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ETHYL ISOPROPYLCYANOACETATE AND ITS MONO-TRIDEUTEROMETHYL-ISOPROPYL ANALOGUE

MAGNETIC NONEQUIVALENCE IN THE ISOPROPYL GROUP

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Abstract—Ethyl isopropylcyanoacetate and ethyl mono-trideuteromethyl-isopropylcyanoacetate have been prepared by reaction of ethyl ethylidenecyanoacetate with methylmagnesium iodide and trideuteromethylmagnesium iodide, respectively. The doubling of the methyl doublet in the NMR spectra of these two compounds shows that the methyl groups of the former compound are magnetic non-equivalent and that the latter compound is obtained as both the *erythro* and *threo* diastereomer.

The recent appearance of papers[1,2] on the doubling of the methyl doublet in the PMR spectra of some isopropylcarbinols and isopropyl esters with an asymmetric centre and on the determination of diastereomeric mixtures by NMR[3] prompts us to report some results obtained from ethyl isopropylcyanoacetate and a trideutero derivative. Ethyl isopropylcyanacetate and the mono-trideuteromethyl analogue (prepared with special reference to studies on mass spectra of cyanoacetates[4]) were prepared in good yields by addition of methylmagnesium iodide and trideuteromethylmagnesium iodide, respectively, to ethyl ethylidenecyanoacetate at 0°. 1,4-Addition of Grignard reagents to alkylidenecyanoacetates is a well-known reaction.[5] From the reaction of n-butylmagnesium bromide with ethyl isopropylidenecyanoacetate Nielsen *et al.*[6] isolated some ethyl isopropylcyanoacetate formed by reduction of the alkylidene ester; ethyl isopropylcyanoacetate has further been prepared by catalytic hydrogenation of ethyl isopropylidenecyanoacetate[7] and by alkylation of ethyl cyanoacetate.[8,9] The ethyl ethylidenecyanoacetate used in the Grignard reaction was prepared according to Popp and Catatala[10] by condensation of acetaldehyde with ethyl cyanoacetate and from the NMR spectrum of the product we conclude that the product is one of the two geometric isomers (*cis or trans* ester*) and not a mixture of these. The NMR spectrum shows only one CH_3-doublet (δ 2·22 ppm; $J_{CH_3-H} = 7{\cdot}2$ c/s) and only one

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* Following the notation given in Ref. 11.

[1] C. van der Vlies, *Rec. Trav. Chim.* **84**, 1289 (1965) and Refs contained therein.

[2] N. S. Bowman, D. E. Rice and B. R. Switzer, *J. Amer. Chem. Soc.* **87**, 4477 (1965) and Refs contained therein.

[3] M. Raban and K. Mislow, *Tetrahedron Letters* No. 48, 4249 (1965).

[4] J. H. Bowie, R. Grigg, S.-O. Lawesson, P. Madsen, G. Schroll and D. H. Williams, *J. Amer. Chem. Soc.* in press.

[5] A. Brändström and I. Forsblad, *Arkiv Kemi* **6**, 561 (1954) and Refs contained therein.

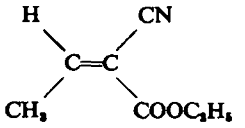
[6] E. B. Nielsen, J. Munch-Petersen, P. M. Jørgensen and S. Refn, *Acta Chem. Scand.* **13**, 1943 (1959).

[7] A. C. Cope (to Merck and Co., Inc.) U.S., 2,655,526; *Chem. Abstr.* **48**, 11484 (1954).

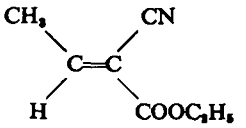
[8] E. Fischer and E. Flatau, *Ber. Dtsch. Chem. Ges.* **42**, 2981 (1908).

[9] S.-O. Lawesson and C. Frisell, *Arkiv Kemi* **17**, 409 (1961).

