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PARTIAL ASYMMETRIC SYNTHESIS OF *trans*-2-PHENYLCYCLOPROPANECARBOXYLIC ACID[1]

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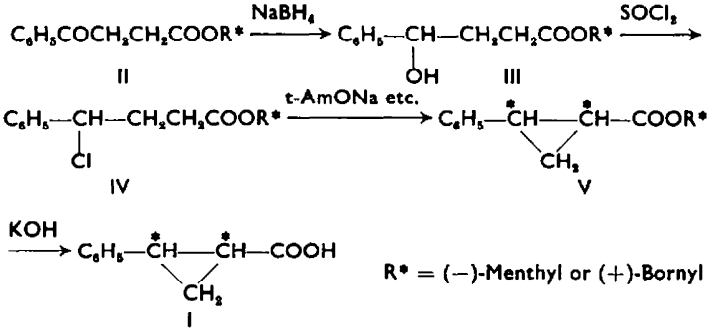
Abstract—Optically active *trans*-2-phenylcyclopropanecarboxylic acid (I) was obtained by hydrolysing the reaction products of (1) cycloalkylation of (−)-menthyl or (+)-bornyl (±)-γ-chloro-γ-phenylbutyrate (IV) and of (2) condensation of styrene oxide and (−)-menthyl or (+)-bornyl phosphonoacetate (VI). The effects of reaction conditions on the optical rotation of I were examined.

A recent paper of Tömösközi[2] concerning the asymmetric synthesis of *trans*-2-phenylcyclopropanecarboxylic acid (I) has prompted the publication of the following investigation on the same subject. The reaction recorded by Julia *et al.*[3] for the preparation of optically inactive acids, utilizes the cycloalkylation of γ-chloro-γ-phenylbutyrates (IV) in the presence of sodium or potassium alkoxides. Another method analogous to the Tömösközi's involves condensation of styrene oxide with optically active phosphonoacetates (VI), but the cyclopropanecarboxylic acid (I) resulting from the same reaction components as those used by Tömösközi has been found to possess a *different* sign and larger magnitude of rotation.

(−)-Menthyl and (+)-bornyl esters (IV) of (+)-γ-chloro-γ-phenylbutyric acid[4] were prepared from the corresponding β-benzoylpropionates (II) according to the following scheme:



Each of the hydroxy esters (III) was a viscous oil and easily decomposed on distillation *in vacuo* to give a mixture of γ-phenylbutyrolactone and alcohol. The chloro esters (IV) were also thermally unstable giving unsaturated esters. As listed in

[1] Partly presented at the 15th and 16th Annual Meetings of Japan Chemical Society, Kyôto, Japan, April 2–5, 1962 and Tôkyô, Japan, March 31–April 3, 1963.

[2] I. Tömösközi, *Angew. Chem.* **75**, 294 (1963).

[3] M. Julia, S. Julia and B. Bémont, *C. R. Acad. Sci., Paris* **245**, 2304 (1957); *Bull. Soc. chim.* Fr. 307 (1960).

[4] The preparation of γ-chloro-γ-phenylbutyrate (IV) by the interaction of γ-chloro-γ-phenylbutyryl chloride with (−)-menthol or (+)-borneol according to the method of Julia *et al.*[3] was unsuccessful.

Table 1, three of the esters III and IV gave correct analytical values before distillation though analyses of one of the chloro esters IV were unsatisfactory. Since comparison of IR spectra of these esters indicated that no appreciable amount of impurity was present, these two chloro esters (IV) were subjected to cyclization without further purification.

