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Geometric Configurations of α-Cyano-β-methyl-β-alkylglycidic Esters

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α-Cyanoglycidic ester derivatives have been prepared from alkylidenecyanoacetic esters with hydrogen peroxide. The NMR technique has been applied to the study of the geometric configurations of the stereoisomeric mixture of the glycidic esters. It has been found that the β-methyl protons *cis* to the ester group respond at a higher field than do the *trans* protons.

Our search for practical methods of determining the geometric configurations of α-cyano-β-alkoxy-β-alkylacrilic esters[1] and alkylidenecyanoacetic esters[2] led to a study of nuclear magnetic resonance spectroscopy. During these studies it became apparent that the NMR non-equivalence of signals arising from geometrically-related groups of β-methylglycidic-ester derivatives which possess an oxirane ring replaced by four different groups could also serve such a purpose. Recently, Valente and Woffhagen[3] have introduced the use of this technique in the determination of the geometric configuration of β-phenylglycidic esters. We wish now to report on the chemical shifts for a number of α-cyano and α-carbamoyl-β-methyl-β-alkylglycidic esters which were gathered in order to delineate the scope of the NMR method for determining the geometric configuration.

Various conditions for epoxidation are described in the literature. The epoxidation of an alkene-bearing carbonyl substituent by a usual reagent, such as peroxy benzoic or peroxyacetic acid, is generally very slow.[4] The treatment of α,β-unsaturated nitrile with hydrogen peroxide under alkaline conditions results in the formation of epoxyamide rather than epoxynitrile.[5] We have found that the direct epoxidation of alkylidenecyanoacetic esters with hydrogen peroxide without a catalyst is satisfactory in giving the corresponding epoxynitriles. By refluxing a solution of the alkylidenecyanoacetic ester in aqueous alcohol with a small excess of 30% hydrogen peroxide for varying lengths of time, good yields of eight 2-cyano-3-methylglycidic ester derivatives (compounds I-VIII) have been obtained. That all of these compounds except 2-cyano-2,3-epoxybutanoic esters are mixtures of *cis-trans* isomers is confirmed by their NMR spectra. Table 1 shows the most important features of the NMR spectra of compounds I—VIII. The synthetic steps are shown in Chart 1.

TABLE 1. NMR SPECTRA (β-METHYL AND ESTER GROUPS) OF EPOXY ESTERS I—XVII (PPM DOWNFIELD FROM TMS).

Compound	β-CH_3		$COOCH_3$
I	1.65		4.37 ($COOC\underline{H}_2CH_3$)
			1.36 ($COOCH_2C\underline{H}_3$)
II*	1.47	1.69	3.94
IIIa	1.44	1.66	3.94
IIIb	1.41	1.65	4.37 ($COOC\underline{H}_2CH_3$)
			1.38 ($COOCH_2C\underline{H}_3$)
IV	1.42	1.66	3.94
V*	1.30	1.55	3.94
VI	1.32	1.56	3.95
VII	1.40	1.65	3.95
VIII	1.50	1.75	3.94
IX	1.45		4.33 ($COOC\underline{H}_2CH_3$)
			1.33 ($COOCH_2C\underline{H}_3$)
X*	1.42	1.46	3.86
XI	1.40	1.45	3.89
XII	1.37	1.42	3.85
XIII*	1.27	1.32	3.85
XIV	1.25	1.30	3.87
XV	1.39	1.44	3.88
XVI*	1.32		3.89
XVII	1.46	1.52	3.88

* Ref. 12.

