# Studies on Geometric Isomerism by Nuclear Magnetic Resonance. II.[1]
# Geometric Configurations of Alkylidenecyanoacetic Esters

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A number of studies of the mechanism of the Knoevenagel reaction has been published,[2-9] but little information is available concerning the stereochemistry of the reaction. Baker and Howes[10] have shown that the condensation of salicylaldehyde or its methyl ether with cyanoacetic acid or its ester gives only the isomers with the trans configuration.[11] However, this study has so far not been extended to alkylidenecyanoacetic esters.

In the preceding paper, the present authors have reported the successful application of the NMR technique to the configurational determinations of the compounds of the $R_1(R_2O)C=C(CN)\cdot COOR_3$ type. Therefore, it seems that it would be interesting to apply this technique to alkylidenecyanoacetic esters of the $R_1MeC=C(CN)COOR_2$ type.

For the present purpose, it is assumed that the $\beta$-methyl[12] signal of an isomer of these esters consists of only one peak, due to the absence of any resolved spin-spin coupling across the C=C bond. Hence, the esters of this type are believed to be a class of compounds which is suitable for studies of cis-trans isomerism. However, since no stereoisomer of a known configuration was available, the assignment of each of two signals for the $\beta$-methyl group to the correct stereoisomer had to be based on the previous assumption,[1] which states that the chemical shift for the $\beta$-methyl group occurs at a higher field in the trans- than in the cis-configuration with respect to the alkoxycarbonyl group, whereas the reverse is true for the $\gamma$-methyl group. The results obtained have been supported by the relative stability of the isomers.

## Experimental

**Materials.**—All the alkylidenecyanoacetic esters examined were prepared according to the method of Cope.[9] Each compound was distilled under reduced pressure at least twice, and the boiling points and nitrogen contents were checked against the literature values.

An equilibrium mixture of cis-trans isomers was obtained by the addition of a trace amount of sodium ethoxide, after which the mixture was allowed to stand at room temperature for at least one week.

**NMR Spectra.**—All NMR spectra were taken with a JNM-C-60 high-resolution NMR spectrometer working

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[1] Part I: T. Hayashi, I. Hori, H. Baba and H. Midorikawa, *J. Org. Chem.*, **30**, 695 (1965). Presented partly at the 3rd Symposium on NMR, Osaka, November, 1963.

[2] E. Knoevenagel, *Ann.*, **281**, 25 (1894).

[3] A. C. O. Hann and A. Lapworth, *J. Chem. Soc.*, **85**, 46 (1904).

[4] H. Rogerson and J. F. Thorpe, ibid., **87**, 1685 (1905).

[5] V. J. Harding, W. N. Haworth and W. H. Perkin, ibid., **93**, 1943 (1908).

[6] W. N. Haworth, ibid., **95**, 480 (1909).

[7] C. K. Ingold, ibid., **119**, 329 (1921).

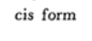
[8] E. P. Kohler and B. B. Corson, *J. Am. Chem. Soc.*, **45**, 1975 (1923).

[9] A. C. Cope, ibid., **59**, 2327 (1937).

[10] W. Baker and C. S. Howes, *J. Chem. Soc.*, **1953**, 119.

[11] By a trans isomer is meant the form in which the phenyl and carbonyl groups are on opposite sides of the C=C bond.

[12] The notations used here to distinguish the various methyl and methylene groups are shown below, each group being referred to as cis or trans with respect to the alkoxycarbonyl group. The isomer in which the $\beta$-methyl group and alkoxycarbonyl groups are on the same side of the C=C bond is referred to as the isomer.



cis form

at 60 Mc. and at a temperature of 19—20°C. The samples were examined in a ca. 8 per cent (w/v) solution in carbon tetrachloride, using tetramethylsilane as an internal reference. The chemical shifts are given as p. p. m. downfield from tetramethylsilane.

The data recorded in Table II were obtained by averaging the results of at least three measurements. The values are accurate to ±0.025 p. p. m,; the relative values between *cis*- and *trans*-β-methyl protons are accurate to ±0.005 p. p. m.