TABLE 1. β-BENZOYLPROPIONATES (II), γ-HYDROXY-γ-PHENYLBUTYRATES (III) AND γ-CHLORO-γ-PHENYLBUTYRATES (IV)

Esters	Analyses (%) Found C	H	Calc. C	H	$[\alpha]_D$	I.R. (cm^{-1})
(−)-Menthyl II[a]	75·91	8·90	75·91	8·92	−50·9	1730 1690
(+)-Bornyl II[b]	76·61	8·59	76·40	8·34	+25·3	1740 1695
(−)-Menthyl III[c]	75·42	9·62	75·43	9·50	−55·8	3380 1730
(+)-Bornyl III[d]	75·75	9·12	75·91	8·92	+26·8	3390 1740
(−)-Menthyl IV[d]	71·19	8·89	71·30	8·68	−52·7	1735 730
(+)-Bornyl IV[d]	70·71	8·16	71·73	8·13	+21·0	1740 735

[a] M.p. 92–93°. D. M. Bovey and E. E. Turner, *J. Chem. Soc.* 3223 (1951), reported m.p. 92°
[b] B.p. 175–180° at 0·15 mm
[c] B.p. 172–176° at 0·1 mm
[d] Analyses were performed with undistilled products.

Hydrolysis of the optically active γ-hydroxy esters (III) gave γ-phenyl-γ-butyrolactone which was completely inactive. Thermal dehydration of III also gave the identical optically inactive lactone. These observations show that the phenyl-substituted, asymmetric carbon of each of the intermediates III and IV is practically racemic.

Cyclization of the γ-chloro esters (IV) was performed by the action of sodium or potassium alkoxide in *t*-butyl or *t*-amyl alcohol at room temp during 40 hr. Saponificaton of the reaction product with alcoholic potassium hydroxide at room temp, followed by repeated alkali extraction and chromatography on a silica-gel column, gave analytically pure *trans*-2-phenylcyclopropanecarboxylic acid (I), which was found to be optically active. The IR spectra of all samples of optically active I in carbon disulfide solutions were completely superimposable on that of (±)-*trans*-I prepared by cyclizing ethyl chlorobutyrate (IV, $R^* = C_2H_5$). Optical rotations of I obtained under various conditions are summarized in Table 2.

Attempted resolution of racemic I as well as of partially active I with bases such as brucine, cinchonine or quinine failed. Degradation of a sample of I ($[\alpha]_D$ −5·7°) with ozone and hydrogen peroxide gave cyclopropane-*trans*-1,2-dicarboxylic acid, with $[\alpha]_D$ −4·8° and an IR spectrum identical with that of a racemic, authentic specimen.[5] Since the recorded rotation of optically pure cyclopropane-*trans*-1,2-dicarboxylic acid is $[\alpha]_D$ −84·5°,[6] the observed rotation indicates that the optical purity of this sample is 5·6% and also that the original mono-basic acid (I) could be assumed

[5] H. L. deWaal and G. W. Perold, *Chem. Ber.* **85**, 574 (1952).
[6] E. Buchner and R. v. d. Heide, *Ber. Dtsch. Chem. Ges* **38**, 3112 (1905).

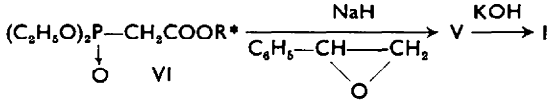
TABLE 2. *trans*-2-PHENYLCYCLOPROPANECARBOXYLIC ACID OBTAINED FROM γ-CHLORO-γ-PHENYLBUTYRATES (IV)

Ester (IV)	Reagent	Yield (%)	α_D (obs.)	c (g/100 ml)	$[\alpha]_D$ (Dioxane)	M.p. (°C)
(Solvent: t-AmOH)						
(−)-Menthyl	Na	39	+0·07	2·1	+3·4	82–85
		55	+0·13	6·2	+2·1	85–87·5
	NaH[a]	33	−0·43	1·5	−28·9	85–89
		19	−0·67	2·4	−27·4[c]	79–85
	NaH[b]	4	−0·25	1·2	−20·3[c]	
	K	35	−0·09	1·8	−5·1	84–87
		47	−0·03	2·0	−1·5	82–86
(+)-Bornyl	Na	31	+0·22	3·3	+6·6[c]	82–89
	NaH	16	+0·36	1·1	+34·1	86–88
	K	41	+0·21	2·2	+9·5	82–86
(Solvent: t-BuOH)						
(−)-Menthyl	Na	33	+0·04	2·4	+1·7	84–87
	K	54	−0·04	2·7	−1·5	87·5–89
		12	−0·06	1·6	−3·8	81–85
(+)-Bornyl	Na	14	−0·10	1·5	+6·5	84·5–86
	K	42	−0·15	2·1	+7·2	86–87

[a] Commercial sodium hydride suspended in mineral oil was dissolved in alcohol.
[b] Commercial sodium hydride suspension was washed repeatedly with anhydrous ether and dried in a desiccator under reduced pressure.
[c] Specific rotation was measured prior to purification by chromatography.

to be of this order of magnitude.[7] Discussions on the relationship of optical rotations of I and reaction conditions will be given later.

