90 min after addition of the base. The nucleotide was completely soluble in formamide, but there was no release of *p*-nitrophenoxide 90 min after addition of the base. Chromatography in solvent 1 confirmed that no reaction had taken place. The nucleotide was completely soluble in dimethylformamide and on addition of base the solution immediately turned yellow. A slight precipitate was produced at the same time. When the release of *p*-nitrophenoxide was complete, the product was examined chromatographically in solvent 1. The major product was thymidine-3′,5′ cyclic phosphate; however, some *p*-nitrophenyl ester was present. Presumably this was precipitated on addition of the base. Rates of reactions are depicted in Figure 3.

Attempted Reaction of Adenosine-5′ *p*-Nitrophenyl Phosphate with Triethylamine in Dimethyl Sulfoxide.—The nucleotide as its sodium salt (5 μmoles) in dimethyl sulphoxide (1.0 ml) containing triethylamine (1.0 mmole) was heated at 100° for 15 min. There was no release of *p*-nitrophenoxide.

Treatment of Thymidine-5′ 2,4-Dinitrophenyl Phosphate, P¹,P²-Dithymidine-5′ Pyrophosphate, Thymidine-5′ Pyrophosphate, and Thymidylyl-(5′→3′)-thymidine with Potassium *t*-Butoxide in Dimethyl Sulfoxide.—The nucleotide (approximately 10 μmoles) in dimethyl sulfoxide (1.9 ml) was treated with 1 *M* potassium *t*-butoxide in *t*-butyl alcohol (0.1 ml) at 20°. With thymidine-5′ 2,4-dinitrophenyl phosphate[1] the release of 2,4-dinitrophenoxide was followed spectrophotometrically at 400 mμ and was complete in 1 min (Figure 4). Chromatography in solvent 1 showed that the product was thymidine-3′,5′ cyclic phosphate together with a lesser amount of thymidine-5′ phosphate.

After 30 min, chromatography in solvent showed that P¹,P²-dithymidine-5′ pyrophosphate, thymidine-5′ pyrophosphate, and thymidylyl-(5′→3′)-thymidine were completely unaffected.

Treatment of Adenosine-5′ 2,4-Dinitrophenyl Phosphate, P¹-Diphenyl-P²-Adenosine-5′ Pyrophosphate, and Adenosine-5′ Phosphorofluoridate with Potassium *t*-Butoxide in Dimethyl Sulfoxide.—The nucleotides (approximately 10 μmoles) in dimethyl sulfoxide (1.9 ml) were treated with 1 *M* potassium *t*-butoxide in *t*-butyl alcohol (0.1 ml) at 20°. Aliquots were removed at intervals, neutralized with Dowex 50 W (ammonium form), and examined chromatographically in solvents 1 and 2 except with P¹-diphenyl-P²-adenosine-5′ pyrophosphate[55] where solvent 5 was used. Reaction was complete in less than 5 min for the first two nucleotides (first aliquot) the products being adenosine-3′,5′ cyclic phosphate together with traces of adenosine-5′ phosphate and, except in the reaction of the phosphorofluoridate, P¹,P²-diadenosine-5′ pyrophosphate. With adenosine-5′ phosphorofluoridate[61] conversion to adenosine-3′,5′ cyclic phosphate was complete in 1 hr (Figure 4).

Studies on Geometric Isomerism by Nuclear Magnetic Resonance. III. Stereochemistry of α-Cyanocinnamic Esters[1]

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The nmr technique has revealed that the Cope–Knoevenagel reaction of aromatic ketones with cyanoacetic esters gives a stereoisomeric mixture of α-cyanocinnamic esters. Configurational assignments have been made by the analysis of the chemical shifts of the carboaluxy group; the signal for the *trans* isomer appears at lower field than that for the *cis* isomer. It has been found that, as the size of a β substituent becomes larger, the amount of the *cis* isomer increases. Further, on the basis of some assumption the angle of twist of the benzene ring from coplanarity has been calculated.

In the preceding paper[1] it has been established that the Cope–Knoevenagel reaction of unsymmetrical aliphatic ketones with cyanoacetic esters leads to the preferential formation of the isomers in which the bulkier alkyl group and the carboalkoxy group are on opposite sides of the carbon–carbon double bond. On the other hand, previous investigators[2,3] have shown that the condensation of aromatic aldehydes with cyanoacetic esters gives only α-cyano-*trans*-cinnamic esters. These facts agree with what would be expected on steric grounds, because the bulkiest groups are at a distance. In the course of study, however, it was found that the condensation of some aromatic ketones with cyanoacetic esters leads to the predominant formation of the *cis* isomers.[4] This appeared not to agree with the steric considerations. Therefore, it is of interest to determine which of two stereoisomers would be preferentially produced.

Since, however, no stereoisomer of a known configuration was available, assignments should be made according to the same method as had been used in the previous papers.[1,5] However, in the present paper we wish to show that it is much better to assign configurations by the analysis of the chemical shifts of the carboalkoxy protons. Further, we have discussed the conformations of these esters on the basis of the nuclear magnetic resonance and ultraviolet spectroscopic studies.

