings of 6–7 and 2–3 Hz. It does seem that the carbon coupling constants are subject to rather wide variations from compound to compound. Thus far, only methyl groups among alkyl groups can be successfully studied in our hands (benzyl carbons are extensively coupled to protons in the ring).

All three lines of evidence suggest a preference for conformers having gauche CN groups in the threo isomers, and a strong contribution from such conformers in certain erythro isomers, especially in polar solvents. With regard to the Pople et al. hyperconjugative explanation of the reason for gauche X groups,[12] no consistent preference is noted for conformers such as T_{G2} (which has hydrogen trans to cyanides) over T_T.[49] It is rather difficult to assess the Epiotis explanation for gauche X groups, but, as discussed earlier, the positions of greatest electron density (nitrogen of the cyanides) tend to be rather distant from one another even if the cyanides are gauche, and it is questionable whether the interaction of the electrons would be large enough to account for the tendency for cyanides to be gauche.

Experimental Section

The general method of synthesis was the condensation of an appropriately substituted ethyl cyanoacetate with the cyanohydrin of the appropriate aldehyde. The resulting product was hydrolyzed and decarboxylated according to the following equations.



The general method was that of Higson and Thorpe.[50]

1,2-Dicyano-1-phenylpropane (2 and 3). Procedure A. To a 500-ml flask fitted with condenser and magnetic stirrer was added 5.8 g (0.25 g-atom) of sodium metal and 100 ml of absolute ethanol. After reaction, 28 g (0.25 mol) of ethyl cyanoacetate was added to the cooled solution followed by 32.8 g (0.247 mol) of benzaldehyde cyanohydrin (the latter was added gradually with stirring and cooling). The solid sodium salt of ethyl cyanoacetate gradually went into solution during addition of the cyanohydrin, leaving a brown solution at the end of addition. The resulting solution was allowed to stand for 12 hr at room temperature. To this solution, 42.6 g (0.3 mol) of methyl iodide was added with cooling, and the mixture was warmed on a water bath until a test portion was neutral to litmus. The reaction mixture was poured into water. The oil that separated was extracted into ether. The ether solution was washed with water, dried ($MgSO_4$), and evaporated to give the crude product, ethyl 2-methyl-3-phenyl-2,3-dicyanopropionate, yield 22.4 g (75%). The NMR spectrum of the crude product showed it to be a roughly equal mixture of erythro and threo isomers.

Procedure B. In a 250-ml round-bottom flask fitted with a condenser, 10 g of potassium hydroxide in 100 ml of dry methanol was added plus 24.2 g (0.1 mol) of ethyl 2-methyl-3-phenyl-2,3-dicyanopropionate. The mixture was stirred overnight, during which time a precipitate formed. The precipitate was filtered off and washed with ether, and then dissolved in water. The aqueous solution was acidified with concentrated hydrochloric acid, which yielded a heavy oil which was extracted into ether. The ether solution was washed with water, dried ($MgSO_4$), and evaporated. The gummy oil that resulted was decarboxylated by heating under reduced pressure. When gas evolution ceased, the remaining oil was dissolved in a small amount of chloroform and added to a chromatography column [150 g of silica gel (Baker)]. From the fourth fraction of 75 ml (chloroform eluent), 5 g of a mixture of diastereomeric products was collected. The diastereomers were separated by repeated crystallization from chloroform and petroleum ether. The erythro isomer (2) separated as small white needles, mp 76–78° (lit.[50] mp 80°), mass spectrum *m/e* 170 (parent ion).

Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.64; H, 5.88. Found: C, 77.77; H, 5.93.

The threo isomer separated as a brown oil, contaminated with ca. 20% of the erythro isomer. Repeated attempts at separation from the erythro isomer were unsuccessful.

Anal. Calcd for $C_{11}H_{10}N_2$; C, 77.64; H, 5.88. Found: C, 77.73; H, 5.88.

4-Methyl-2,3-dicyanopentane (4 and 5). Ethyl 2,4-dimethyl-2,3-dicyanopentanoate was prepared by the procedure A as outlined above. From 6.25 g (0.27 g-atom) of sodium, 28.25 g (0.25 mol) of ethyl cyanoacetate, 24.9 g (0.25 mol) of isobutyraldehyde cyanohydrin, and 42.4 g (0.3 mol) of methyl iodide, 27.8 g (54%) of the product ester was obtained, by 115–117° (4 mm).

