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Asymmetric Epoxidation of *l*-Menthyl Alkylidenecyanoacetates*[1]

Minoru IGARASHI and Hiroshi MIDORIKAWA

The Institute of Physical and Chemical Research, Yamato-machi, Saitama

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l-Menthyl alkylidenecyanoacetates have been prepared. The reaction of the esters with hydrogen peroxide in the presence of a base is accompanied by a partial asymmetric synthesis, as is shown by the hydrolysis of the resulting epoxy esters to epoxy acids.

For a study of asymmetric epoxidation, it appeared that an optically active menthyl ester of alkylidenecyanoacetic acid would be of use because the ester is epoxidized readily[1,2] with hydrogen peroxide. The epoxidation of this ester leads to the diastereoisomeric epoxides, and if an asymmetry in the ester results in an asymmetric epoxidation, these epoxides will be formed in unequal amounts. In the present work, such an epoxidation has been investigated.*[2]

l-Menthyl 2-cyano-3-methyl-2-pentenoate (I), bp 179—180°C/5 mmHg $[\alpha]_D$ −86.2°, was prepared from ethyl methyl ketone and *l*-menthyl cyanoacetate by Cope's method.[3] Ester I, on epoxidation with hydrogen peroxide in the presence of sodium tungstate or trisodium phosphate in ethanol, gave *l*-menthyl 2-carbamoyl-2, 3-epoxy-3-methylpentanoate (II) as a light yellow oil, $[\alpha]_D$ −50—−52°. The hydrolysis of the total *l*-menthyl ester II formed gave a (+)-rotatory specimen ($[\alpha]_D$ +1.3—+1.4°) of 2-carbamoyl-2, 3-epoxy-3-methylpentanoic acid (III).

This reaction constitutes a partial asymmetric synthesis: the original center of asymmetry has been eliminated by hydrolysis, and the new centers of asymmetry formed afford the optical activity for the resulting epoxy acid III, in which the possible configurations are present in unequal amounts.

The reaction was characterized by a remarkable reproducibility of the degree*[3] of asymmetric synthesis, irrespective of variations in the reaction conditions. Variations in, for example, the concentrations of the reactants, the duration of the heating of the reaction mixture, the catalyst-unsaturated ester-hydrogen peroxide ratios, and the solvents used had little effect upon the specific rotation of the epoxy acid obtained.

In another experiment, the reaction gave a crystalline epoxide II, mp 84—88°C $[\alpha]_D$ −53°, together with an oil probably containing a diastereoisomer. The melting point of the crystals rose to 99—100°C upon three recrystallizations. The hydrolysis of this specimen led to the ultimate isolation, in a high yield, of III with $[\alpha]_D$ +3.7° in ethanol. Also, the oil, on reaction with alkali, formed the same epoxy acid, which had no detectable optical activity.

We have recently reported[4] on the reaction mechanism of the alkylidenecyanoacetic ester with hydrogen peroxide in the presence of sodium tungstate or trisodium phosphate; the intermediate product is the 2-cyano-2, 3-epoxycarboxylic ester. The initial step in this reaction was assumed to be a nucleophilic attack by a sodium pertungstate anion or a perhydroxyl anion on the β-carbon atom of the ester, yielding the epoxy nitrile, with the elimination of the tungstate or hydroxyl anions.

No asymmetric synthesis can result if the addition of the anion, and hence the epoxidation, occurs with equal ease on either side of the double bond. Hence, the asymmetric carbon atom must determine the conformation in which the molecule is attacked, *i. e.*, asymmetric addition precedes, and leads to, asymmetric epoxidation.

From a discussion of the stereochemistry of asymmetric synthesis, Prelog *et al.*[5] conclude, with regard to a "substrate" molecule, that the side which is attacked is, in general, less hindered, and

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*1 This work is based partly on the doctoral dissertation of M. I., The University of Tokyo.

1) G. B. Payne, *J. Org. Chem.*, **26**, 663 (1961).

2) M. Igarashi and H. Midorikawa, *ibid.*, **28**, 3088 (1963).

*2 Although asymmetric induction of this type *i. e.* epoxidation of a double bond bearing an optically active substituent followed by removal of the original dissymmetric center has already been described by Pigulevskii *et al.* (G. V. Pigulevskii and G. V. Markina, *Doklady Akad. Nauk. SSSR*, **63**, 677 (1948)), it is interesting to learn that asymmetric induction will cause asymmetric epoxidation of a negatively substituted olefin by the Weitz-Scheffer technique (E. Weitz and A. Scheffer, *Ber.*, **54**, 2327 (1921)).