[10] F. D. Popp and A. Catatala, *J. Org. Chem.* **26**, 2738 (1961).



cis ester

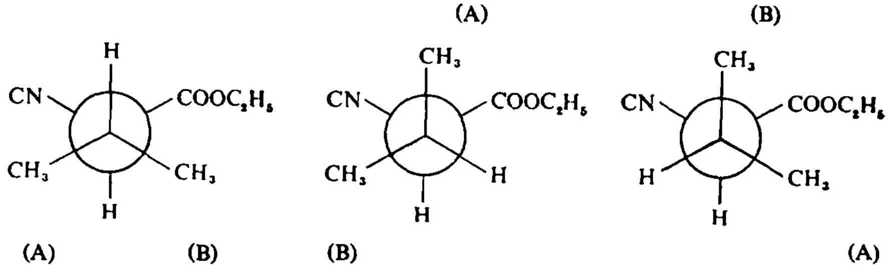


trans ester

ethylenic proton (quartet, δ 7·66 ppm, $J_{CH_3-H} = 7\cdot2$ c/s); these findings together with the recent work by Hayashi *et al.*[11] on NMR studies of geometric isomerism in similar esters justifies our conclusion. However, no conclusions regarding to which isomer is present could be drawn as only one of the isomers was available. Examination by gas chromatography also confirms the presence of only one isomer.

The NMR spectrum of ethyl isopropylcyanoacetate (Fig. 1) (CCl_4 solution; apparatus temp) shows a chemical shift difference, $\bar{\nu}_A - \bar{\nu}_B$, between the two isopropyl methyl doublets. The separation of the magnetic nonequivalent methyl groups is 2·2 c/s (at 60 Mc/s) which is of the same order of magnitude as observed for the separation of the doublets in 4-methyl-butanol-2 (1·2 c/s in CCl_4) confirming the statement by van der Vlies[1] that the size and character of the substituents have no great influence on the magnetic nonequivalence. However, the great improvement in nonequivalence found by replacement of the methyl group at the asymmetric carbon in 4-methyl-butanol-2 by a phenyl nucleus[1] has not yet been investigated for compounds where the asymmetric carbon in addition to the phenyl group is carrying an unsaturated group(s).

The magnetic nonequivalence of the isopropyl methyl groups in ethyl isopropylcyanoacetate is easily understood from the three possible staggered conformations which show that the two methyl groups are in different environments. Furthermore,



(one enantiomer)

it is clear that the average chemical shifts $\bar{\nu}_A$ and $\bar{\nu}_B$, and with it the difference $\bar{\nu}_A - \bar{\nu}_B$, depend on the relative populations of the three rotamers (and the chemical shifts in each rotamer) but also that some difference due to intrinsic asymmetry must persist even if all are present in equal proportions. The chemical shift dependence of populations of the three rotamers makes the chemical shift difference ($\bar{\nu}_A - \bar{\nu}_B$) temperature dependent until the state of equal populations has been reached. From the temperature-dependence of $\bar{\nu}_A - \bar{\nu}_B$ (Table 1) it is seen that the chemical shift difference is decreasing with increasing temperature over the entire temperature range investigated indicating that the state of equal populations of rotamers was not obtained.