Another route to optically active I, reported independently by Tömösközi,[2] consists in the condensation of styrene oxide with optically active phosphonoacetates (VI) followed by hydrolysis. (−)-Menthyl and (+)-bornyl phosphonoacetates (VI)



were prepared by the Arbusow reactions[8] of triethyl phosphite with the corresponding bromoacetates. The condensation of VI with styrene oxide was performed according to the method of Wadsworth and Emmons.[9] The IR spectra of the resulting cyclopropanecarboxylic acid (I) were identical with those of authentic samples. Optical rotations are summarized in Table 3. In contrast to the results recorded by Tömösközi,[2] the acid I prepared from (−)-menthyl phosphonoacetate (VI) was *levorotatory*.

[7] According to the preliminary communication by I. Tömösközi[2] optically pure acid (I) should have $[\alpha]_D \div 270°$. On this assumption, optical yields of our partial asymmetric synthesis should be much lower than estimated.

[8] G. H. Kosolaroff, *J. Amer. Chem. Soc.* **66**, 109 (1944).

[9] W. S. Wadsworth, Jr. and W. D. Emmons, *J. Amer. Chem. Soc.* **83**, 1733 (1961).

Some comments are necessary in connection with the results presented in Tables 2 and 3. First, the Prelog–Cram model[10] is not applicable to these reactions. Both the sign and magnitude of optical rotations of I are changed by the reaction conditions and are not determined solely by the configuration of asymmetric carbon atom attached directly to the alkoxy oxygen of the esters. Further, (+)-bornyl chloro ester (IV) gives higher rotation values of I than (−)-menthyl ester under the same reaction condition (Table 2), while exactly the reverse holds in the condensation of phosphonoacetates (Table 3). Finally, no appreciable changes have been observed for the cyclization of IV, whether the solvent is t-butyl or t-amyl alcohol.

TABLE 3. *trans*-2-PHENYLCYCLOPROPANECARBOXYLIC ACID FROM STYRENE OXIDE AND PHOSPHONOACETATES (VI)

Ester (VI)	Yield (%)	Acid (I) α_D (obs.)	Acid (I) c (g/100 ml)	Acid (I) $[\alpha]_D$ (dioxane)	M.p. (°C)
(−)-Menthyl	17	−3·64	8·97	−40·6	86–89
	22	−3·43	7·56	−45·4	87–90
	20	−5·87	7·49	−78·5	86–90
(+)-Bornyl	43	−0·66	9·22	−7·2	87–89
	56	−0·53	8·42	−6·7	88·5–89·5
	55	−0·50	8·70	−5·7	88–89

The cyclization of (−)-menthyl γ-chloro-γ-phenylbutyrate (IV) is apparently sensitive to a variation of condensing agent. Further experiments designed for elucidating this problem have been carried out and the results are summarized in Table 4.

The rotational sign of I appears to be influenced by the origin of the sodium alkoxide. As shown in Table 2, a condensing agent prepared from metallic sodium gives *dextrorotatory* I, while one prepared from commercial sodium hydride gives *levorotatory* I. In the latter case sodium hydride suspended in mineral oil was dissolved in alcohol without removing the oil. This oil or commercial kerosene[11] has, however, been found to possess no appreciable effect on the steric course of the cyclization (Table 4). Significant effects have been observed in cases where a small amount of water was added to the reaction mixture (Table 4). The reversion of rotational sign and considerable increase of rotation were observed with (−)-menthyl ester (IV). Addition of water affected also the cyclization of (+)-bornyl ester (IV) and increased the rotational value of the resulting I, but no change of rotational sign was observed in the latter case. Thus, the apparent influence of the origin of sodium alkoxide should be ascribed to the presence of a small amount of sodium hydroxide present in the commercial sodium hydride. Effects of inorganic catalysts on the steric course of asymmetric syntheses have been recorded by Walborsky[12] and by Inouye.[13]

[10] See, for example, E. L. Eliel, *Stereochemistry of Carbon Compounds* p. 68. McGraw-Hill, New York (1962).