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1) T. Hayashi, I. Hori, H. Baba and H. Midorikawa, *J. Org. Chem.*, **30**, 695 (1965).
2) T. Hayashi, M. Igarashi, S. Hayashi and H. Midorikawa, This Bulletin, **38**, 2063 (1965).
3) V. R. Valente and J. L. Wolfhagen, *J. Org. Chem.*, **31**, 2509 (1966).
4) D. Swern, *J. Amer. Chem. Soc.*, **69**, 1692 (1947).
5) G. B. Payne and P. H. Williams, *J. Org. Chem.*, **26**, 651 (1961).

$$R(CH_3)C{=}C(CN)COOR' \longrightarrow R(CH_3)C\underset{\diagdown O \diagup}{-}C(CN)COOR' \longrightarrow R(CH_3)C\underset{\diagdown O \diagup}{-}C(CONH_2)COOR'$$

	R	R'
I	H	C_2H_5
II	CH_3	CH_3
IIIa	C_2H_5	CH_3
IIIb	C_2H_5	C_2H_5
IV	n-C_3H_7	CH_3
V	i-C_3H_7	CH_3
VI	s-C_4H_9	CH_3
VII	i-C_4H_9	CH_3
VIII	CH_2-t-C_4H_9	CH_3
IX	H	C_2H_5
X	CH_3	CH_3
XI	C_2H_5	CH_3
XII	n-C_3H_7	CH_3
XIII	i-C_3H_7	CH_3
XIV	s-C_4H_9	CH_3
XV	i-C_4H_9	CH_3
XVI	t-C_4H_9	CH_3
XVII	CH_2-t-C_4H_9	CH_3

Chart 1

The resonance positions of the methyl protons of the methoxycarbonyl group were always located in the 3.94±0.01 ppm range, while those of the methylene and methyl protons of the ethoxycarbonyl group always appeared in the 4.36±0.01 ppm and 1.37±0.01 ppm ranges respectively. The replacement of the methoxycarbonyl group by the ethoxycarbonyl group has practically no effect on the chemical shifts of the β-methyl group in the corresponding ester. Similar results have been observed in alkylidenecyanoacetic esters by some of the present authors.[2]

In the α-cyano-β,β-dimethylglycidic ester (II), the signals due to two β-methyl groups were at 1.69 and 1.47 ppm. This result indicated that the magnitude of such a chemical-shift difference was sufficient to be of practical value in the quantitative determination of geometrical isomers. In the epoxy ester, III—VIII, made by the epoxidation of alkylidenecyanoacetic esters (*cis-trans* mixture[6]), the spectra show two signals of an unequal intensity, separated by about 0.22—0.25 ppm, for the β-methyl protons. These results indicate that they contain both geometric isomers. After the products had been repeatedly distilled, their NMR showed the same pattern. It was desirable that the spectra be correlated with structures on the bases of the known configuration of the *cis* and *trans* epoxides.[7] However, no stereoisomers of a known configuration of β-alkylglycidic esters were available. Attempts to separate stereoisomers of these esters by gas and thin-layer chromatographies were unsuccessful.

In the preceding paper,[2] it was shown that the relative stabilities of the stereoisomeres of alkylidenecyanoacetic esters can be determined by means of the simple steric interaction between the β-alkyl substituent and the alkoxycarbonyl group. A similar effect may be expected for the epoxy esters. In the compounds III—VIII, models show 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 can be assigned to the *cis* isomer, and the less intense, to the *trans*.

It is known that the ethylidenecyanoacetic ester produced by the condensation of acetaldehyde with the cyanoacetic ester is only the *trans* isomer from the NMR spectrum.[8] We have attempted to convert the *trans* isomer into the *cis* isomer. However, so far our attempts have been unsuccessful. The *trans* ethylidenecyanoacetic ester was converted into the 2-cyano-2,3-epoxybutanoic ester (I) by refluxing it with excess hydrogen peroxide or by treating it with a calculated amount of hydrogen peroxide at room temperature under alkaline conditions. The NMR spectra of the products show only one β-methyl doublet (1.65 ppm) (Fig. 1). This resonance position corresponds to that of the methyl protons at a lower field in other epoxy esters. In the case of compound I, it seems reasonable to say that the methyl group prefers a *trans* orientation, for there is a substantial difference in the steric requirements of the methyl and hydrogen groups. Thus, the result supports the structural assignment that the *trans* β-methyl group responds at a lower field than does the *cis* β-methyl group.

