Assignment of Stereochemistry to Cyclohexenylidenecyanoacetates by ^{1}H NMR Spectroscopy†

Vassilios Bardakos and Constantine Sandris*
Laboratory of Organic Chemistry, National Technical University, 42 Patission Street, Athens-147, Greece

The stereochemistry of various pairs of isomeric 2-cyclohexen-1-ylidenecyanoacetates was assigned using ^{1}H NMR spectroscopy. The isomers with the γ-methylene or the γ-vinyl protons *cis* to the carbalkoxy group were found to have the signals of these protons at approximately 0.3 ppm and 1 ppm, respectively, downfield relative to their geometrical isomers or the corresponding 2-cyclohexen-1-ylidenemalononitriles. The observation regarding the γ-vinyl proton proved useful for the assignment of configuration to cyclohexenylidenecyanoacetates derived from cholest-4-en-3-one. The large and constant downfield shift (*c.* 1 ppm) of the γ-vinyl proton when *cis* to the ester group results from the rigid cyclohexenylidenecyanoacetate system, in which the vinylic proton can approach more closely to the magnetically anisotropic ester carbonyl group.

INTRODUCTION

It was shown by Jackman and Wiley[2,3] that, in substituted ethylenes, substituents containing the carbonyl function can so deshield a *cis*-β-vinylic proton or the protons of a *cis*-β-methyl group that significant differences are to be expected in the chemical shifts of these protons in *cis-trans* isomers. Hayashi *et al.*[4] deduced the stereochemistry of β-alkyloxy-β-alkyl-α-cyanoacrylates on the assumption that the greater δ value should be connected with the greater anisotropic deshielding of the ester group: the protons of the β-carbons are thus more deshielded when they are *cis* to the ester group than when they are *trans*. This assumption was again found to be true in the case of alkylidenecyanoacetic esters.[5,6,7]

We now report the differential shifts observed for the γ-methylene and γ-vinyl protons in isomeric 2-cyclohexen-1-ylidenecyanoacetates (see formulae in Table 1), which can be correlated with the *E* and *Z* configuration of the exocyclic double bond of these compounds. The chemical shifts of the γ-vinyl protons appear to be markedly sensitive to the presence of a *cis*-ester group and, compared with those of the corresponding cyclohexenylidenemalononitriles, are a useful criterion for the assignment of stereochemistry in these systems.

RESULTS

As previously reported,[8,9] two isomeric methyl esters, m.p. 74–76° and 60–64°, were obtained by the condensation of methyl cyanoacetate with 1-methylcyclohex-1-en-3-one. The IR spectra of the two esters are practically identical, even in the fingerprint region, and show absorptions at 2215 (unsaturated CN), 1715 (ester CO) and 1610 cm^{-1} (C=C). The low-melting isomer is assigned the *E* (**2a**) and the high-melting isomer the *Z* (**3a**) configuration on the basis of the shifts of the γ-methylene triplets (Table 1): the low field γ-CH$_2$ group, which is deshielded by 0.31 ppm in **2a** relative to **3a**, occupies a position *cis* to the ester group. Simultaneously, the shift values of the γ-vinyl quartets in **2a** and **3a** differ markedly and again the low field vinyl proton, deshielded by 1.04 ppm in **3a** relative to **2a**, occupies a position *cis* to the ester group. Consequently, isomer **2a** with the low field γ-methylene signal has a high field γ-vinyl proton signal, and the converse applies for **3a**.

The above assignments are directly confirmed by comparing the NMR data of **2a** and **3a** with the spectrum of the corresponding cyclohexenylidenemalononitrile **1**. The shift positions of the γ-vinyl and γ-methylene protons of **1**, both *cis* to a nitrile group, coincide with the corresponding shifts of **2a** and **3a**. The configurations of the pure isomers[8,9] **3b** and **2c** are also established unambiguously by a direct comparison of their γ-methylene and γ-vinyl proton shifts with the corresponding absorptions in **1**.

Similar differential shifts of the γ-methylene and γ-vinyl proton absorptions were observed in the case of cyclohexenylidenecyanoacetates derived from isophorone (Table 1). The methyl and ethyl esters obtained from the condensation reactions[10] were shown to be 1:1 mixtures of the *E* and *Z* isomers, while a pure isomer **6a**, isolated from the mixture of the methyl esters, clearly has the *Z* configuration.