The NMR spectrum of ethyl mono-trideuteromethyl-isopropylcyanoacetate

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

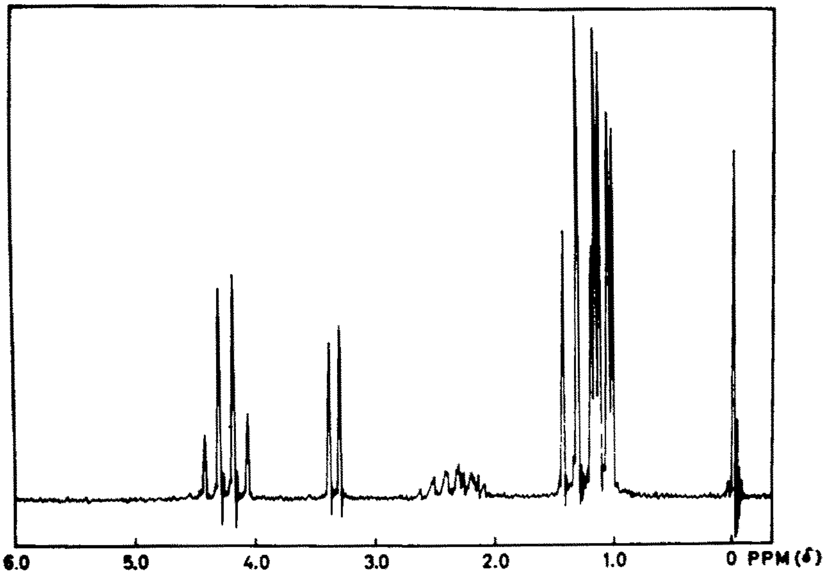


Fig. 1. NMR spectrum of $(CH_3)_2CHCH(CN)COOC_2H_5$ in CCl_4.

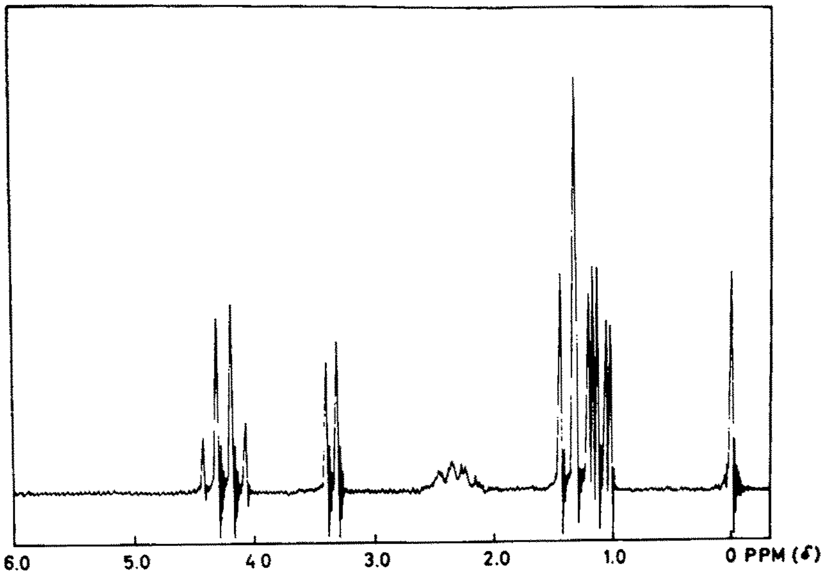


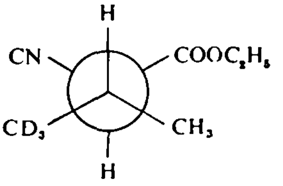
Fig. 2. NMR spectrum of $CH_3(CD_3)CHCH(CN)COOC_2H_5$ in CCl_4.

TABLE 1. TEMPERATURE-DEPENDENCE OF THE CHEMICAL SHIFT DIFFERENCE ($\bar{\nu}_A - \bar{\nu}_B$), IN c/s, OF THE TWO METHYL DOUBLETS

	$(CH_3)_2CHCH(CN)COOC_2H_5$		$CH_3(CD_3)CHCH(CN)COOC_2H_5$	
	CCl_4	Pure Liq.	CCl_4	Pure Liq.
−40°	5·2	—	5·0	—
−20°	4·3	5·3	4·1	5·3
0°	3·5	4·5	3·4	4·4
15°	2·9	4·0	2·8	4·0
30°	2·4	3·3	2·3	3·4
50°	1·8	2·7	1·8	2·7
70°	1·2	2·1	1·2	2·1
100°	—	1·4	—	1·3
125°	—	0·9	—	0·8
150°	—	<0·6	—	0·6
30°	3·9*		4·0*	