[11] IR spectrum of kerosene was essentially identical with that of recovered mineral oil.

[12] H. M. Walborsky, L. Barash and T. C. Davis, *J. Org. Chem.* **26**, 4778 (1961).

[13] Y. Inouye and H. M. Walborsky, *J. Org. Chem.* **27**, 2706 (1962).

TABLE 4. *trans*-2-PHENYLCYCLOPROPANECARBOXYLIC ACID OBTAINED FROM (−)-MENTHYL γ-CHLORO-γ-PHENYLBUTYRATE IN THE PRESENCE OF LIQUID HYDROCARBON OR WATER[a]

Reagent	Yield (%)	α_D (obs.)	c (g/100 ml)	$[\alpha]_D$ (Dioxane)	M.p. (°C)
Na + Mineral oil[b] (1:1 by wt.)	42	+0·07	1·9	+3·7	89–90
	23	+0·02	1·5	+1·3	87–89
	43	−1·31	1·5	−76·6[f]	91–92
Na + kerosene[c] (1:2)	25	+0·08	1·8	+4·4	88–89
Na + kerosene (1:10)	44	+0·10	3·2	+3·1[e]	
Na + H_2O (30 mole%)	39	−0·32	1·3	−23·9	88–90
Na + H_2O (15 mole%)	35	−0·02	1·1	−1·8	82–86
Na + H_2O (5 mole%)	37	−0·02	1·5	−1·3	87–90
Na + H_2O (30 mole%)[d]	33	+0·21	1·6	+13·5	82–86
K + Mineral oil (1:1)	46	−0·07	1·7	−4·2	82–85
	31	−0·05	1·7	−2·9[e]	78–79
K + H_2O (30 mole%)	25	−0·02	1·7	−1·2	82–85

[a] The reaction was carried out in *t*-amyl alcohol.
[b] Mineral oil was recovered from commercial sodium hydride suspension by decomposition with aqueous methanol followed by extraction with benzene.
[c] See foot-note 11.
[d] (+)-Bornyl ester (IV) was used as a starting material.
[e] Specific rotation was measured prior to purification by chromatography.
[f] In this run, *levorotatory* acid (I) with high optical rotation was obtained as a sole product, but this could not be duplicated. The anomaly may be due to incomplete washing and drying of recovered mineral oil.

Another point of interest is the difference observed between sodium and potassium alkoxides as cyclization agents for (−)-menthyl chloro ester (IV). This could be ascribed to the presence of a small amount of potassium hydroxide in analogy with the above-mentioned observation, but actually the addition of water to the solution of potassium t-amyloxide did not affect appreciably the rotation of the resulting acid I. Neither a change of rotational sign nor an increase in rotational magnitude was observed in the case of potassium alkoxide (Table 4). It may, therefore, be assumed that alkali cations in some way influence the steric course of cyclization.

Further experiments are required before these observations including the discrepancy of the experimental results of Tömösközi and our own can be explained.

EXPERIMENTAL

All b.ps. and m.ps. are uncorrected. Microanalyses were performed by Miss K. Ogawa of this laboratory. Unless otherwise mentioned, optical rotations were measured in dioxane.

Starting materials. (−)-Menthyl and (+)-bornyl β-benzoylpropionates (II) were obtained from β-benzoylpropionic acid and the corresponding alcohols. A xylene solution of the components was refluxed in the presence of *p*-toluenesulfonic acid and continuous removal of the resulting water.