The methyl 1-methylpropylidenecyanoacetate used in the other experiments was prepared by the condensation of methyl ethyl ketone with cyanoacetic acid,[8] followed by esterification with diazomethane. From the NMR spectrum of the product, it has been concluded that the ester is the *cis* isomer and not a mixture of the two geometric isomers. The *cis* ester underwent 30% isomerization to the *trans* ester when refluxed in an aqueous methanol solution for six hours (NMR analysis of the product mixture). After ten hours refluxing, 47% isomerization had taken place. A longer refluxing gave no change in the *trans-cis* ratio. A more rapid isomerization of *cis* to *trans* takes place in the reaction mixture containing 0.1 N alkali. Therefore, owing to experimental difficulties arising

6) Following the notation given in Ref. 2.

7) The isomeric forms of a series of the esters are denoted as (i) *cis* (in which the β-methyl and alkoxycarbonyl groups are both on the same side of the $C\underset{\diagdown O \diagup}{-}C$ bond) and (ii) *trans* (in which these groups are on opposite sides).

8) M. J. Hamelin, *C. R. Acad. Sc. Paris*, Ser. C **263**, 553 (1966).

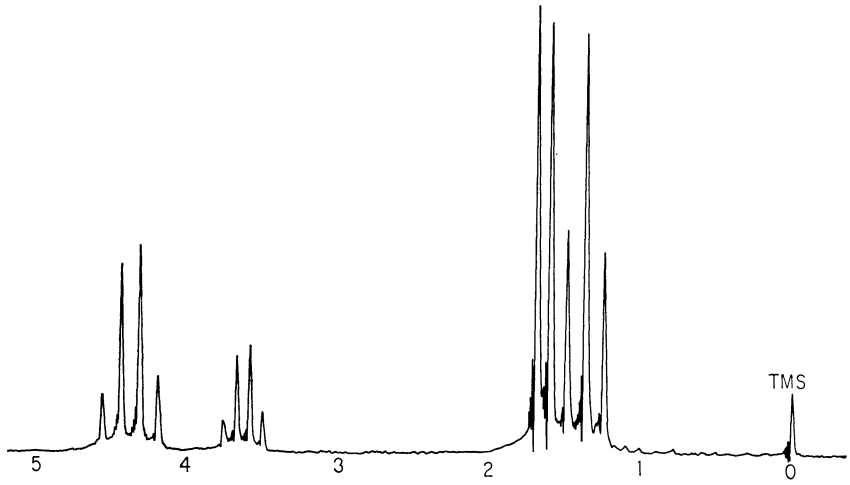

Fig. 1. The NMR spectrum of ethyl 2-cyano-2,3-epoxybutyrate.

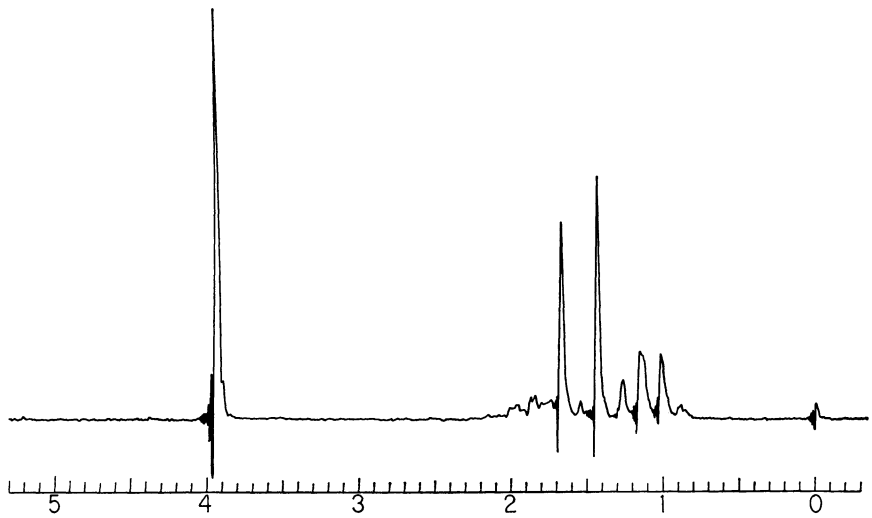

Fig. 2. The NMR spectrum of methyl 2-cyano-3-methyl-2,3-epoxyvalerate.