The above ester was hydrolyzed by mixing 26 g (0.13 mol) of the ester with 15 g of potassium hydroxide in 100 ml of dry methanol, following procedure B. After the solvent was removed the remaining oil was distilled, during which the vigorous evolution of carbon dioxide occurred. The product was collected at 105° (2.5 mm), giving 3.5 g of the mixed diastereomers as determined by NMR. The diastereomers were separated using preparative VPC techniques (specifically, using a 1.5-m, 9.4-mm diameter column packed with Chromosorb W having ca. 10% QF-1 as the liquid phase at 200°). In a larger scale run, the diastereomers were separated by using a 50-cm spinning band distillation column. The fraction collected at 92° (2.3 mm) proved to be the erythro isomer (ca. 57% of the total mixture), mass spectrum (70 eV) *m/e* 136 (parent ion).

Anal. Calcd for $C_8H_{12}N_2$: C, 70.59; H, 8.82. Found: C, 70.32; H, 9.09.

The threo isomer distilled at 110° (2.3 mm), and accounted for ca. 43% of the mixture, mass spectrum (70 eV) *m/e* 136 (parent ion).

Anal. Calcd for $C_8H_{12}N_2$: C, 70.59; H, 8.82. Found: C, 70.37; H, 9.09.

1-Phenyl-4-methyl-2,3-dicyanopentane (6 and 7). According to procedure A, 12.5 g (0.54 g-atom) of sodium, 56.5 g (0.5 mol) of ethyl cyanoacetate, 49.5 g (0.5 mol) of isobutyraldehyde cyanohydrin, and 63.1 g (0.5 mol) of benzyl chloride were allowed to react to form 100 g (70%) of crude ethyl 2-benzyl-4-methyl-2,3-dicyanopentanoate.

The above ester was hydrolyzed by procedure B using 28.4 g (0.1 mol) of the above ester mixed with 10 g of potassium hydroxide in 100 of dry methanol. After decarboxylation under vacuum, the residue was taken up with carbon tetrachloride and chloroform. On cooling some crystals appeared which were filtered off and recrystallized from carbon tetrachloride and chloroform, yielding 9.5 g of product, mp 90–98°. However, the NMR spectrum showed this material to be a mixture of diastereomers. Chromatography on 75 g of silica gel (Baker) using benzene as eluent afforded a solid, mp 99–101°, in fractions 4 and 5 (75 ml each). This material was recrystallized from the same solvents, giving a material later identified as the erythro isomer, mp 104–107°, mass spectrum (70 eV) *m/e* 212 (parent ion).

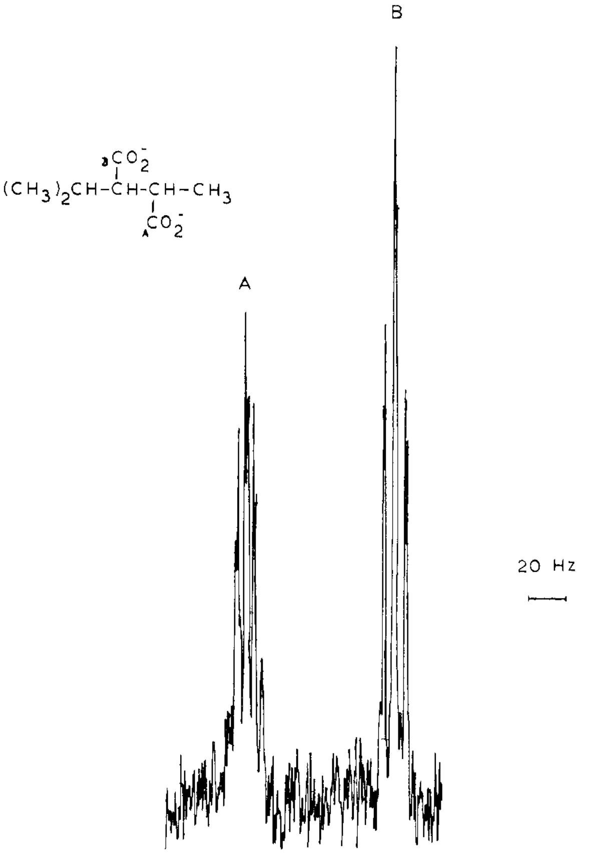


Figure 1. Coupled spectrum of 14 in D_2O (carbonyl region only).

Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.25; H, 7.55. Found: C, 79.07; H, 7.74.

Fraction 8 of the chromatography contained the threo isomer, mp 70–72°, mass spectrum (70 eV) *m/e* 212 (parent ion).

Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.25; H, 7.55. Found: C, 79.17; H, 7.65.