TABLE I. PROPERTIES OF ALKYLIDENCYANOACETIC ESTERS

| Compound $R_1MeC=C(CN)COOR_2$ | $R_1$ | $R_2$ | B. p. °C/mmHg | Formula | Calcd. | Found. | Yield[a] % |
|---|---|---|---|---|---|---|---|
| I | Me | Me[b] | 98—99/6 | $C_7H_9O_2N$ | 10.07 | 10.27 | — |
| II | Me | Et[c] | 104—105/6 (m. p. 31°C) | $C_8H_{11}O_2N$ | 9.14 | 9.21 | — |
| III | Et | Me[d] | 107—108/7 | $C_8H_{11}O_2N$ | 9.14 | 9.07 | — |
| IV | Et | Et[e] | 119—120/11 | $C_9H_{13}O_2N$ | 8.38 | 8.33 | — |
| V | *n*-Pr | Me[f] | 116—117/6 | $C_9H_{13}O_2N$ | 8.38 | 8.24 | — |
| VI | *n*-Pr | Et[g] | 135—136/11 | $C_{10}H_{15}O_2N$ | 7.73 | 7.90 | — |
| VII | *i*-Pr | Me | 107—108/6 | $C_9H_{13}O_2N$ | 8.38 | 8.26 | 80 |
| VIII | *i*-Pr | Et[h] | 121—124/7 | $C_{10}H_{15}O_2N$ | 7.73 | 7.53 | — |
| IX | *i*-Bu | Et[i] | 119—120/8 | $C_{10}H_{15}O_2N$ | 7.73 | 7.49 | — |
| X | *i*-Bu | Et[j] | 121—122/5 | $C_{11}H_{17}O_2N$ | 7.17 | 7.10 | — |
| XI | *t*-Bu | Me | 117—120/11 | $C_{10}H_{15}O_2N$ | 7.73 | 7.50 | 7 |
| XII | *t*-BuCH$_2$ | Me | 127—128/6 | $C_{11}H_{17}O_2N$ | 7.17 | 7.08 | 70 |
| XIII | *t*-BuCH$_2$ | Et | 140—141/10 | $C_{12}H_{19}O_2N$ | 6.69 | 6.67 | 75 |

a) Yield is shown only for a new compound. b) lit.,[9] b. p. 99—101°C/9 mmHg. c) lit., m. p. 27—28°C, F. S. Prout, *J. Org. Chem.*, **18**, 928 (1953). d) lit.,[9] b. p. 105—106°C/9 mmHg. e) lit., b. p. 116—118°C/11 mmHg, A. C. Cope, C, Wyckoff and E. Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941). f) lit.,[9] b. p. 116—118°C/9 mmHg. g) lit., b. p. 138—139°C/19 mmHg, Ref. e. h) lit., b. p. 115—120°C/8 mmHg, A. Brändström, *Acta Chem. Scand.*, **13**, 963 (1959). i) lit.,[9] b. p. 119—123°C/9 mmHg. j) b. p. 130—133°C/12 mmHg, Ref. e.

TABLE II. NMR SPECTRA OF ALKYLIDENECYANOACETIC ESTERS (p. p. m. DOWNFIELD FROM TMS)