Results and Discussion

Proton resonance data for the esters studied in the present work are given in Tables I and II, together with the stereoisomeric composition. Representative nmr spectra of the esters are shown in Figures 1 and 2.

As seen from the tables, the chemical shifts for the alkyl and aryl groups on the β position are practically unchanged on going from the carbomethoxy group to the carboethoxy group. This fact was often useful not only in differentiating the signals of the ester alkyl protons from those of other alkyl groups, but also in assigning the signals superimposed upon by those of either the carbomethoxy group or the carboethoxy group.

Assignments.—In the preceding papers[1,5] the author has determined the geometric configurations of the compounds of the $R_1R_2C{=}C(CN)\ COOR_3$ type on the basis of some assumption, which states that the chemical shift for the β-methyl group occurs at a higher field in the *trans* than in the *cis* configuration with respect to the carboalkoxy group, whereas the reverse is true for the γ-methyl. However, it is doubtful whether

(1) Part II: T. Hayashi, M. Igarashi, S. Hayashi, and H. Midorikawa, *Bull. Chem. Soc. Japan*, **38**, 2063 (1965). Presented partly at the 17th Annual Meeting of the Chemical Society of Japan, Tokyo, April 1964.

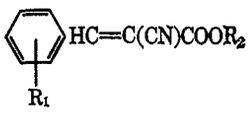
(2) W. Baker and C. S. Howes, *J. Chem. Soc.*, 119 (1953).

(3) J. Zabicky, *ibid.*, 683 (1961).

(4) In the present paper the isomer, in which the phenyl and carboalkoxy groups are on opposite sides of the carbon–carbon double bond, is referred to as the *trans* isomer.

(5) T. Hayashi, I. Hori, H. Baba, and H. Midorikawa, *J. Org. Chem.*, **30**, 695 (1965).

TABLE I

CHEMICAL SHIFTS[a] OF α-CYANOCINNAMIC ESTERS OF THE TYPE 

							—COOCH₂CH₃—				—Aromatic protons—			
Compd	R_1	R_2	Configuration	Vinylic proton	Δ	$CCOCH_3$	Δ	CH_3	Δ	CH_2	Δ	H_X	H_R	J^b
I	H	Me	*trans*	8.22	0.96	3.92	0.08					*Ca.* 7.48	*Ca.* 7.95	
			cis	7.26		3.84						Not located		
II	H	Et	*trans*	8.22	0.96			1.40	0.08	4.33	0.07	*Ca.* 7.48	*Ca.* 7.95	
			cis	7.26				1.32		4.26		Not located		
III	*o*-OMe	Me	*trans*	8.75		3.91						(6.85–8.35)[c]		
IV	*o*-OMe	Et	*trans*	8.56	0.76			1.40	0.12	4.34	0.10	(6.75–7.28)[c]		
			cis	7.80				1.28		4.24		Not located		
V	*p*-OMe	Me	*trans*	8.16		3.92						7.00	8.00	9.0
VI	*p*-Me	Me	*trans*	8.16		3.88						7.25	7.85	8.4
VII	*p*-$N(Me)_2$	Me	*trans*	8.02		3.88						7.66	7.88	9.6
VIII	*p*-NO_2	Me	*cis*	8.24		3.96						8.36	8.12	9.0

[a] Parts per million from tetramethylsilane (TMS) in $CDCl_3$. [b] J in cycles per second. [c] A parenthesis shows an resolved broad complex of absorption.

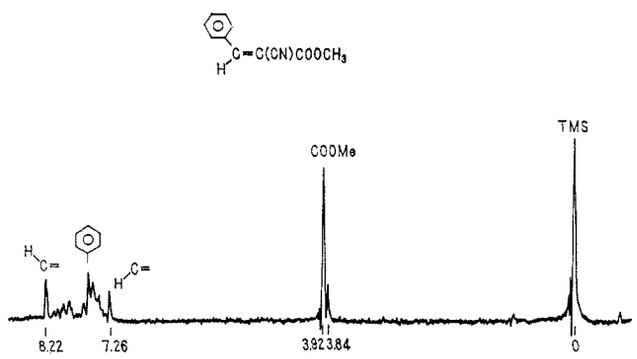


Figure 1. Nmr spectrum of methyl α-cyanocinnamate irradiated.

or not the assumption can be applied to the present case, because the conformation of the benzene ring would be expected to have significant effects on the chemical shift of the β-methyl group. Therefore, this question had to be submitted to experimental tests. In Table III the isomers having the chemical shift of the carboalkoxy group at lower field are designated as T and the isomers having that at higher field, as C. The chemical shift of the carbomethoxy group for the isomer T constantly appears in the 3.75–3.84-ppm range except for XXII T, and that of the carboethoxy group always occurs in the 1.37 ± 0.03 and 4.31 ± 0.03 ppm ranges, whereas the chemical shifts of the carboalkoxy groups for the isomer C are shifted to distinctly higher field. It should be noticed that the resonance-line positions of the carboalkoxy groups for the isomer T appear in almost the same positions as those for alkylidenecyanoacetic esters (3.83, 1.36, and 4.31 ppm, respectively[1]). This fact suggests that the carboalkoxy protons of the isomer T may experience little long-range anisotropy effect of the benzene ring. This means that the benzene ring and the carboalkoxy group are on opposite sides of the carbon–carbon double bond.