1,3-Diphenyl-1,2-dicyanopropane. According to procedure A, 5.8 g (0.25 g-atom) of sodium, 28 g (0.25 mol) of ethyl cyanoacetate, 32.9 g (0.25 mol) of benzaldehyde cyanohydrin, and 31.3 g (0.247 mol) of benzyl chloride yielded 73 g (93%) of the crude ethyl 2-benzyl-3-phenyl-2,3-dicyanopropionate.

According to procedure B, the above ester (31.8 g, 0.10 mol), was mixed with 10 g of potassium hydroxide in 100 ml of dry methanol. After decarboxylation in vacuo, the remaining oil was taken up in hot ethanol. Upon cooling, a material subsequently shown to be the erythro isomer separated as long needles (3.2 g) mp 138–140°, mass spectrum (70 eV) *m/e* 246 (parent ion).

Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.93; H, 5.65. Found: C, 83.06; H, 5.69.

The filtrate was evaporated to yield a gummy oil which was dissolved in a 3:1 mixture of chloroform and carbon tetrachloride. On cooling, the threo isomer separated as long needles (2.7 g), mp 85–87°, mass spectrum (70 eV) *m/e* 246.

Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.93; H, 5.65. Found: C, 82.88; H, 5.57.

3-Methyl-2-phenylbutanedioic Acid (12 and 13). Ethyl 2-methyl-3-phenyl-2,3-dicyanopentanoate (22.0 g, 0.091 mol) was refluxed in 200 ml of concentrated hydrochloric acid for ca. 12 hr. The product (a mixture of the two diastereomers) appeared as crystals upon cooling. There were filtered off, and yielded 9.0 g (48%) of the crude diacids, mp 175–185°. The crystals were dissolved in dilute sodium hydroxide and the solution was neutralized to pH 5 with dilute hydrochloric acid. The monosodium salt of the erythro succinic acid crystallized out, mp >320°. The free acid was recovered by redissolving the monosodium salt in dilute sodium hydroxide and acidifying to pH 1, followed by recrystallization from ether: mp 199–201° (lit.[51] mp 192–193°); NMR ($CDCl_3$–TFA) δ 1.11 (d, 3, CH_3), 3.34 (m, 1, $CHCH_3$), 3.86 (d, 1, CHPh), and 7.34 (s, 5, Ph); ir (KBr) 3200–3500, 1710 cm^{-1}.

After removing the erythro monosodium salt, the filtrate was acidified to pH ca 1. Crystals formed which proved to be about 80% threo and 20% erythro diacid. The pure threo isomer was obtained by repeating the dissolution in base, and precipitation of the erythro monosodium salt, followed by acidification to precipitate the mixture enriched in the threo form. The pure *threo*-**13** had mp 197–199° (lit.[51] mp 170–178°); NMR ($CDCl_3$–TFA) δ 1.49 (d, 3, CH_3), 3.48 (dq, 1, $CHCH_3$), 3.98 (d, 1, CHPh), and 7.38 (s, 5, Ph); ir (KBr) 3200–2500, 1710 cm^{-1}; mass spectrum (70 eV) *m/e* 208 (parent ion).

In another run, 1.6 g (0.093 mol) of *erythro*-**2** was mixed with 50 ml of concentrated hydrochloric acid and 0.1 ml of hydrogen peroxide (30%). The mixture was heated at reflux for 48 hr. The reaction mixture was cooled and diluted with a large volume of water, whereupon the product precipitated, mp 184–186°. The NMR spectrum showed that this material was ca. 90% of the erythro diacid. The diacid was dissolved in ca. 30 ml of water and made basic to a pH of 11; the solution was filtered. To the filtrate was added barium acetate in increments until no further precipitation seemed evident. The mixture was digested upon the steam bath for ca. 1 hr, allowed to cool, and then filtered. The mother liquor was treated with additional barium acetate, but only a slight precipitation occurred. The precipitate was treated with concentrated hydrochloric acid in ca. 30 ml of water. The resulting precipitate was vigorously stirred and filtered. The resulting diacid **12** was air dried, giving 0.9 g (54%) of product, mp 198.5–199.5°.