3) A. C. Cope, C. M. Hofmann, C. Wyckoff and E. Harenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).

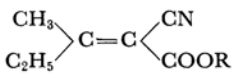
*3 The percentage of asymmetric synthesis cannot be estimated from the rotatory power of (+)-specimens of the epoxy acid because the rotation of the optical pure acid is unknown.

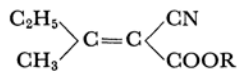
4) M. Igarashi and H. Midorikawa, *J. Org. Chem.*, in press.

5) V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953); V. Prelog, *Bull. soc. chim. France*, **1956**, 987; V. Prelog and H. C. Meier, *ibid.*, **36**, 320 (1953); V. Prelog, E. Philbin, E. Watanabe and M. Wilhelm, *ibid.*, **38**, 303 (1955).

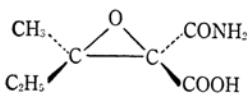
that the reaction proceeds by the addition of the anion to this side of the molecule. Similarly, it may be inferred that the most probable course of the epoxidation of I is the addition on that side of the double bond which is less hindered.

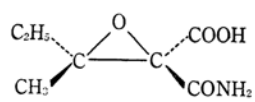
Further, the condensation of ethyl methyl ketone and the cyanoacetic ester by Cope's method yields a geometrical mixture of unequal quantities of A and B.[6] However, an attempt to separate only one isomer by gas chromatography was unsuccessful.


(A)


(B)

Four possible epoxy acids, C—F, may be formed from the mixed esters:


(C)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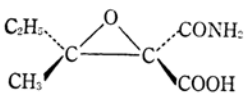
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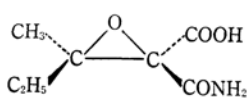
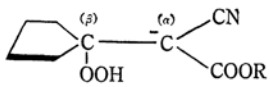

(F)

For example, the epoxidation of form A from below the plane of the paper would produce the epoxy acid D, and the epoxidation of form B from the same side, the diastereoisomer F.

The present reaction, in which two new centers of asymmetry are formed, with two configurations (C and E, or D and F) preponderating, constitutes an asymmetric synthesis. However, the quantitative determination of the ratios of the four isomers did not prove practicable. It is, therefore, difficult, from the data at present available, to select one configuration as certainly more probable than the other.*4

The epoxidation of *l*-menthyl cyclopentylidenecyanoacetate (IV) was also studied because only one new asymmetric center is formed. Sodium tungstate and trisodium phosphate were used as catalysts. The former reagent led to asymmetric synthesis (potassium salt of 2-carbamoyl-2-carboxy-1-oxaspiro[2. 4]heptane (VI), $[\alpha]_D$ −2.4°), whereas the latter was unsuccessful.*5 In this case, it appeared that the size of the attacking group is of importance. The reaction mechanism discussed by the present authors[4] requires the carbanion G as an intermediate, thus implying rotation around the Cα-Cβ bond:


(G)

(or $NaWO_4$)

Table 1. Preparation of II and III from I

Solvent	Catalyst	II[a] mp, °C	II[a] $[\alpha]_D^{25}$[c]	III[b]	III[b] $[\alpha]_D^{25}$[c]
Methanol	Na_2WO_4	84—86	−51.9°	Acid[d]	+1.5°
Ethanol	Na_2WO_4	Oil	−50°	Acid	+1.4°
Ethanol	Na_2WO_4	84—88	−53.0°	K-salt[e]	+1.5°
				Acid	+1.6°[f]
		95—97[g]		K-salt	+3.5°
		99—100[h]		K-salt	+3.7°
n-Propanol	Na_2WO_4	85—89		K-salt	+1.7°
Isopropanol	Na_2WO_4	80—85		Acid	+0.9°
t-Butanol	Na_2WO_4	84—90		K-salt	+2.6°
Tetrahydrofuran	Na_2WO_4	86—90		K-salt	+2.6°
Pyridine	Na_2WO_4	84—88		K-salt	+1.2°
Ethanol	Na_2CO_3	84—87		K-salt	+1.8°
Ethanol	Na_3PO_4	Oil	−52°	K-salt	+1.3°
				Acid	+1.4°
Ethanol	Na_3PO_4	83—87	−51.6°	K-salt	+1.4°

a) The yields of II from I were 60—75%. b) The yields of III from II were 85—90%. c) The free acids were measured in ethanol; the K-salt, in water. d) Acid: II, mp 139—140°C (decomp.). e) K-salt: Potassium salt of II. f) Variations in the reaction times (1—4 hr) and the concentrations (10—30%) of hydrogen peroxide gave same results. g) Twice recrystallized from ligroin. h) Thrice recrystallized.