This conclusion may be supported by the following facts. (1) In α-cyano-β-methylcinnamic esters (XI and XII), the signal of the β-methyl protons[6] for the isomer T appears at lower field than that for the isomer C. In α-cyano-β-isopropylcinnamic esters (XV and XVI), the signals of the γ-methyl protons occur for the isomer T at higher field than those for the isomer C. These agree with the previous assumption.[1,5] (2) In cinnamic esters, the chemical shifts of the carboalkoxy groups also were located at lower field for the isomer T than for the isomer C (Table II). (3) In

TABLE II

NMR DATA FOR METHYL CINNAMATES IN CCl_4[a]

	Hα		Hβ		COOMe	
trans	6.32	0.46	7.56	0.64	3.80	0.15
cis	5.86		6.82		3.65	

[a] All chemical shifts are in parts per million downfield from TMS.

the case of ethyl α-cyano-*o*-methoxycinnamate (IV) which was prepared according to Patai and Rappoport,[7] the signal of the carboethoxy protons appeared at lower field for the isomer T than for the isomer C. (4) Methyl α-cyano-*trans*-cinnamate (I), after the irradiation with ultraviolet light, showed at higher field the signal attributable to the carbomethoxy protons of the isomer C.

On the basis of the above arguments it can be concluded that the isomer T is assigned to the *trans* configuration and the isomer C, to the *cis* one.

Stereoisomeric Compositions of the Products.—The fact that the spectra show two signals of unequal intensity for the carboalkoxy group was ascribed to the simultaneous existence of *cis* and *trans* isomers. The stereoisomeric compositions of the mixtures were evaluated from integration of the areas under the appropriate signals and are given in the last column of the Table II. It was confirmed that the composition ratios of the mixtures as isolated from the Cope–Knoevenagel reaction are almost the same as those of the thermodynamic equilibrium state.

The condensation of benzaldehydes with cyanoacetic esters leads to the exclusive formation of the *trans* isomers, whereas the condensation of aromatic ketones with cyanoacetic esters always gives a stereo-

(6) The notation used to distinguish the alkyl group is the same as used in the preceding paper.[1]

(7) S. Patai and Z. Rappoport, *J. Chem. Soc.*, 396 (1962); Z. Rappoport, C. Degani, and S. Patai, *ibid.*, 4513 (1963).