The *Z* configuration was also assigned to the pure isomers **9a** and **9b** derived from cholest-4-en-3-one (Table 2), where the vinyl protons *cis* to the ester group are again found to be deshielded by a constant value of ~1 ppm relative to either the *E* isomers, **8a** and **8b**, or the corresponding malononitrile **7**.[11] (In the

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† See Ref. 1.
* Author to whom correspondence should be addressed.

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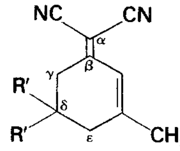
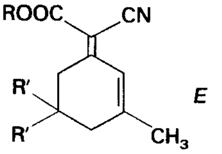
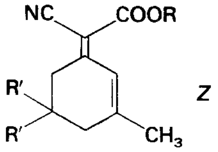
Table 1. ^{1}H NMR spectral data for cyclohexenylidenemalononitriles and cyclohexenylidenecyanoacetates[a]



1 R′ = –H
4 R′ = –CH$_3$



2a R = –CH$_3$, R′ = –H
2b R = –CH$_2$CH$_3$, R′ = –H
2c R = R′ = –H
5a R = R′ = –CH$_3$
5b R = –CH$_2$CH$_3$, R′ = –CH$_3$



3a R = –CH$_3$, R′ = –H
3b R = –CH$_2$CH$_3$, R′ = –H
3c R = R′ = –H
6a R = R′ = –CH$_3$
6b R = –CH$_2$CH$_3$, R′ = –CH$_3$

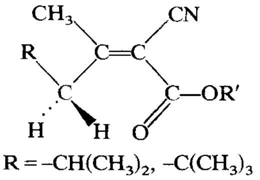
Compound	=C—H[b]	=C—CH$_3$[c]	γ-CH$_2$[d]	δ-CH$_2$[e] or δ-C—CH$_3$[f]	ε-CH$_2$[g]	—COOR
1	6.63	2.10	2.75	1.88	2.33	
2a	6.62	2.08	3.05	1.80	2.28	3.80, s
3a	7.66	2.03	2.74	1.87	2.28	3.83, s
2a+**3a** (approx. 1 : 1)	7.65, 6.65	2.05	3.05, 2.73	[h]	2.28	3.82, s
3b	7.66	2.02	2.73	1.87	2.27	4.27, q; 1.37, t[j]
2b+**3b** (approx. 1 : 1)	7.62, 6.62	2.06	3.04, 2.72	[h]	2.32	4.26, q; 1.35, t[j]
2c	6.69	2.07	3.05	1.80	2.30	10.80, s
2c+**3c** (approx. 1 : 1.2)	7.48, 6.62	2.04	3.04, 2.77	[h]	2.30	11.20, s
4	6.65	2.01	2.51	1.03	2.10	
6a	7.65	2.01	2.52	1.03	2.10	3.83, s
5a+**6a** (approx. 1 : 1)	7.65, 6.65	2.01	2.87, 2.52	1.03, 0.99[i]	2.10	3.83, s
5b+**6b** (approx. 1 : 1)	7.63, 6.66	2.01	2.90, 2.56	1.02, 0.99[i]	2.13	4.26, q; 1.35, t[j]

[a] All spectra were recorded in CCl$_4$ solution except for **2c** and **3c** and the mixture of **5b** and **6b** (CDCl$_3$) and shift values are reported in ppm (δ) relative to TMS.
[b] Quartet, $J = 1.3$ Hz.
[c] Doublet, $J = 1.3$ Hz.
[d] Triplet, $J = 6.5$ Hz, for R′ = –H and singlet for R′ = –CH$_3$.
[e] Distorted quintet, $J = 6.5$ Hz.
[f] Singlet.
[g] Triplet, $J = 6.5$ Hz, for R′ = –H and broad singlet for R′ = –CH$_3$.
[h] Distorted multiplet centred at 1.88 ppm.
[i] Two singlets.
[j] $J = 7$ Hz.

case of the steroid compounds of Table 2, the γ-vinyl proton absorption is the only interpretable signal.) In all cyclohexenylidenecyanoacetates examined (Tables 1 and 2), the γ-vinyl proton absorption appears at a constant shift value: 6.60 ± 0.10 ppm for the *E* configuration (or the corresponding malononitriles) and 7.60 ± 0.10 ppm for the *Z* configuration. [The γ-vinyl proton absorption for the Knoevenagel condensation products between malononitrile and various cyclic enones (1-methylcyclohex-1-en-3-one, 1,4,4-trimethylcyclohex-1-en-3-one, 1,6,6-trimethylcyclohex-1-en-3-one and testosterone) were reported[11] to occur at δ6.62, 6.58, 6.50 and 6.44 ppm, respectively, in CDCl$_3$ solution].