from the fast isomerization of the starting material, we could not obtain the pure *cis* epoxy ester.

As a typical example, the present authors analyzed the spectrum of methyl 2-cyano-3-methyl-2,3-epoxyvalerate (IIIa) (Fig. 2). The β-methyl signal appears as a doublet of an unequal intensity, with the more intense signal at the higher field (1.66 and 1.44 ppm). The intensity ratio from the analysis of the β-methylene multiplet was less certain. The γ-methyl protons appear as a doublet of an unequal intensity, with the more intense signal at the lower field (1.15 and 1.01 ppm). On the basis of the evidence just given, the more intense signal of the β-methyl protons can be assigned to that of the *cis* isomer, and the weaker signal, to that of the *trans*.

Table 2 shows the isomeric compositions of six epoxy esters and their starting unsaturated esters, which were estimated from the integration of the area under the appropriate NMR signals. The composition is little affected by the reaction conditions except in the case of VIII. Methyl 2-cyano-2,3-epoxy-3,5,5-trimethylcaproate (VIII) (*trans* percentage 60) was prepared from methyl 2-cyano-3,5,5-trimethylhexanoate (*trans* percentage 47) by heating it (70—80°C) with 30% hydrogen peroxide, while VIII (*trans* percentage 38) was obtained from the same starting ester in the presence of sodium bicarbonate at room temperature. It has already been pointed out that the *trans* isomer of this unsaturated ester is much increased by heating it to 71°C (*trans* percentage 61).[2] Accordingly, the results (Table 2) show that the *cis-trans* ratios of the products are almost the same as those of the starting materials.

On the other hand, it is known that the epoxidation of alkylidenecyanoacetic esters under alkaline conditions results in the formation of epoxy-

Table 2. *cis-trans* Composition ratios of the epoxy nitriles and their starting unsaturated esters

Compound	Method*	Composition per cent		Composition per cent of the starting material**	
		trans	*cis*	*trans*	*cis*
I	A, B	100	0	100	0
II	A, B	50	50	50	50
IIIa	A, B	43	57	47	53
V	A, B	40	60	38	62
VII	A	39	61	35	65
VIII	A	60	40	47	53
	B	38	62	47	53

* Capital letters refer to epoxidation methods designated by these letters in the Experimental Section.

** Following the method given in Ref. 2.

amides rather than epoxynitriles.[9] In the present study, the epoxynitrile was converted into epoxyamide by hydration with hydrogen peroxide in the presence of alkali. These compounds also possess an oxirane ring substituted by four different groups. Therefore, it would be interesting to use the above technique in the determination of the geometric configurations of these compounds. The NMR data are listed in Table 1.

The NMR absorptions of the β-methyl protons of the two isomers (*cis* and *trans*) were well separated, but the ratios could not be accurately determined (except for the case of XVII) from the relative areas of the two signals because of their overlap with the signals of the other alkyl groups. Therefore, when the difference in the steric requirements of the methyl and alkyl groups is relatively small, it is hard to assign signals to the two isomers by the above method.