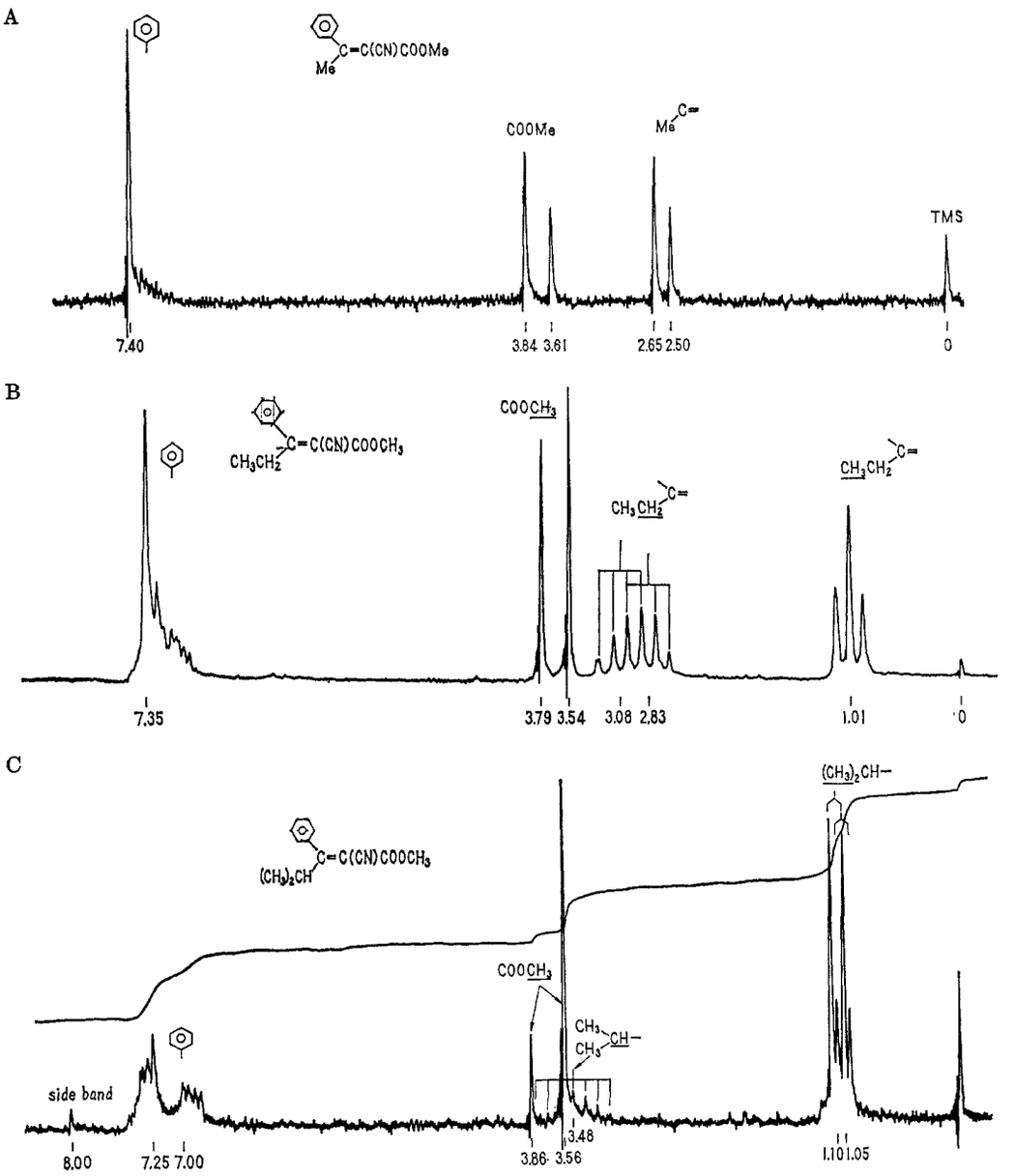


Figure 2.—Nmr spectra of a stereoisomeric mixture of (A) methyl α-cyano-β-methylcinnamate; (B) methyl α-cyano-β-ethylcinnamate; and (C) methyl α-cyano-β-isopropylcinnamate.

isomeric mixture of *cis* and *trans* isomers. The percentage of the *cis* isomer, as the β substituent becomes bulkier, increases in the following order: H < methyl < ethyl < methoxy < isopropyl. In addition, the introduction of a substituent into the *ortho* position results in the increase of the *cis* isomer, while the introduction into the *para* position has essentially no influence on the composition ratio of the mixture.

The above results may be explained in terms of steric effects as follows. Examination of molecular models indicates that deviation of the benzene ring from coplanarity with the ethylenic linkage depends chiefly upon the steric requirement of the β or *ortho* substituent and much less upon that of the α substituent.[8,9] Accordingly, the introduction of a bulky group into the β or *ortho* position should decrease steric hindrance of the benzene ring to the *cis*-carboalkoxy group and hence should favor the formation of the *cis* isomer.

(8) Y. Urushibara and M. Hirota, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **88**, 354 (1961).

(9) M. Oki, *Chemistry* (Kyoto), **17**, 606 (1962).

Conformations.—It is interesting to note that the introduction of the bulkier group into the β or *ortho* position caused the larger peak separation of the carboalkoxy group between *cis* and *trans* isomers. In the first approximation, it will be assumed that the local shielding,[10] dispersion,[11] and direct field[12] effects for *cis* and *trans* isomers are equal. Accordingly, it seems reasonable to suppose that the magnitude of the peak separation may be related chiefly to the amount of twist of the benzene ring. Actually, the ultraviolet spectroscopic studies showed that, as a β or *ortho* substituent becomes larger, twisting of the benzene ring from the ethylenic linkage is much increased.[13] The

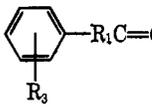
(10) A. Saika and C. P. Slichter, *J. Chem. Phys.*, **22**, 261 (1954); J. A. Pople, *Proc. Roy. Soc.* (London), **A239**, 550 (1957).

(11) T. Schaefer, W. F. Reynolds, and T. Yonamoto, *ibid.*, **41**, 2969 (1963); A. Bothner-By, *J. Mol. Spectry.*, **5**, 52 (1960).

(12) A. D. Buckingham, *Can. J. Chem.*, **38**, 300 (1960).

(13) The angle $\theta°$ of twist of the benzene ring was calculated from the ultraviolet spectroscopic data by applying the equation $\cos^2\theta = \epsilon/\epsilon_0$ on the assumption that ϵ_0 will be the same as for the *trans* isomer of II. Here it is assumed that twisting of the carboalkoxy group from coplanarity has essentially little effect on the changes in the intensity.[8]