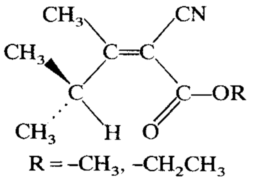
DISCUSSION

It has been reported[5] that, in alkylidenecyanoacetates, γ-methylene protons are deshielded by 0.26–0.32 ppm, while γ-methine protons are deshielded by 0.65 ppm when *cis* to the carbalkoxy group as compared to their geometrical isomers with these protons *cis* to the nitrile group. It was therefore suggested[5] that conformations such as I and II are heavily populated. A similar differential shift has also been reported[12] for the γ-methylene protons of methyl cyclohexylidenecyanoacetate (**10**). An example of isomeric alkenylidenecyanoacetates was recently studied by Martelli *et al.*[13] The conformation of the two double bonds in compounds **11** and **12** was accepted as being



R = –CH(CH$_3$)$_2$, –C(CH$_3$)$_3$
R′ = –CH$_3$, –CH$_2$CH$_3$

I



R = –CH$_3$, –CH$_2$CH$_3$

II

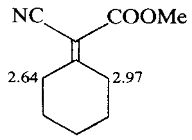


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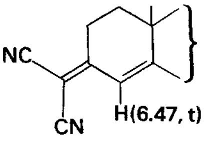
Table 2. ^{1}H NMR spectral data for 4-cholesten-3-ylidenemalononitrile and 4-cholesten-3-ylidene-3-cyanoacetates[a,b]



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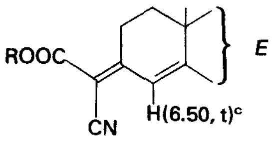
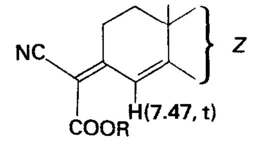


8a R = $-CH_3$[d]
8b R = $-CH_2CH_3$[e]



9a R = $-CH_3$[d]
9b R = $-CH_2CH_3$[e]

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[a] All spectra were recorded in CCl_4 solution and shift values are reported in ppm (δ) relative to TMS.

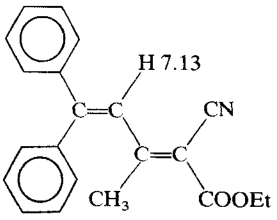
[b] The vinyl proton signals are triplets, $J = 1.3$ Hz.

[c] This value was determined from the mixture of the isomeric esters (see Experimental Section).

[d] $-COOCH_3$: 3.82, s.

[e] $-COOCH_2CH_3$: 4.27, q and 1.37, t, $J = 7$ Hz.

s-trans and the γ-vinylic proton was found to be deshielded by 0.54 ppm when *cis* to the ester group.



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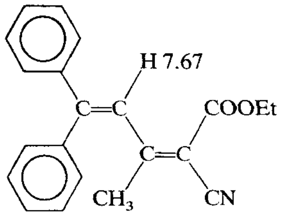
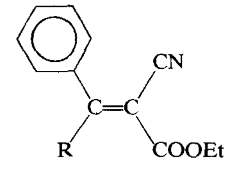
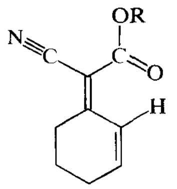


12

The γ-methylene protons of the cyclohexenylidenecyanoacetates studied here are deshielded by 0.31–0.35 ppm when *cis* to the ester group (differential shifts in **2–3** and **5–6**); this value is of the same order as in the case of **10** and the alkylidenecyanoacetates shown in conformation I. The peak separation of the γ-vinyl protons, which are closer to the ester carbonyl, is expected to be larger than that of the γ-methylene protons. However, the large and fairly constant deshielding of 1 ppm observed in **2–3**, **5–6** and **8–9** differs considerably from the analogous systems of the alkylidenecyanoacetates shown in conformation II (γ-methine proton, differential shift of 0.65 ppm) and of alkenylidenecyanoacetates **11–12** (0.54 ppm). Apparently, in the cyclohexenylidenecyanoacetate system, in which the *s-trans* coplanar conformation of the two double bonds is more rigidly fixed, the vinylic proton can approach more closely to the magnetically anisotropic ester carbonyl group.