By the epoxidation of *trans* ethyl ethylidenecyanoacetate or the hydration of *trans* ethyl 2-cyano-2,3-epoxybutyrate, ethyl 2-carbamoyl-2,3-epoxybutyrate (IX) was obtained. That this compound is a pure stereoisomer is confirmed by its NMR spectrum. The spectrum showed β-methyl protons at 1.45 ppm. This resonance position corresponds to those of signals of the lower fields of other epoxyamides (X—XII, XV) in which *cis* isomers coexist with *trans* isomers. In methyl 2-carbamoyl-2,3-epoxy-3,4,4-trimethylvalerate (XVI), prepared from the corresponding unsaturated nitrile (*trans* : *cis*=2 : 98). the only signal due to the β-methyl protons is at 1.32 ppm. In methyl 2-carbamoyl-2,3-epoxy-3,5,5-trimethylcaproate (XVII), prepared from methyl 2-cyano-2,3-epoxy-3,5,5-trimethylcaproate (VIII) (*trans* : *cis*=40 : 60), the signals due to the β-methyl protons are at 1.52 and 1.46 ppm, with the signal at the higher field much the more intense. Since there is a substantial difference between the steric requirements of methyl and hydrogen, *tert*-butyl and methyl, and neopentyl and methyl groups, it appears that the methyl group in IX, the *tert*-butyl group in XVI, and the neopentyl group in XVII prefer a *trans* orientation. By fractional crystallization, methyl 2-carbamoyl-3,4-dimethyl-2,3-epoxyvalerate (XIII) (*cis-trans* mixture) gave one isomer which was confirmed by the NMR spectrum (β-methyl protons: at 1.27 ppm). With the above data in hand, a tentative assignment of the configuration may be made. In the nine epoxyamides discussed here, the signals due to the β-methyl protons are at a higher field when they are *cis* to the ester group, and at a lower field when they are *trans*.

In the preceding papers the authors determined the geometric configurations of $R_1R_2C{=}C(CN)\text{-}COOR_3$ on the basis of the assumption[2] that the response for the β-methyl protons is at a higher field in the *trans* than in the *cis* configuration with respect to the ester group. The β-methyl group is more deshielded in the *cis* than in the *trans* arrangements. This trend is not followed in the case of the epoxy esters discussed here. The β-methyl protons *cis* to the ester group respond at a higher field than do the *trans* β-methyl protons because the former is more shielded. These observations can be explained consistently by considering the magnetic anisotropy of the carbonyl group. It is well established that protons located in or near the carbonyl plane experience additional deshielding, while additional shielding is observed for protons out of the plane.

Experimental

NMR Spectra. All the NMR spectra were taken with a JNM-C-60 high-resolution NMR spectrometer working at 60 MHz at a temperature of 19—20°C. The samples were examined in a chloroform solution, using tetramethylsilane as the internal reference. The chemical shifts are given as ppm downfield from tetramethylsilane.

Alkylidenecyanoacetic Esters. The ethyl ethylidenecyanoacetate was prepared according to the method of Popp and Catala.[10] The other unsaturated esters were prepared according to the method of Cope.[11] The methyl 1-methylpropylidenecyanoacetate (*cis*) was prepared by the condensation of methyl ethyl ketone with cyanoacetic acid, followed by esterification with diazomethane according to the method of Hamelin.[8]

Epoxidation of Alkylidenecyanoacetic Esters. A. A mixture of the alkylidenecyanoacetic ester (0.1 mol), 30% hydrogen peroxide (0.2 mol), and alcohol (30 ml) was refluxed for 7 hr on a water bath. To the

9) G. B. Payne, *J. Org. Chem.*, **26**, 663 (1961); M. Igarashi and H. Midorikawa, *ibid.*, **28**, 3088 (1963).

10) F. D. Popp and A. Catala, *ibid.*, **26**, 2738 (1961).

11) A. C. Cope, C. M. Hofmann, C. Wyckoff and E. Hardenbergh, *J. Amer. Chem. Soc.*, **63**, 3452 (1941).