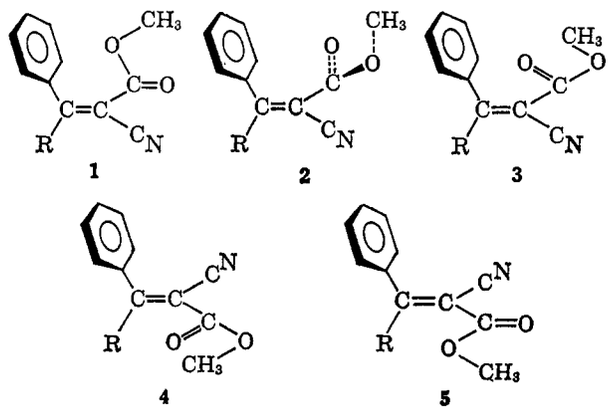
TABLE III

CHEMICAL SHIFTS[a] OF β-SUBSTITUTED α-CYANOCINNAMIC ESTERS OF THE TYPE  IN CCl_4

Compd	R_1	R_2	R_3	Configuration	R_1: β-Me	Δ	R_1: γ-Me	Δ	R_2: $COOCH_3$	Δ	R_2: CH_3 (COOEt)	Δ	R_2: CH_2 (COOEt)	Δ	Aromatic protons: H	H	R_3	% of isomer[b]
XI	Me	Me	H	T	2.65	0.15			3.84	0.23					7.41	7.41		62
				C	2.50				3.61						7.41	7.41		38
XII	Me	Et	H	T	2.66	0.16					1.40	0.32	4.33	0.29	7.35	7.35		61
				C	2.50						1.08		4.04		7.35	7.35		39
XIII	Et	Me	H	T	3.08[c]	0.25	1.01	0.00	3.75	0.25					(7.10–7.50)[d]			45
				C	2.83		1.01		3.54									55
XIV	Et	Et	H	T	3.08[c]	0.25	1.03	0.00			1.35	0.32	4.30	0.30	(7.10–7.50)[d]			46
				C	2.83		1.03				1.03		4.00					54
XV	*i*-Pr	Me	H	T	4.02[e]	0.54	1.05	0.05	3.80	0.30					*Ca.* 6.95	*Ca.* 6.30[f]		21
				C	3.48		1.10		3.56						*Ca.* 6.95	*Ca.* 6.30[f]		79
XVI	*i*-Pr	Et	H	T	4.01[e]	0.55	1.04	0.05			1.38	0.34	4.29	0.34	*Ca.* 6.95	*Ca.* 6.30[f]		21
				C	3.46		1.09				1.04		3.95					79
XVII	MeO	Me	H	T			3.77	0.09	3.84	0.20					*Ca.* 7.25	*Ca.* 7.50[f]		33
				C			3.68		3.64									67
XVIII	MeO	Et	H	T			3.76	0.09			1.34	0.21	4.29	0.24	*Ca.* 7.25	*Ca.* 7.50[f]		33
				C			3.67				1.13		4.05					67
XIX	Me	Me	*p*-Me	T	2.59	0.16			3.76	0.23					7.02	7.22	2.33	68
				C	2.43				3.56								2.33	38
XX	Me	Me	*o*-NO_2	T	2.60	0.08			3.76	0.27					(7.00–8.20)[d]			30
				C	2.52				3.52									70
XXI	Me	Et	*o*-NO_2	T	2.62	0.07					1.38	0.25	4.32	0.32	(7.00–8.28)[d]			31
				C	2.55						1.13		4.00					69
XXII	Me	Me	*p*-NO_2	T	2.73	0.16			3.91	0.23					8.24	7.34		59
				C	2.57				3.68									41

[a] All chemical shifts reported are in parts per million from TMS. [b] Percentages of isomers were determined by integration. [c] The value of the β-methylene protons. [d] A parenthesis shows an resolved broad multiplet. [e] The value of the β-methine protons. [f] The two incompletely resolved broad sets of absorption.

magnetic shielding around a benzene ring can be calculated according to Waugh and Fessenden[14] and Johnson and Bovey.[15] However, in the present case the chemical shift of the carboalkoxy group is a function of the angle of twist of the carboalkoxy group as well as of the benzene ring. Therefore, assuming the three limiting conformations of the carbomethoxy group, **1**, **2**, and **3**, for the *cis* isomer and the two limiting conformations, **4** and **5**, for the *trans* isomer, we calculated the chemical shift of the carbomethoxy group as a function of the angle of twist of the benzene ring with respect to each conformation (Figure 3). Here, the parameter required in the calculation were estimated from Dreiding models according to Cross and Harrison.[16] Curves 1–4 in Figure 3 represent the shielding values calculated for the conformations **1**–**4**, respectively. In the case of the *trans* form, whichever of the two conformations the group will assume, it caused no significant difference between the calculated values. Accordingly, with respect to each conformation the peak separation between the signals should be represented by the difference between the curve associated with the conformation in question and the curve 4. Although the data are rather limited, the values obtained are in substantial agreement with the ultraviolet spectroscopic data (Table IV) and are suggestive of a preferred orientation of the esters. Comparison between these values indicates that in the *cis* isomer the carbomethoxy group may be heavily populated between the conformations **1** and **3**. Conjugation between the C=O bond and C=C bond tends to keep the C=O bond coplanar with the C=C bond, whereas the carbonyl group with the negative end of the dipole will suffer an electrostatic repulsion by the electron-rich phenyl group. Therefore, as the result of energy balance, the carbonyl group will assume an intermediate position between the conformations **1** and **3**.