R = –H, $-CH_3$, $-CH_2CH_3$
13



III

Molecular models indicate that the carbalkoxy group has considerable rotational freedom. However, analysis[14] of the NMR spectra of ethyl α-cyanocinnamates of the *E* configuration (**13**) indicated a preferred *s-cis* conformation in which the deshielding of the carbonyl group should be at its most effective.[15] On this basis, the favourable position of the vinylic proton in cyclohexenylidenecyanoacetates should also be related to a possible, heavily populated, *s-cis* conformation of the ester carbonyl group, as shown in III.

All cyclohexenylidenecyanoacetates, as obtained from the condensation reactions described in the Experimental Section, were found to be approximately 1 : 1 mixtures of the two isomers from their NMR spectra. Alkaline isomerization of pure isomers (e.g. **2a** and **3a**, see Experimental Section) also yielded 1 : 1 mixtures of the isomeric esters. The relative stabilities of the stereoisomers of alkylidenecyanoacetates, such as those depicted in I and II, were considered to be determined by simple steric interactions between the β-alkyl substituents and the alkoxycarbonyl group.[5] From this point of view, the magnitude of the steric requirements of the γ-methylene and of the γ-vinyl groups in cyclohexenylidenecyanoacetates seems to be almost the same.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. IR spectra were obtained with a Beckman IR 5A spectrometer as Nujol mulls or liquid films. ^{1}H NMR spectra were recorded on a Varian EM-360 spectrometer; concentrations were in the range of 80 mg/ml; chemical shifts are given in ppm (δ) downfield from TMS as an internal standard and are accurate to ±0.02 ppm.

Condensation reactions

Condensation products between the cyclic enones, 1-methylcyclohex-1-en-3-one,[16] isophorone or cholest-4-en-3-one, and malononitrile or cyanoacetic esters were prepared by the ammonium acetate *catalysed*

Table 3. Physical data of the condensation products

Compound	B.p. or M.p. (recr. solvent)	Yield %	Literature
1	m.p. 89–92° (MeOH)	25	m.p. 75–76°,[10] 88–89°[13]
2a+**3a** (approx. 1 : 1)	b.p. 210–212°/22 mm (solidifies on cooling, m.p. 37–45°)	80	b.p. 165–175°/2 mm[9]
3a	m.p. 74–76° (light petroleum)	22	m.p. 64–66°,[8] 74°[9]
2a	m.p. 60–64° (light petroleum)	2	m.p. 37–38.5°,[8] 60°[9]
2b+**3b** (approx. 1 : 1)	b.p. 178–190°/11 mm	82	b.p. 178–190°/12 mm,[8] 190°/16 mm[9]
3b	m.p. 57–58° (light petroleum)	23	m.p. 55–57°,[8] 58°[9]
4	m.p. 76–79° (MeOH)	20	m.p. 79–80°[10]
5a+**6a** (approx. 1 : 1)	b.p. 192–194.5°/12 mm, solidifies, m.p. 50–60°	85	
6a	m.p. 80–82° (light petroleum)	15	
5b+**6b** (approx. 1 : 1)	b.p. 190–193°/19 mm	63	b.p. 175–180°/15 mm[10]
7[a]	m.p. 116–117° (MeOH)	52	
8a+**9a** (approx. 1 : 1)	m.p. 105–115°[b]	90	
9a[c]	m.p. 151–154° (MeOH–acetone)	3	
8b+**9b** (approx. 1 : 1)	m.p. 70–105° ($EtOH—H_2O$)	30	
9b[d]	m.p. 127–130° (EtOH–acetone)	8	

[a] $[\alpha]_D^{31°}+225°$ (c 1, $CHCl_3$).

[b] The oily residue was dissolved in warm methanol and acetone was added to precipitate the product.

[c] $[\alpha]_D^{31°}+121°$ (c 0.88, $CHCl_3$).

[d] $[\alpha]_D^{30°}+182°$ (c 1, $CHCl_3$).

Knoevenagel process.[17] A mixture of the ketone (0.1 mol), the active methylene compound (0.1 mol), ammonium acetate (0.02 mol) and acetic acid (0.1 mol) in 25–50 ml of benzene was refluxed for 24–48 h with continuous removal of water. After cooling, the benzene layer was washed twice with water, dried over Na_2SO_4 and the solvent was removed under reduced pressure.