(−)-Menthyl and (+)-bornyl bromoacetates were prepared from bromoacetyl bromide and the corresponding alcohol in the presence of dimethylaniline. (−)-Menthyl bromoacetate: b.p. 107–112° at 5 mm, $[\alpha]_D^{17}$ −74·67° (neat); (+)-bornyl bromoacetate: b.p. 110–112° at 3 mm, $[\alpha]_D^{17}$ +40·52° (neat).

(−)-*Menthyl γ-hydroxy-γ-phenylbutyrate* (III). To a solution of 10 g (0·032 mole) (−)-menthyl β-benzoylpropionate (II) dissolved in 100 ml of a 1:1 mixture of ether and ethanol, a solution of 0·6 g (0·016 mole) sodium borohydride in 3 ml water was added under ice-cooling. After stirring at 5° for an additional 2 hr, excess sodium borohydride was decomposed with aqueous acetic acid. The reaction mixture was diluted with 30 ml water, extracted with ether, washed with aqueous sodium bicarbonate solution and water, and dried ($MgSO_4$). Evaporation of the solvent at red. press. and distillation of the residual oil gave 8·6 g (85% yield) viscous oil, b.p. 172–176° at 0·1 mm.

Crude (+)-*bornyl γ-hydroxy-γ-phenylbutyrate* was obtained from 9·5 g (0·03 mole) (+)-bornyl β-benzoylpropionate dissolved in 50 ml ethanol by reduction with 0·6 g (0·016 mole) sodium borohydride in the same manner.

Crude hydroxy ester (III), which was obtained in quantitative yield, was immediately submitted for the chlorination.

Hydrolysis of optically active γ-hydroxy-γ-phenylbutyrate (III). A solution of 6 g crude (−)-menthyl γ-hydroxy-γ-phenylbutyrate (III) dissolved in 150 ml 1N alcoholic potash was stirred at room temp during 24 hr. After evaporation of the solvent at 40–50°, residual oil was diluted with 20 ml water and extracted thoroughly with ether. Aqueous phase was acidified with dil. hydrochloric acid and extracted with ether. Ethereal solution was washed with water and dried ($MgSO_4$). Evaporation of the solvent at red. press. followed by distillation of the resulting oil afforded 2·7 g (88% yield, γ-phenylbutyrolactone, b.p. 135–140° at 2 mm. The optical activity was hardly observed (α_D +0·01) *c* 4·53, ethanol).

(−)-*Menthyl and* (+)-*bornyl γ-chloro-γ-phenylbutyrates* (IV). A mixture of 10 g (0·03 mole) γ-hydroxy-γ-phenylbutyrate (III) and 3·2 g (0·04 mole) pyridine dissolved in 50 ml benzene was treated with 4·2 g (0·035 mole) freshly distilled thionyl chloride[14] at 5° for 3 hr. The benzene solution was separated from the precipitated solids, washed successively with water, Na_2CO_3Aq, dil HCl and then water, and dried ($MgSO_4$). Evaporation of the solvent gave a viscous oil (IV) in almost quantitative yield. The specific rotations and analyses are given in Table 1.

trans-2-*Phenylcyclopropanecarboxylic acid* (I) *by cyclization of γ-chloro-γ-phenylbutyrate* (IV). To a solution of sodium t-amyloxide prepared from 0·7 g (0·03 atom) sodium and 40 ml t-amyl alcohol was added 10 g (0·03 mole) crude (−)-menthyl γ-chloro-γ-phenylbutyrate. After stirring at room temp during 40 hr, the reaction mixture was warmed to 30–40° for 3 hr, diluted with 30 ml water, and extracted with 100 ml portions of ether three times. The ethereal solution was washed and evaporated. The residual oil was dissolved in 100 ml 2N alcoholic potash and the solution was stirred at room temp during 30 hr. After evaporation of the solvent at 40–50°, the residue was diluted with water and repeatedly extracted with ether.[15] The aqueous layer was then acidified with dil HCl and the product taken up in ether. The alkali extraction was repeated until the IR absorption near 1800 cm^{-1} due to lactonic impurity was absent in the acidic fraction. Further purification of the crystalline acid by chromatography on a silica-gel column with benzene as an eluant afforded 2·0 g (39% yield) analytically pure *trans*-2-phenylcyclopropanecarboxylic acid, m.p. 82–85°. Recrystallizations of acid I ($[\alpha]_D$ −27·4°) from ligroin or water gave a sample more sharply melting at 89–91°, the specific rotation of which was extremely low (α_D −0·01°, *c* 2·2). The acid I recovered from the mother liquor of recrystallizations formed an amorphous wax which had $[\alpha]_D$ −132° (α_D −2·63°, *c* 2·0) and its IR spectrum was identical with that of (±)-*trans* I.[16] Results of duplicated experiments under various conditions are given in Tables 2 and 4.