TABLE 3. NEW EPOXY COMPOUNDS

Compound	Bp, °C/mmHg (Mp °C)	Formula	Calcd			Found		
			C, %	H, %	N, %	C, %	H, %	N, %
I	86—88/5	$C_7H_9O_3N$	54.19	5.85	9.03	54.33	5.86	9.14
IIIa	94—96/6	$C_8H_{11}O_3N$	56.79	6.55	8.28	56.80	6.57	8.54
IIIb	101—103/6	$C_9H_{13}O_3N$	59.00	7.15	7.65	58.98	7.12	7.98
IV	103—106/8	$C_9H_{13}O_3N$	59·00	7.15	7.65	59.19	7.06	7.97
VI	102—104/6	$C_{10}H_{15}O_3N$	60.89	7.67	7.10	60.53	7.57	7.33
VII	108—111/7	$C_{10}H_{15}O_3N$	60.89	7.67	7.10	60.41	7.60	7.41
VIII	110—112/13	$C_{11}H_{17}O_3N$	62.54	8.11	6.63	62.60	7.70	6.83
IX	(136—138)	$C_7H_{11}O_4N$	48.55	6.40	8.09	48.50	6.30	8.14
XI	(96—98)	$C_8H_{13}O_4N$	51.33	7.00	7.48	51.54	6.56	7.65
XII	(82—84)	$C_9H_{15}O_4N$	53.72	7.51	6.96	53.91	7.92	6.67
XIV	(95—98)	$C_{10}H_{17}O_4N$	55.80	7.96	6.51	55.49	7.76	6.24
XV	(77—79)	$C_{10}H_{17}O_4N$	55.80	7.96	6.51	55.58	7.69	6.40
XVII	(108—109)	$C_{11}H_{19}O_4N$	57.62	8.35	6.11	57.06	8.54	6.24

mixture water (100 m*l*) was added, and then it was extracted with chloroform. After the removal of the solvent, the residual oil was distilled to give epoxy nitrile.

B. To a flask equipped with a thermometer, a dropping funnel, and a stirrer, the alkylidenecyanoacetic ester (0.1 mol), sodium bicarbonate (0.05 mol), and alcohol (30 m*l*) were added. Into this 30% hydrogen peroxide (0.2 mol) was stirred, drop by drop, at room temperature. After stirring for 3 hr, the mixture was allowed to stand overnight. To the solution thus obtained we added water (100 m*l*), and then it was extracted with chloroform. After the removal of the solvent, the residual oil was distilled in a vaccum to give epoxy nitrile. The properties of the products are shown in Table 3.

Reaction of Epoxy Nitriles I—VIII with Hydrogen Peroxide. To the products (I-VIII) obtained above (0.01 mol) in alcohol (5 m*l*), we added 30% hydrogen peroxide (0.05 mol) and sodium tungstate dihydrate (0.005 mol). The mixture was then kept for 3 hr at 70—80°C on a water bath. After the removal of the solvent, the residue was extracted by the use of chloroform, and then the solvent was evaporated. The oily residue was shaken with petroleum ether to give colorless crystals (epoxy amides IX—XV, XVII).

Epoxy amide XVI was prepared from methyl 2-cyano-3,4,4-trimethylpentenoate[2] according to the method of the present authors.[12]

These epoxy amides were used for the measurement of the NMR spectra without further purification because the *cis-trans* ratios were affected by recrystallization. The samples were recrystallized from chloroform-petroleum ether prior to analyses.

Methyl 2-Carbamoyl-3,4-dimethyl-2,3-epoxyvalerate (XIII-*cis*). Compound XIII (*cis-trans* mixture) was prepared according to the general procedure. The repeated recrystallization of the product from chloroform-petroleum ether gave colorless needles; mp 135—136°C (NMR: β-methyl, 1.27 ppm).

Found: C, 53.99; H, 7.14; N, 6.95%. Calcd for $C_9H_{15}O_4N$: C, 53.72; H, 7.51; N, 6.96%.

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12) M. Igarashi and H. Midorikawa, *J. Org. Chem.*, **32**, 3399 (1967).