6) T. Hayashi, M. Igarashi, S. Hayashi and H. Midorikawa, This Bulletin, **38**, 2063 (1965).

*4 Analysis of the composition of the mixed acids C—F is required. Later work has indicated that such analysis should be possible by the method of NMR spectra. These results will be reported in the near future.

*5 Trisodium phosphate-catalyzed epoxidation gave optically inactive epoxide VI as is shown in Table 2.

Therefore, substantially less asymmetric synthesis may occur during the formation of an epoxy ring by the use of trisodium phosphate. On the other hand, the retention of asymmetry during the similar epoxidation in the presence of sodium tungstate suggests that the rotation is definitely restricted. This may be due to the great steric hindrance of the WO_5 group; the steric hindrance of the OOH group is less important.

On the other hand, *d*-bornyl cyclopentylidenecyanoacetate (VII) gave a (−)-rotatory specimen of VI by epoxidation in the presence of sodium tungstate, the degree of asymmetric synthesis being nearly equivalent to that in the case of the *l*-menthyl ester IV. Thus the *d*-bornyl ester gave the epoxy acid of same configuration as that obtained from the *l*-menthyl ester. Therefore, it appeared that no simple relation exists between the configuration of the alcohol and that of the resulting acid.[7]

These results are summarized in Tables 1 and 2.

TABLE 2. PREPARATION OF V AND VI FROM IV

Solvent	Catalyst	V[a] mp, °C	V[a] $[\alpha]_D^{25}$ (ethanol)	VI[b] $[\alpha]_D^{25}$ (water)
Ethanol	Na_2WO_4	102—105	−52.3°	−2.4°
		144—145[c]	−57.9°	−16.8°
		144—145[d]	−58.0°	−16.8°
Ethanol	Na_2CO_3	102—105	−51.8°	0
		125—130[e]	−54.7°	−8.0°
Ethanol	Na_3PO_4	100—105	−51.9°	0

a) The yields of V from IV were 55—65%.
b) The yields of VI from V were 85—90%.
c) Four times recrystallized from ligroin.
d) Five times recrystallized.
e) Once recrystallized.

Experimental

***l*-Menthyl 2-Cyano-3-methyl-2-pentenoate (I).** Following the method of Cope,[3] *l*-methyl cyanoacetate[8] (55.8 g, 0.25 mol), ethyl methyl ketone (21.6 g, 0.3 mol), ammonium acetate (3.8 g, 0.05 mol), glacial acetic acid (6.0 g, 0.1 mol), and 150 m*l* of benzene were placed in a flask attached to a constant water separator. The flask was heated in an oil bath (145—150°C) for 4.5 hr. The mixture was then cooled and washed with water, and the solvent was removed by distillation. The fractional distillation of the residue gave I; bp 179—180°C/5 mmHg, $[\alpha]_D^{27}$ −86.2° (*c* 2.1, ethanol), yield 90%.

Found: C, 73.76; H, 9.80; N, 5.02%. Calcd for $C_{17}H_{27}NO_2$: C, 73.60; H, 9.81; N, 5.05%.

***l*-Menthyl 2-Carbamoyl-2,3-epoxy-3-methylpentanoate (II).** I (1.0 g) was dissolved in 30 m*l* of ethanol. To this solution 0.5 g of sodium tungstate dihydrate (or trisodium phosphate dodecahydrate) and 10 m*l* of 30% hydrogen peroxide were added. The mixture was then heated on a water bath at 70—80°C for 1 hr. After an additional 1 hour, the ethanol was removed by distillation. The oily layer was separated from the aqueous layer. The product was used for the following reaction without further purification.

When sodium carbonate was used as a catalyst, the reaction temperature was held at 35—40°C.

In another experiment, the oil obtained above was allowed to stand in an ice box. The solid obtained was recrystallized thrice from ligroin. Mp 99—100°C, $[\alpha]_D^{25}$ −54.5° (*c* 2.0, ethanol).

Found: C, 65.59; H, 9.30; N, 4.49%. Calcd for $C_{17}H_{29}NO_4$: C, 65.56; H, 9.39; N, 4.50%.

The epoxidation was repeated under various conditions (see Table 1).

Hydrolysis of II. To a three-necked flask equipped with a stirrer, a dropping funnel, and a thermometer, a solution of *l*-menthyl ester II in ethanol was charged; ethanol containing a slight excess of potassium hydroxide was then stirred in, drop by drop, at 20—25°C. After the mixture had been allowed to stand overnight, the resulting white precipitate was separated by filtration, washed with ethanol, and dried.