The residue was either distilled or recrystallized to give the products reported in Table 3. All condensation products of cyanoacetic esters were found to be approximately 1 : 1 mixtures of the two geometrical isomers, as evidenced from their NMR spectra. The pure isomers reported in Table 3 were obtained after repeated recrystallizations of the corresponding mixtures. Condensation products of malononitrile showed IR absorptions at 2220 (unsaturated CN) and 1610 cm^{-1} (C=C), while condensation products of cyanoacetic esters showed absorptions at 2215, 1715 (ester CO) and 1610 cm^{-1}. All new products gave satisfactory elemental analyses (C, H, N).

Equilibration of compounds 2a and 3a

A solution of pure isomer **3a** (750 mg) in 5 ml of methanol was added to a cooled solution of sodium (0.1 g) in 4 ml of methanol. The mixture was kept for 1 h at 0°, then poured into 15 ml of water and extracted with ether. The ether layer was washed with water, dried over Na_2SO_4 and the solvent evaporated to give 0.4 g of an oily residue; the NMR spectrum showed this to be a 1 : 1 mixture of isomers **2a** and **3a**.

A similar isomerization of 0.3 g of pure isomer **2a** afforded 0.24 g of an oily residue, also consisting of a 1 : 1 mixture of isomers **2a** and **3a**.

Compounds 2c and 3c

15 g of mixture **2b** and **3b** were refluxed for 30 min with 75 ml of a 10% KOH solution in ethanol–water 3 : 1. Water was added to the cooled mixture, ethanol was distilled off and the residue was extracted with ether. The cold aqueous layer was acidified with concentrated HCl and the acidic product was dissolved in acetone. Concentration of this solution yielded first 0.4 g of pure isomer **2c** (NMR, Table 1), m.p. 175–181°, and then 1.4 g of a product, m.p. 148–151° (lit. 147–148.5°[8] and 149°[9]), a mixture of 1 : 1.2 of isomers **2c** and **3c** (NMR, Table 1). Further recrystallization of isomer **2c** from acetone–water yielded an analytical sample, m.p. 181–184°.

REFERENCES

1. Presented in part at the 4th Chemistry Week, Nuclear Research Center Demokritos, Athens, Greece (March 1979).
2. L. M. Jackman and R. H. Wiley, *J. Chem. Soc.* 2881 (1960).
3. L. M. Jackman and R. H. Wiley, *J. Chem. Soc.* 2886 (1960).
4. T. Hayashi, I. Hori, H. Baba and H. Midorikawa, *J. Org. Chem.* **30**, 695 (1965).
5. T. Hayashi, M. Igarashi, S. Hayashi and H. Midorikawa, *Bull. Chem. Soc. Jpn* **38**, 2063 (1965).
6. J. Hamelin, *C.R. Acad. Sci. Ser. C* **263**, 553 (1966).
7. M. Schwarz, *Chem. Commun.* 212 (1969).
8. E. Knoevenagel and S. Mottek, *Ber. Dtsch. Chem. Ges.* **37**, 4464 (1904).

9. E. H. Farmer and J. Ross, *J. Chem. Soc.* 1570 (1926).
10. Kodak Soc., anon., Belgian Patent Spec. No. 557 656 (15 June, 1957); *Chem. Abstr.* **54,** 2057f (1960).
11. J. W. ApSimon, J. W. Hooper and B. A. Laishes, *Can. J. Chem.* **48,** 3064 (1970).
12. D. E. McGreer, R. S. McDaniel and M. G. Vinge, *Can. J. Chem.* **43,** 1389 (1965).
13. J. Martelli, M. Bargain and R. Carrié, *C.R. Acad. Sci. Ser. C* **276,** 523 (1973).
14. P. Rivet-Le Guellec, F. Tonnard and J. Meinnel, *J. Chim. Phys.* **70,** 1268 (1973).
15. J. W. ApSimon, P. V. Demarco, D. W. Mathieson, W. G. Craig, A. Karim, L. Saunders and W. B. Whalley, *Tetrahedron* **26,** 119 (1970).
16. S. Natelson and S. P. Gottfried, *J. Am. Chem. Soc.* **61,** 1001 (1939).
17. A. C. Cope, C. M. Hofmann, C. Wyckoff and E. Hardenbergh, *J. Am. Chem. Soc.* **63,** 3452 (1941).

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