| Compound, $R_1MeC=C(CN)COOR_2$ | $R_1$ | $R_2$ | β-$CH_3$ | | β-$CH_2$ | | γ-$CH_3$ | | $COOCH_3$ | $COOCH_2\underline{CH_3}$ | $COO\underline{CH_2}CH_3$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ia | Me | Me | 2.31 | 0.09 | | | | | 3.81 | | |
| Ib | Me | Me | 2.40 | | | | | | | | |
| IIa | Me | Et | 2.31 | 0.09 | | | | | | 1.33 | 4.23 |
| IIb | Me | Et | 2.40 | | | | | | | | |
| IIIa | Et | Me | 2.28 | 0.09 | 2.59 | 0.03 | 1.13 | 0.06 | 3.79 | | |
| IIIb | Et | Me | 2.37 | | 2.57 | | 1.19 | | | | |
| IVa | Et | Et | 2.26 | 0.08 | 2.59 | 0.03 | 1.14 | 0.06 | | 1.33 | 4.23 |
| IVb | Et | Et | 2.34 | | 2.57 | | 1.20 | | | | |
| Va | *n*-Pr | Me | 2.27 | 0.08 | 2.76 | 0.20 | 0.99[a] | 0.03 | 3.80 | | |
| Vb | *n*-Pr | Me | 2.35 | | 2.56 | | 1.02 | | | | |
| VIa | *n*-Pr | Et | 2.27 | 0.07 | 2.76 | 0.20 | 1.00[a] | 0.03 | | 1.34 | 4.23 |
| VIb | *n*-Pr | Et | 2.34 | | 2.56 | | 1.03 | | | | |
| VIIa | *i*-Pr | Me | 2.17 | 0.07 | 3.97[b] | 0.65 | 1.10 | 0.06 | 3.80 | | |
| VIIb | *i*-Pr | Me | 2.24 | | 3.32 | | 1.16 | | | | |
| VIIIa | *i*-Pr | Et | 2.17 | 0.07 | 3.95[b] | 0.65 | 1.10 | 0.06 | | 1.33 | 4.23 |
| VIIIb | *i*-Pr | Et | 2.24 | | 3.29 | | 1.16 | | | | |
| IXa | *i*-Bu | Me | 2.26 | 0.08 | 2.66 | 0.26 | 0.92[a] | 0.06 | 3.80 | | |
| IXb | *i*-Bu | Me | 2.34 | | 2.40 | | 0.99 | | | | |
| Xa | *i*-Bu | Et | 2.25 | 0.07 | 2.66 | 0.26 | 0.93[a] | 0.05 | | 1.33 | 4.23 |
| Xb | *i*-Bu | Et | 2.32 | | 2.40 | | 0.98 | | | | |
| XIa | *t*-Bu | Me | 2.18 | 0.07 | | | 1.11 | 0.08 | 3.81 | | |
| XIb | *t*-Bu | Me | 2.25 | | | | 1.19 | | | | |
| XIIa | *t*-BuCH$_2$ | Me | 2.28 | 0.07 | 2.86 | 0.32 | 0.98[a] | 0.08 | 3.81 | | |
| XIIb | *t*-BuCH$_2$ | Me | 2.35 | | 2.54 | | 1.06 | | | | |
| XIIIa | *t*-BuCH$_2$ | Et | 2.28 | 0.07 | 2.86 | 0.32 | 0.98[a] | 0.08 | | 1.33 | 4.23 |
| XIIIb | *t*-BuCH$_2$ | Et | 2.35 | | 2.54 | | 1.06 | | | | |
| XIV | H | Et | 2.21 | | 2.41[c] | | | | | 1.33 | 4.22 |

a) The chemical shift of the δ-methyl protons. b) The chemical shift of the β-methine proton.
c) The chemical shift of the β-proton.

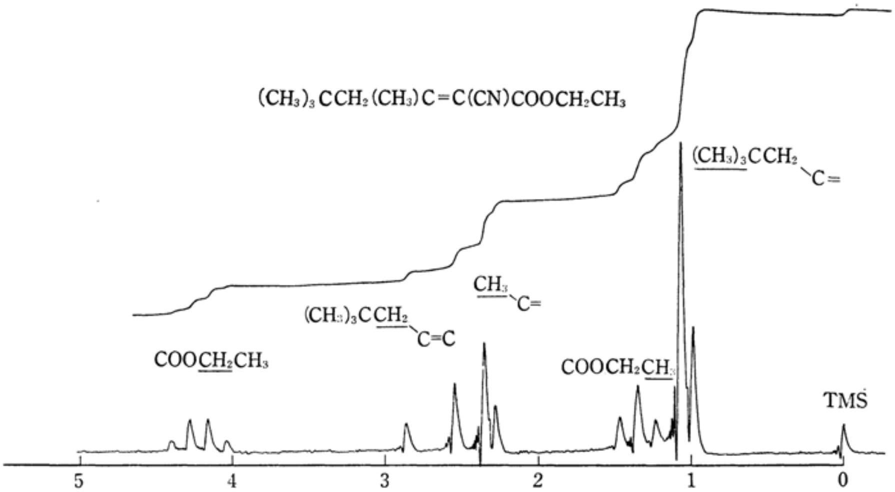


Fig. 1A. The NMR spectrum of a stereoisomeric mixture of ethyl $\alpha$-cyano-$\beta$-neopentylcrotonate at 19°C.

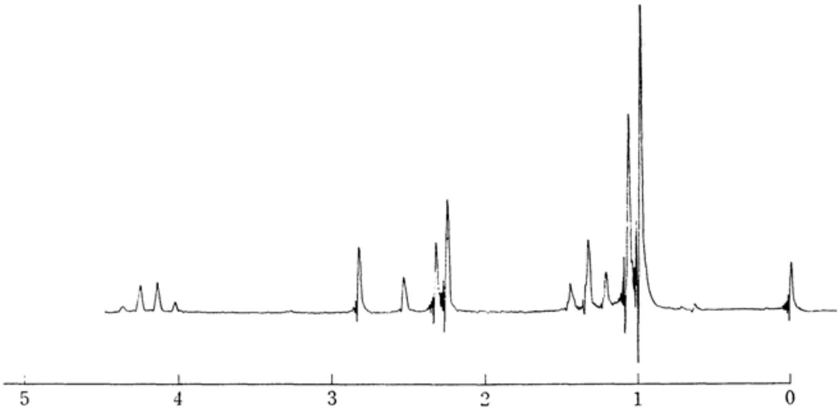


Fig. 1B. The NMR spectrum of a stereoisomeric mixture of ethyl $\alpha$-cyano-$\beta$-neopentylcrotonate at 71°C.