Diethyl (−)-*menthyloxycarbonylmethylphosphonate and diethyl* (+)-*bornyloxycarbonylmethylphosphonate* (VI). A mixture of 20·5 g (0·074 mole) (−)-menthyl bromoacetate and 12·3 g (0·074 mole) triethylphosphite was stirred at 150° during 4 hr. Fractional distillation of the reaction product

[14] The use of thionyl chloride which was not freshly distilled gave a considerable amount of lactonic impurity, as shown by IR spectrum.

[15] The absence of carbonyl component in this neutral part was proved by IR spectrum. Accordingly, the possibility of asymmetric saponification was completely excluded.

[16] Generally speaking, optically purer acid (I) had broader m.p. range and formed a noncrystallizable wax.

gave 20·3 g (83% yield) (−)-menthyl phosphonoacetate, b.p. 154–157° at 0·5 mm, n_D^{20} 1·4568, $[\alpha]_D^{31}$ −47·3° (α_D^{31} −7·32°, *c* 15·46). (Found: C, 56·27; H, 9·88; $C_{16}H_{31}O_5P$ requires: C, 57·47; H, 9·35%).

(+)-Bornyl phosphonoacetate was similarly obtained in 86% yield, b.p. 160–163° at 1·0 mm, n_D^{20} 1·4734, $[\alpha]_D^{31}$ +21·0° (α_D^{31} +3·16°, *c* 15·07). Found: C, 55·51; H, 9·04; $C_{16}H_{29}O_5P$ requires: C, 57·82; H, 8·79%). The analyses of both phosphonoacetates were unsatisfactory, but the absence of appreciable amounts of impurity was shown by the IR spectra.

trans-2-*Phenylcyclopropanecarboxylic acid* (I) *from phosphonoacetate* (VI). To a solution of 2·0 g (0·042 mole) 50% sodium hydride suspension in mineral oil dissolved in 80 ml 1,2-dimethoxyethane, 12 g (0·036 mole) (−)-menthyl phosphonoacetate (VI) was added at 25° with stirring. After continued stirring at room temp until the evolution of hydrogen gas had ceased, 4·3 g (0·036 mole) styrene oxide was added and stirred at 85° during 4 hr. Treatment with water, extraction with ether and evaporation of the solvent gave crude cyclopropanecarboxylate (V), which was treated with an excess of alcoholic potash at room temp during 20 hr. After evaporation of the solvent, dilution with water and removal of neutral part by ether extraction,[15] the aqueous phase was acidified with dil. HCl. The acidic mixture was extracted with ether, and the ether solution was dried (Na_2SO_4) and evaporated under red. press., yielding 1·0 g (17·3% yield) crude *trans*-2-phenylcyclopropanecarboxylic acid, m.p. 86–89°, $[\alpha]_D^{16}$ −40·6° (α_D^{16} −3·64°, *c* 8·97). Further purification by chromatography on a silica-gel column did not change its rotation. Results of other experiments are summarized in Table 3.

Cyclopropane-trans-1,2-*dicarboxylic acid.* When 1·5 g (0·009 mole) *trans*-2-phenylcyclopropanecarboxylic acid ($[\alpha]_D$ −5·7°) was degraded by ozone and hydrogen peroxide according to the method of deWaal and Perold,[5] there was obtained 0·74 g (62% yield) dicarboxylic acid, m.p. 167–171°, $[\alpha]_D^{26}$ −4·8° (α_D^{26} −0·35°, *c* 7·35, water).

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