2-Methyl-3-isopropylbutanedioic Acid (14 and 15). This compound can be prepared from hydrolysis of **5** or **6**, or by hydrolysis of ethyl 2,4-dimethyl-2,3-dicyanopentanoate. In a typical run, 3 g (0.022 mol) of a mixture of **5** and **6** in 20 ml of concentrated hydrochloric acid was refluxed overnight (ca. 12 hr), after which some white crystals were noticeable. The solution was cooled and the crystals were collected by filtration, yielding 1.3 g of the erythro product (34% yield): mp 178–180° (lit.[52] mp 171°); NMR ($CDCl_3$–TFA) δ 1.06 (d, 3, CH_3), 1.08 [d, 3, $(CH_3)_2CH$], 1.36 [d, 3, $(CH_3)_2CH$], 2.05 [m, 1, $(CH_3)_2CH$], 2.78 (dd, 1, CH-*i*-Pr), and 3.04 (dq, 1, $CHCH_3$); ir (KBr) 3200–2500, 1700 cm^{-1}.

The filtrate was evaporated to dryness giving the impure threo isomer, **15**, which was exceedingly difficult to purify or handle (this isomer appeared to be quite water soluble).

2-Phenyl-3-benzylbutanedioic Acids (16 and 17). Hydrolysis of ethyl 2-benzyl-3-phenyl-2,3-dicyanopropanoate with hydrochloric acid, or with combinations of various acids, was not successful. This material was prepared by hydrolysis of the dinitriles **8** or **9**. To a solution of 80 ml of concentrated hydrochloric acid, 40 ml of concentrated sulfuric acid, and 40 ml of concentrated acetic acid (these must be *mixed with care*, as gaseous hydrochloric acid is evolved) was added 1.5 g (0.006 mol) of **9** and the mixture was refluxed for ca. 12 hr. On cooling the diacids (1.75 g) precipitated. In other runs some phenyl benzylsuccinimide, mp 126–130°, mass spectrum (70 eV) *m/e* 265 (parent ion), was also formed.

The best purification of these acids was belatedly found to be by means of preferential precipitation of the barium salt of one isomer. In a typical run, 2.5 g of the mixture of **16** and **17** (mp 178–180°) (shown by NMR to be a ca. 35–65% mixture) was dissolved in dilute sodium hydroxide solution. The calculated molar equivalent of barium acetate (with respect to the minor component), ca. 1 g, was added to the solution of the diacids. An immediate precipitate formed, and the mixture was digested on a steam bath for ca. 0.5 hr, allowed to cool, and filtered. Additional barium acetate was added in the same manner in increments followed by filtration, until no further material precipitated. The first two crops of precipitate were used and the much smaller third and fourth crops were discarded. This barium salt was acidified with dilute hydrochloric acid, and the resulting precipitate stirred for ca. 0.5 hr and filtered. This material was readded to dilute sodium hydroxide and precipitated again as the barium salt. The barium salt was washed with water and acidified. The free acid was collected by filtration, giving 0.5 g of **16** as the first crop, mp 184–187°, and 0.55 g as the second crop, mp 182–184°.

The mother liquor from the original barium salt precipitations was acidified to pH 1 with hydrochloric acid, and the fluffy precipitate was filtered off and allowed to air dry, mp 196–203°. This acid (**17**) was redissolved in dilute sodium hydroxide, and additional barium acetate was added in increments; and the precipitates (very slight) were discarded. Reacidification and filtration gave 1.4 g of **17**: mp 200–202° (lit.[38h,53] mp 176°); NMR ($CDCl_3$–TFA) δ 2.85 (m, 2, CH_2Ph), 3.6 (m, 1, $CHCH_2Ph$), 4.02 (d, 1, CHPh), and 7.0–7.5 (m, 10, Ph). The threo diacid **17** from other runs, purified by a recrystallization route, had mp 172–175°, very close to the literature value. The NMR spectrum was very similar to the mp 200° material.

In another run, *erythro*-**8** (1.5 g, 0.059 mol) was heated in 40 ml of concentrated hydrochloric acid, 20 ml of acetic acid, and 20 ml of sulfuric acid at reflux for 48 hr. On cooling, a precipitate appeared which was collected by filtration. The NMR spectrum showed it to be mostly **16**. The acid was dissolved in dilute sodium hydroxide, and precipitated as the barium salt as described above; this was done twice. The resulting diacid, **16** (1.35 g, 80%), had mp 187–189° (lit.[38h] mp 183°); NMR ($CDCl_3$–TFA) δ 3.1 (m, 2, CH_2Ph), 3.6 (m, 1, $CHCH_2Ph$), 4.05 (d, 1, CHPh), and 7.2–7.5 (m, 10, Ph).