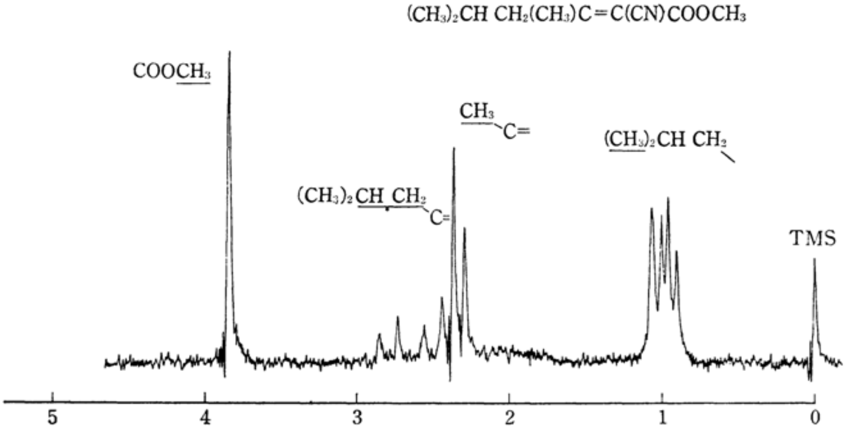


Fig. 2. The NMR spectrum of a stereoisomeric mixture of methyl $\alpha$-cyano-$\beta$-isobutylcrotonate at 19°C.

## Results and Discussion

The esters studied in this work are listed in Table I, together with the pertinent physical and chemical data, while the chemical shifts are shown in Table II. The isomeric compositions of fourteen esters are shown in Table III, together with the equilibrium ratios. Representative NMR spectra of the esters are shown in Figs. 1 and 2.

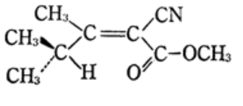
The resonance line-positions of the methyl protons of the methoxycarbonyl group were constantly located in the $3.80+0.01$ p.p.m. range, while those of the methyl and methylene protons of the ethoxycarbonyl group always appeared in the $1.33+0.01$ and $4.23+0.01$ p.p.m. ranges respectively. The replacement of the methoxycarbonyl group by the ethoxycarbonyl group has practically no effect on the chemical shifts of the β-methyl and β-alkyl protons in the corresponding ester. This fact was often useful in assigning signals superimposed upon by signals of the alkoxycarbonyl group.

The fact that the spectra show two signals of an unequal intensity, separated by about 0.08 p.p.m., for the β-methyl group was ascribed to the co-existence of cis and trans isomers. As has been mentioned previously, the assignment of the configuration was made on the basis of a previous assumption.[1)] This leads to the assignment of the β-methyl resonance at the higher field to the group which is in a position trans to the alkoxycarbonyl group.

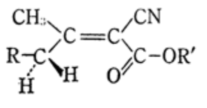
In the case of these esters, the relative stabilities of the stereoisomers may be expected to be determined by simple steric interactions between the β-alkyl substituent and the alkoxycarbonyl group. An examination of molecular models suggests that the cis configurations are to be favored over the trans. On the basis of this consideration, the more intense of the two signals of the β-methyl group is assigned to the cis isomer, and the less intense, to the trans. The conclusions reached by the two methods of assigning the peaks in the NMR spectrum are consistent with each other.