1 **2** **3**

4 **5**

TABLE IV

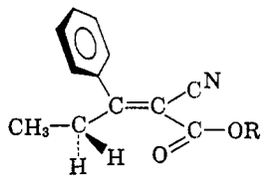
THE CALCULATED ANGLES OF TWIST OF THE BENZENE

Compd	1[a]	2[b]	3[c]	Ultraviolet data[d,e]
I	36	40	41	
XI	44	54	64	48
XIII	45	55	65	52
XV	47	61	90	69
XVIII	42	52	58	
XIX	45	54	64	
XX	47	58	70	
XXI	45	54	64	

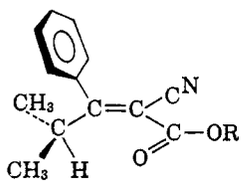
[a] The values calculated for the conformation **1**. [b] The values calculated for the conformation **2**. [c] The values calculated for the conformation **3**. [d] Details will be reported in the following paper. [e] T. Miwa, private communication; R. Carrie, *Bull. Soc. Sci. Bretagne*, 37, 1962; J. Zabicky, *J. Chem. Soc.*, 683 (1961).

(14) J. S. Waugh and R. W. Fessenden, *J. Am. Chem. Soc.*, **79**, 846 (1958).
(15) G. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).
(16) A. D. Cross and I. T. Harrison, *J. Am. Chem. Soc.*, **85**, 3123 (1963).

Further, it should be noticed that the peak separation of the β-methylene signals between *cis* and *trans* isomers is much larger than that of the β-methyl (XI–XIV), while the peak separation of the γ-methyl is much smaller than that of the β-methine (XV and XVI). On the basis of the same arguments as made by Jackman and Wiley,[17] it is supposed that the conformations **6** and **7** for XIII–XVI are heavily populated.



6



7

One further problem to explain concerns the aromatic proton signals. The nmr spectra of α-cyano-*trans*-cinnamic esters (I and II) showed the aromatic protons as two incompletely resolved broad sets of absorption, whereas those of α-cyano-β-methylcinnamic esters showed the fairly sharp aromatic absorption (Figures 1 and 2). Two possible explanations for this may be offered. The first is that, in the former, the energy barrier to rotate is high enough to lock the benzene ring in a plane coplanar with the C=C bond. In such models it would be reasonable to suppose that the chemical shifts of the *ortho* and *meta* protons on the inward side of the benzene ring should be shifted from those of the outward protons, owing to the long-range anisotropy effect of the cyano group. For the present purpose, it is convenient to use the *para*-substituted compounds, since the spectra of the unsubstituted compounds are too complex to analyze. However, since all the spectra of these esters had an aromatic proton spectra of the A_2B_2 type, it seems not to be in accord with the above postulation of restricted rotation of the benzene ring.[18]

The second is that the *ortho* and *para* protons are shifted from the *meta* protons by the resonance effect between the C=C bond and the benzene ring. It is evident from the tables that this effect may be a considerably important factor. However, since α-cyano-β-ethyl- and isopropylcinnamic esters (XIII–XVI) showed a relative complex multiplet of the aromatic protons, the behavior of the aromatic proton spectra cannot be fully explained in terms of resonance effects. This problem is now under investigation.

Experimental Section

Nmr Spectra.—All nmr spectra were obtained on the JNM-C-60 high resolution nmr spectrometer operating at 60 Mc at a temperature of 19–20°. Chemical shift values are reported in parts per million downfield from tetramethylsilane as the internal zero of reference. Samples were examined in *ca.* 8% (w/v) carbon tetrachloride solution and deuteriochloroform solution. It was verified that the solvent effect is negligible for the compounds studied. Line positions are accurate to ±0.03 ppm; relative values between the two corresponding signals of *cis* and *trans* isomers are accurate to ±0.01 ppm.

(17) L. M. Jackman and R. H. Wiley, *J. Chem. Soc.*, 2886 (1960).

(18) Similar arguments have been made in the case of 1,2-diphenylcyclopentane: D. Y. Curtin, H. Gruen, Y. G. Hendrickson, and H. E. Knipmeyer, *J. Am. Chem. Soc.*, **83**, 4838 (1961); **84**, 863 (1962); D. Y. Curtin and S. Dayagi, *Can. J. Cem.*, **42**, 867 (1964).