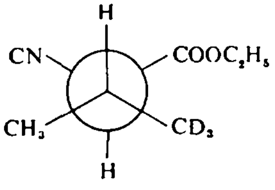
* C_6H_6 solution

(Fig. 2) (CCl_4 solution, apparatus temp) is similar to the spectrum of ethyl isopropylcyanoacetate except for the reduced (½) intensity of the two isopropyl methyl doublets and for the less complexity of the signal from the tertiary isopropyl proton. From the occurrence of the two equally intense doublets in the NMR spectrum of ethyl monotrideuteromethyl-isopropylcyanoacetate we conclude that the two diastereomers (*erythro* and *threo**) of this compound are present in equal proportions. As these diastereomers are formed by addition of trideuteromethylmagnesium iodide to only one of the isomers of ethyl ethylidenecyanoacetate the final result of the Grignard reaction is a *cis* and *trans* addition (1 : 1) of CD_3-H across the ethylenic double bond in the α,β-unsaturated ester. This finding is in accordance with the generally accepted mechanism[6] for the addition of Grignard reagents to α,β-unsaturated esters which is shown below; hydrolysis followed by rearrangement of the enol structure gives isomers corresponding to adding R—H non-stereospecific across the ethylenic



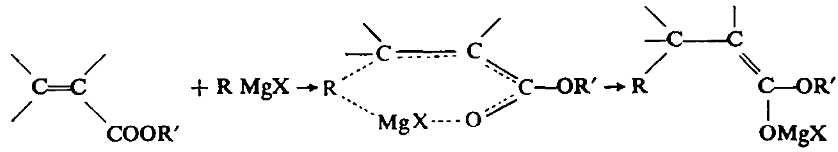
(B)

erythro (d or l)



(A)

threo (d′ or l′)



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* The prefixes *erythro* and *threo* are applied according to E. S. Gould, *Mechanism and Structure in Organic Chemistry* p. 605. Holt, Rinehart and Winston, New York (1962); the substituents on each of the two carbon atoms are here designated as $COOC_2H_5$ (L), CN(M) and H(S); CD_3(L), CH_3(M) and H(S); L (largest), M (medium-sized) and S (smallest).

double bond. However, a stereospecific addition followed by racemization of the α-hydrogen would also account for an all-over non-stereospecific reaction. The observation that spectra recorded immediately after isolation of the product showed the presence of the *erythro* and *threo* isomers in equal proportions makes the latter mechanism less probable.

EXPERIMENTAL

NMR spectra were recorded at 60 Mc/s on a Varian Associates A-60 spectrometer equipped with a V-6057 variable temp probe. Measurements were made at 33° ± 2° on 20% by volume solutions, unless otherwise stated, using tetramethylsilane as internal standard. The chemical shifts are expressed in ppm from TMS taken as 0·00 (δ units). The calibration of the instrument was checked frequently according to the manual procedure. The chemical shift difference between the two methyl doublets were measured with an accuracy of ±0·2 c/s on the 50 c/s scale. The temp calibration is correct within ±2°. Trideuteromethyl iodide was supplied by C.E.N., Dept. des Radioisotopes, Mol. Belgique. Boiling points are uncorrected.

Ethyl isopropylcyanoacetate. MeMgI from 5·0 g (0·035 mole) MeI and 0·97 g (0·040 mole) Mg turnings in 25 ml dry ether was cooled to 0°. Ethyl ethylidenecyanoacetate[10] (3·9 g, 0·028 mole) in 20 ml dry ether was added to the stirred Grignard reagent during 30 min and the mixture stirred for 1 hr. After hydrolysis with dil HCl in ice water the phases were separated, the water phase extracted with ether, the combined ether phases washed neutral and finally dried over Na_2SO_4. Concentration and fractionation yielded 3·1 g (71%) of ethyl isopropylcyanoacetate, b.p. 96°/12 mm Hg; n_D^{25} = 1·4217. (Litt.[9] b.p. 53–55°/0·5 mm; n_D^{20} = 1·4250; Litt.[6] b.p. 92–93°/13 mm; n_D^{20} = 1·4238.)

Ethyl mono-trideuteromethyl-isopropylcyanoacetate. Starting from trideuteromethyliodide (3·9 g) the title compound was prepared as described above, yield 3·0 g (68%); b.p. 95·5–96·5°/12 mm; n_D^{25} = 1·4215.