The potassium salt was again dissolved in a small amount of water, cooled in an ice bath, and acidified with dilute hydrochloric acid. The resulting precipitate was collected by filtration, washed with a small amount of cold water, and dried.

A sample was recrystallized from ethanol prior to analysis. 2-Carbamoyl-2, 3-epoxy-3-methylpentanoic acid (III), mp 140°C (decomp.) (lit.[2] mp 140—141°C (decomp.)), was thus obtained.

Found: C, 48.37; H, 6.32; N, 8.00%. Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40; N, 8.09%.

An optical examination was made of both the potassium salt and free acid. These results are shown in Table 1.

***l*-Menthyl Cyclopentylidenecyanoacetate (IV).** This compound was prepared from *l*-menthyl cyanoacetate and cyclopentanone by the method described above. Bp 210—213°C/8 mmHg, $[\alpha]_D^{26}$ −81.1° (*c* 3.2, ethanol), yield 80%.

Found: C, 74.66; H, 9.80; N, 4.74%. Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84%.

2-Carbamoyl-2-*l*-menthoxycarbonyl-*l*-oxaspiro-[2. 4]heptane (V). The epoxidation of IV was carried out as described above. V was thus obtained in a 55—65% yield. A sample was recrystallized from ligroin prior to analysis. Mp 144—145°C, $[\alpha]_D^{25}$ −57.9° (*c* 1.8, ethanol).

Found: C, 66.78; H, 9.07; N, 4.28%. Calcd for $C_{18}H_{29}NO_4$: C, 66.84; H, 9.04; N, 4.33%.

Hydrolysis of V. To a solution of V in ethanol, a slight excess of ethanolic potassium hydroxide was added at room temperature. A white crystalline precipitate formed during the addition. After the mixture had stood overnight, it was separated by filtration, washed with ethanol, and dried. The yield of potassium salt of 2-carbamoyl-2-carboxyl-1-oxaspiro[2. 4]-heptane (VI) was 85—90%.

The rotatory power of the salt was measured because

7) *Cf.* M. H. Palmer and J. A. Reid, *J. Chem. Soc.*, **1960**, 931; K. Shishido, H. Nozaki and O. Kurihara, *J. Am. Chem. Soc.*, **74**, 6254 (1952).
8) W. A. Pavelich and R. W. Taft, Jr., *ibid.*, **79**, 4935 (1957).

its free acid is unstable.[2] These results are shown in Table 2.

***d*-Bornyl Cyclopentylidenecyanoacetate (VII).** Cyanoacetic acid (10 g) was esterified in the usual manner with 20 g of *d*-borneol, 0.5 g of concentrated sulfuric acid, and 50 m*l* of benzene. The solution was shaken with an aqueous solution of potassium carbonate and then dried over sodium sulfate. The distillation of benzene from the solution left 20 g of a light yellow oil, $[\alpha]_D^{28}$ +31.5° (*c* 0.3 ethanol). This material was used for the following reaction without further treatment.

Following the procedure of Cope,[3] the *d*-bornyl cyanoacetate obtained above (4 g), 3 g of cyclopentanone, 0.3 g of ammonium acetate, 0.6 m*l* of glacial acetic acid, and 20 m*l* of benzene were heated for 3 hr. The reaction mixture was then cooled, washed with three 10 m*l* portions of water, and dried over sodium sulfate. The distillation of benzene from the dried solution left 6.7 g of a very viscous oil.

Found: N, 4.13%. Calcd for $C_{18}H_{25}NO_2$: N, 4.87%.

Epoxidation and Subsequent Hydrolysis of VII. The product obtained above (6.0 g) was dissolved in 50 m*l* of ethanol, and then 3.0 g of sodium tungstate dihydrate and 35 m*l* of 30% hydrogen peroxide were added. The mixture was worked up as has been described in the case of the previous epoxidation. The crude epoxy bornyl ester (viscous oil) obtained was hydrolyzed by treatment with alcoholic potassium hydroxide. The yield of the potassium salt was 4.0 g. The rotatory power of the salt was measured and found to be $[\alpha]_D^{27}$ −2.5° (*c* 5.6, water).

The viscous oil (crude epoxy bornyl ester) obtained above partly solidified when kept. The solid was collected by filtration. The hydrolysis of the product was repeated under conditions similar to the above. The potassium salt obtained had $[\alpha]_D^{28}$ −12° (*c* 3.4, water). This salt was converted into cyclopentaneglyoxylamide, mp 134°C, by treatment with dilute hydrochloric acid.[2] (Found: N, 9.89%. Calcd for $C_7H_{11}NO_2$: N, 9.92%.)

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