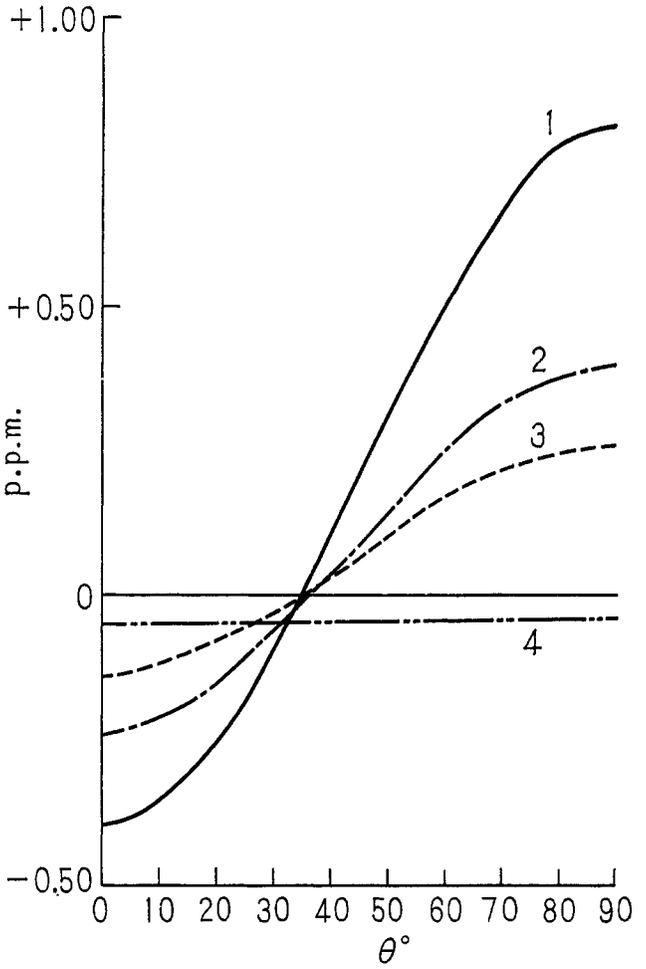


Figure 3. The calculated chemical shift of the methoxycarbonyl protons as a function of the angle of twist of the benzene ring θ°.

Ultraviolet Absorption Spectra.—The ultraviolet absorption spectra were recorded by the use of a Cary Model 14 recording spectrometer with a 1.00-cm quartz cell. Absolute ethanol was used as a solvent and the temperature was kept at 19–20°.

Materials.—All α-cyano-β-alkylcinnamic esters used in this work were prepared according to the method of Cope.[19] All α-cyanocinnamic esters listed in Table I were prepared by condensation between benzaldehydes and cyanoacetic esters in the presence of piperidine in ethanol solution.

α-Cyano-β-methoxycinnamic esters were prepared according to Hori and Midorikawa.[20] Each compound was distilled under reduced pressure at least twice, and boiling points and nitrogen contents were checked against literature values. The esters prepared for the first time in this work are listed in Table V, together with the pertinent physical and chemical data.

Stereoisomeric Mixture of α-Cyanocinnamic Esters.—The *cis* isomer of this ester was produced by the irradiation with ultraviolet light. A solution of 5.0 g of the ester in 20 ml of benzene was irradiated in a quartz flask supported over a Toshiba H-400P Mercury vapor lamp so as to maintain the solution at gentle reflux. After 12 hr of irradiation, solvent was removed *in vacuo* at room temperature. The residue was taken up in deuteriochloroform and examined in the nmr spectrometer.

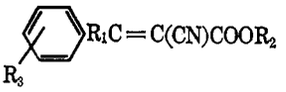
An Equilibrium between the *cis* and *trans* Isomers.—A thermodynamic equilibrium mixture of the *cis* and *trans* isomers was obtained by addition of a trace amount of sodium ethoxide followed by standing at room temperature through at least 1 week. Then the ester was distilled under reduced pressure.

Ethyl α-Cyano-*o*-methoxycinnamate.—The *cis* isomer of the ester was prepared according to the modified method of Rappoport, Degani, and Patai.[7]

(19) A. C. Cope, *J. Am. Chem. Soc.*, **59**, 2327 (1937).

(20) I. Hori and H. Midorikawa, *Sci. Papers Inst. Phys. Chem. Res.* (Tokyo), **56**, 216 (1962).