As a typical example, the present authors analyzed the spectrum of ethyl α-cyano-β-neopentylcrotonate (XIII, Fig. 1A). The β-methyl signal appears as a doublet* of an unequal intensity, with the more intense signal at the lower field (2.28 and 2.35 p.p.m.). The β-methylene signal also appears as a doublet of an unequal intensity, with the more intense signal at the higher field (2.45 and 2.86 p.p.m.). On the basis of the arguments just given, the more intense signals are assigned to those of the cis isomer, and the weaker signals, to those of the trans. Since the β-methylene group of the cis isomer is in a position trans to the ethoxycarbonyl group, the results show that both the β-methyl and the β-methylene groups are more deshiedled by 0.08 p.p.m. in the cis- than in the trans-arrangement with respect to the ethoxycarbonyl group. The γ-methyl protons appear as a doublet of an unequal intensity, with the more intense signal at the lower field (0.98 and 1.06 p.p.m.), indicating that, contrary to the case of the β-methyl protons, the γ-methyl protons occur at the higher field when located cis to the ethoxycarbonyl group. Similar observations have already been made in the case of α-cyano-β-alkoxy-β-alkylacrylic esters.[1)]

It may be noticed in Table II that, in general, the peak separation of the β-methylene protons, except for III and IV, is much larger than that of the β-methyl protons, and that the peak separation of the β-methine proton (0.65 p.p.m. for VII and VIII) is much larger than that of the β-methylene protons. These facts suggest that the VIIa and XIIa conformations are heavily populated, as has been pointed out by Jackman and



(VIIa)



(XIIa)

Table III. cis-trans Composition ratios of the condensation products

| Compound | Composition per cent of isomer | Equilibrium per cent of isomer |
|---|---|---|
| Ia | 50 | 50 |
| Ib | 50 | 50 |
| IIa | 50 | |
| IIb | 50 | |
| IIIa | 47 | |
| IIIb | 53 | |
| IVa | 46 | 44 |
| IVb | 54 | 56 |
| Va | 43 | |
| Vb | 57 | |
| VIa | 43 | 41 |
| VIb | 57 | 59 |
| VIIa | 38 | |
| VIIb | 62 | |
| VIIIa | 38 | 37 |
| VIIIb | 62 | 63 |
| IXa | 35 | 36 |
| IXb | 65 | 64 |
| Xa | 40 | |
| Xb | 60 | |
| XIa | 2 | |
| XIb | 98 | |
| XIIa | 47 | |
| XIIb | 53 | |
| XIIIa | 38 | 29 |
| XIIIb | 62 | 70 |

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* In this discussion the terms "singlet" and "doublet" refer to multiplicity resulting from the co-existence of stereoisomers and not spin-spin coupling.

Wiley in the case of methyl $\beta$-methylglutaconate.[13)]

The isomeric compositions of fourteen esters, as evaluated from the integration of the area under the appropriate NMR signals, are given in Table III. The composition is little affected by the temperature, as was determined by heating it to 71°C, except in the case of XIII. (As may be seen from Fig. 1B, the trans isomer of XIII was surprisingly much increased by heating it to 71°C (trans per cent, 61).) Attempts to separate the stereoisomers of these esters by gas chromatography were unsuccessful.

It seemed to be important to ascertain whether or not the isomeric compositions of the condensation products are the same in the equilibrium state. It is known that the isomerization of the esters is induced by a trace amount of base.[14,15)] A sample which contained sodium ethoxide was allowed to stand at room temperature for a week and then distilled in vacuo. The results (Table III) show that the cis-trans ratios of the equilibrium mixtures are almost the same as those of the products ratios within the limit of experimental error, except for XIII. Accordingly, it is open to question whether or not the products were formed in these ratios. The present authors rather prefer the explanation that the products, once formed in some unidentified ratios, reached, by isomerization, a thermodynamic equilibrium. These circumstances would make it difficult to elucidate the steric course of the Knoevenagel reaction. However, these considerations are only tentative; they are now being investigated further.

It is interesting to note that the percentage of the cis isomer gradually increases with an increase in the size of the $\beta$-substituted alkyl group in the order; *t*-butyl > neopentyl > isobutyl > isopropyl > *n*-propyl > ethyl > methyl > hydrogen. This observation agrees with what would be expected on steric grounds, because this order is almost parallel with the magnitude of the steric requirement of the $\beta$-substituted alkyl group. Therefore, this finding supports the assumption suggested in Part I.[1)]

## Summary

The Knoevenagel reaction of a methyl alkyl ketone with cyanoacetic ester gives a stereoisomeric mixture of $\alpha$-cyano-$\beta$-alkylcrotonic ester. The NMR technique has been applied to the study of the geometric configurations of the mixture. It has been found that the isomer with a $\beta$-methyl group cis to the alkoxycarbonyl group always occurs predominantly. The magnitude of the cis-trans composition of the mixture is parallel to the steric requirement of the $\beta$-substituted alkyl group.

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

14) S. Patai and Z. Rappoport, ibid., **1962**, 396.

15) Z. Rappoport, C. Degani and S. Patai, ibid., **1963**, 4513.