Dipole Moments. The dipole moments were determined using a WSW DM 01 Dipolmeter. The cell was calibrated using benzene, cyclohexane, and carbon tetrachloride solvent pairs. Five solutions of the unknown compound were made up in carbon tetrachloride as solvent. The dielectric constant of these solutions were determined using the calibration as determined above.[20] The refractive indices of these solutions were determined on an Abbe' refractometer. The dipole moment was calculated from eq 2, where a_e is the slope of the plot of change in dielectric constant relative to pure solvent vs. weight fraction of substrate, and a_n is a plot of change in refractive index (quantities squared) vs. weight fraction of substrate.

$$\mu^2 = \frac{27kT}{4\pi N_2 d_1}\frac{1}{(\epsilon_1 + 2)^2}(a_e - a_n)\,M_2 \qquad (2)$$

NMR Data. The NMR data was taken on a Varian XL-100 instrument, or less often, on a Varian A-60D. The coupling constants were determined from 100-Hz expansions of the spectral region in question. The spectra were simulated at 500 and at 100 Hz using the LAOCOON III program.[54] Variations of the parameters were made until the computer-generated plot was superimposable on the original spectrum, although in some cases a good fit of the original spectrum was not possible either due to the complexity of the spectra or due to extreme closeness of certain chemical shifts; cases in point were **7** and **2** in $CDCl_3$. The vicinal coupling constant J_{AB} is good to ±0.3 Hz, however. The data have been omitted from Table I where the uncertainty was large.

The ^{13}C data were also determined on the XL-100 spectrometer (at 25.2 MHz). In normal runs (data given in Table IV), a 5K spectral width was used with a 0.4-sec acquisition time and a 0.2-sec pulse delay. From 5 to 10K of transients were collected. The sample solutions were as concentrated as possible, usually from 0.1 to 0.3 g of substrate per 3.0 ml of $CDCl_3$. The maximum resolution as indicated by the computer was 0.09 ppm. Assignments were made by observation of the splittings determined from undecoupled spectra.

The coupling constants were determined using highly concentration solutions. The "gated" mode of operation of the decoupler was used or, less frequently, the decoupler was simply not used. A typical run (**13**, carbonyl region) involved a 1K spectral width, a 2.5-sec acquisition time, a 2.0-sec pulse delay (gated mode of decoupler operation), and a 40-μsec pulse width. Considerable difficulty was encountered in these spectra from folded peaks, and only the clearest examples are reported in this paper. For this particular sample 10.2K of transients were collected. The spectrum resulting from a similar run is given in Figure 1. The ^{13}C splittings were also simulated using the LAOCOON program.[54] The splittings were first order for the carbonyl groups of the acids **9** and **10**, and almost first order for **11** (i.e., the line separations taken from the spectrum reproduced the spectrum when fed back into the computer program). First-order splittings were observed for certain CN spectra, and not for others. In some cases, computer simulation was impossible owing to an insufficient number of spins in the program. Coupling constants that were not simulated for this or other reasons and coupling constants whose exact value is unclear are indicated with an approximate sign.

The decisions as to which line separations were related to ^2J and which were ^3J were aided by the study of model compounds. Thus, observation of the cyanide carbon of phenylacetonitrile showed a triplet pattern (two-bond couplings to the CH_2 unit) of 10.8 Hz. The larger splittings of CN in **2–5** were assigned as ^2J. For propanoic acid, observation of the methyl showed a ^2J of ca. 4 Hz, and the methylene gave a similar value. Observation of the carbonyl gave $^2J_{CO-CH_2}$ as 6.9 Hz and $^3J_{CO-CH_3}$ as 5.8 Hz.

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Registry No.—**2**, 56908-39-5; **3**, 56908-40-8; **4**, 56908-41-9; **5**, 56908-42-0; **6**, 56908-43-1; **7**, 56908-44-2; **8**, 56908-45-3; **9**, 56908-46-4; **12**, 56908-47-5; **13**, 56908-48-6; **14**, 56943-30-7; **15**, 56908-49-7; **16**, 56908-50-0; **17**, 56908-51-1; ethyl cyanoacetate, 105-56-6; benzaldehyde cyanohydrin, 532-28-5; ethyl 2-methyl-3-phenyl-2,3-dicyanopropionate, 29840-39-9; ethyl 2,4-dimethyl-2,3-dicyanopentanoate, 56908-52-2; isobutyraldehyde cyanohydrin, 15344-34-0; ethyl 2-benzyl-4-methyl-2,3-dicyanopentanoate, 56908-53-3; ethyl 2-benzyl-3-phenyl-2,3-dicyanopropionate, 56908-54-4; ethyl 2-methyl-3-phenyl-2,3-dicyanopentanoate, 56908-55-5.

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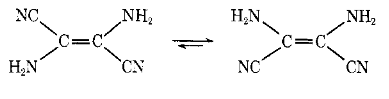

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