TABLE V

PHYSICAL PROPERTIES OF NEW α-CYANOCINNAMIC ESTERS OF THE TYPE 

Compd	R_1	R_2	R_3	Configuration	Mp, °C [bp °C (mm)]	Formula	Calcd, % C	Calcd, % C	Calcd, % H	Found, % H	Found, % N	Found, % N
III	H	Me	*o*-OMe	*trans*	111–112	$C_{12}H_{11}NO_3$	66.35	66.61	5.10	5.40	6.45	6.39
V	H	Me	*p*-OMe	*trans*	104–106	$C_{12}H_{11}NO_3$	66.35	66.53	5.10	5.05	6.45	6.26
VII	H	Me	*p*-N(Me)$_2$	*trans*	142–143	$C_{13}H_{14}N_2O_2$	67.81	...	6.13	...	12.17	12.03
VIII	H	Me	*p*-NO_2	*trans*	153–154	$C_{12}H_{10}N_2O_4$	58.53	58.67	4.09	4.16	11.38	11.14
XIII	Et	Me	H	Mixture	[154 (7)]	$C_{13}H_{13}NO_2$	72.54	72.46	6.09	5.98	6.51	6.76
XIV	Et	Et	H	Mixture	[163 (6)]	$C_{14}H_{15}NO_2$	73.34	73.59	6.59	6.56	6.11	5.95
XV	*i*-Pr	Me	H	Mixture	80–82 [146 (6)]	$C_{14}H_{15}NO_2$	73.34	73.63	6.59	6.60	6.11	5.96
XVI	*i*-Pr	Et	H	Mixture	73–76	$C_{15}H_{17}NO_2$	74.05	74.11	7.04	6.97	5.76	5.50
XIX	Me	Me	*p*-Me	Mixture	64–66 [168 (6)]	$C_{13}H_{13}NO_2$	72.54	72.46	5.09	6.19	6.51	6.54
XXII	Me	Me	*p*-NO_2	*trans*	153–154	$C_{12}H_{10}N_2O_4$	58.53	58.67	4.09	4.16	11.38	11.14

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(21) During the present investigation, a similar study has been made by him independently.

Purine Nucleosides. XIII. The Synthesis of 2-Fluoro- and 2-Chloroinosine and Certain Derived Purine Nucleosides[1]

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The preparation of 2-fluoroinosine (VI) was accomplished first, by catalytic debenzylation of 2-fluoro-6-benzyloxy-9-β-D-ribofuranosylpurine (VIII) and secondly, by oxidative desulfurization of 2-fluoro-9-β-D-ribofuranosyl-6-purinethione. 2-Chloroinosine (III) was similarly prepared from 2-chloro-9-β-D-ribofuranosyl-6-purinethione (II). Treatment of 2-fluoroinosine with dimethylamine gave N^2-dimethylguanosine. 2-Methylamino- and 2-dimethylamino-9-β-D-ribofuranosyl-6-purinethione (IX) were converted to N^2-methyl and N^2-dimethylguanosine, respectively. These reactions provide new synthetic routes to the N-methylated guanosine nucleosides which have been shown to occur naturally in soluble RNA. 2-Methoxyinosine (XI) has been prepared from 2-methoxy-6-benzyloxy-9-β-D-ribofuranosylpurine (XII) by catalytic debenzylation. The synthesis of XII was readily accomplished from 2-fluoro-6-benzyloxy-9-β-D-ribofuranosylpurine (VIII). The interesting derivative, 2-fluoro-6-chloro-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)purine (XVIII), was prepared by diazotization of 2-amino-6-chloro-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)purine in the presence of fluoroboric acid. The preparation of 2,6-dichloro-9-β-D-ribofuranosylpurine (XV) has been achieved for the first time by direct diazotization of 2-amino-6-chloro-9-β-D-ribofuranosylpurine in the presence of concentrated hydrochloric acid. The importance of these new intermediates in the general syntheses of new purine nucleosides is discussed.

A recently devised route for the synthesis of N^2-substituted guanosine[2] involved the synthesis of 2-fluoro-6-benzyloxy-9-β-D-ribofuranosylpurine (VIII) from 2-amino-6-benzyloxy-9-β-D-ribofuranosylpurine (IV). In connection with this earlier work[2] several attempts were made to prepare 2-chloro- and 2-fluoroinosine as intermediates in this investigation. The present study is a report of the successful synthesis of these most useful nucleoside derivatives.

The preparation of 2-fluoroinosine (VI) has now been accomplished in excellent yield from 2-fluoro-6-benzyloxy-9-β-D-ribofuranosylpurine (VIII) by catalytic debenzylation. A second synthesis of 2-fluoroinosine (VI) has also been achieved from 2-fluoro-9-β-D-ribofuranosyl-6-purinethione[3] (V) and hydrogen peroxide in the presence of a small amount of dilute, aqueous ammonia. The synthesis of 2-chloroinosine (III) was also investigated. Previous attempts to prepare 2-chloroinosine from 2,6-dichloro-9-(2′,3′,5′-*O*-acetyl-β-D-ribofuranosyl)purine in our laboratory[2] have been unsuccessful. Diazotization of 2-amino-9-β-D-ribofuranosyl-6-purinethione[4] (I) in the presence of concentrated hydrochloric acid gave 2-chloro-9-β-D-ribofuranosyl-6-purinethione (II). Treatment of II with alkaline hydrogen peroxide gave 2-chloroinosine in good yield. This oxidative removal of sulfur and exchange for hydroxyl proved to be much simpler and greatly superior to the exchange of sulfur for oxygen *via* the β-hydroxyethylthio procedure employed for the conversion of 2-amino-9-(2′-deoxy-β-D-ribofuranosyl)-6-purinethione to 2′-deoxyguanosine.[5] This simple procedure provided a new synthetic route to N^2-

(1) Supported by Research Grant CA-08109 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

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(5) R. H. Iwamoto, E. M. Acton, and L. Goodman, *J. Med. Chem.*, **6**, 684 (1963).