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ABSOLUTE CONFIGURATION AND PARTIAL ASYMMETRIC SYNTHESIS OF 2-PHENYL-1, 1-DIMETHYLCYCLOPROPANE

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Abstract—Reaction of optically active styrene oxide with triethyl α-phosphonopropionate gives 2-phenyl-1-methylcyclopropanecarboxylate in optically active form. When the —CO_2Et group is transformed into —CH_3, the product has but one asymmetric centre originating from styrene oxide. Based on the intramolecular S 2 mechanism of the formation of the cyclopropane ring, the absolute configuration of the title compound is suggested.

IN A previous communication[1] we have demonstrated that the reaction of triethyl phosphonoacetate carbanion with optically active styrene oxide proceeds with inversion at the asymmetric carbon of epoxide leading to *trans*-2-phenylcyclopropanecarboxylic acid. Assignement of configuration to (+)-*trans*-2-phenylcyclopropanecarboxylic acid made by Inouye *et al.* through a rigorous chemical correlation[2] supported our picture about the mechanism based on the original suggestion of Denney *et al.*[3,4]

In continuation of this work, the reaction of trialkyl phosphonopropionates with racemic as well as optically active styrene oxide has been investigated. Although the related phosphoranes apparently cannot react with styrene oxide,[4] trialkyl α-phosphonopropionate carbanions, as a consequence of the greater charge[5] concentrated upon the α-carbon react smoothly with the epoxide giving cyclopropane in moderate to good yields. α-Phosphonopropionates involved in these experiments were prepared by the Arbusov reaction[6] of triethyl phosphite with the appropriate α-bromopropionate (Table 1). Methylation of triethyl phosphonoacetate[7] resulted in a mixture of compounds from which pure phosphonopropionate could be obtained with great difficulty and consequently in poor yield.

Metallation[8] of α-phosphonopropionates was achieved by sodium hydride in 1,2-dimethoxyethane (DME), benzene (B) or tetrahydrahydrofuran (THF), leading to a slightly opalescent solution.

Reaction of styrene oxide with the metallated phosphonopropionates at 70–75° was complete after 4–5 hr giving 2-phenyl-1-methylcyclo-propanecarboxylate (II). Alkaline saponification of the inactive ester gave after several recrystallizations from aqueous ethanol and petroleum ether pure *trans*-acid (II). In the case of active esters no

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[6] B. Ackerman, R. M. Chladek and D. Swern, *J. Amer. Chem. Soc.* **79**, 6524 (1957).
[7] G. M. Kosolapoff and J. S. Powel, *J. Amer. Chem. Soc.* **72**, 4198 (1950).
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TABLE 1

$(EtO)_2P(O)CH(CH_3)CO_2R$	b.p. °C/mm	$[\alpha]_D$	Yield, %
Ia Ethyl	102·5–103/2		64
Ib (−) Menthyl	166–8/2, 173/3	−50·9° (EtOH)	48·5
Ic (−) 2-Octyl	127–8/1·5	− 6·8° (neat, 1 dm)	85
Id (+) 2-Octyl	126–8/1·5	+ 7·1° (neat, 1 dm)	72
Ie (−) Bornyl	141–3/1	−32·5° (EtOH)	56

optical purity: *c* 67, *d* 72, *b* and *e* 100%

effort has been made to isolate pure isomers of II to avoid the possibility of causing partial resolution either by partial saponification[9] or even by recrystallization (Experimental). Thus $[\alpha]_D$ values given in Table 2 refer to crude reaction products.

TABLE 2

I	Styrene oxide α_D (neat, 1 dm)	Solvent	II (R = H) $[\alpha]_D$	Yield %
a	+15·44°*	B	+58°	69
a	−15·53°*	DME	−52·5°	58
b	0	DME	+ 9·2°	42
b	0	B	+ 8·5°	38
c	0	THF	− 0·70°	32
c	0	B	− 0·64°	35
d	0	THF	+ 0·45°	30
e	0	B	+ 4·60°	53

* optical purity: ca. 49%

As seen from Table 2, the sign of rotation of the acids (II) prepared by partial asymmetric synthesis from inactive styrene oxide, does not show a consequent dependence upon the configuration of L, M, S groups of the asymmetric moiety of the phosphonopropionates (Ib, Ic, Ie) containing asymmetric alkyl groups in which the steric pattern of the L, M, S substituents are identical and give II (R = H) a different sign of rotation. In order to eliminate the uncertainty caused by the possible isomers of the acid (II) the carboxyl group was transformed by the conventional method to methyl group.

On the basis of the known reaction mechanism,[1,2,10] the absolute configuration of 2-phenyl-1, 1-dimethylcyclopropane is in accordance with formula IV.

The same transformation was carried out with IIb and IIe resulting in each case in (−)-IV of low optical rotatory power.

In the reaction of phosphonoacetates[1,11] with styrene oxide, (+)*trans*-2-phenylcyclopropanecarboxylic acid having opposite configuration on C-2 as compared to

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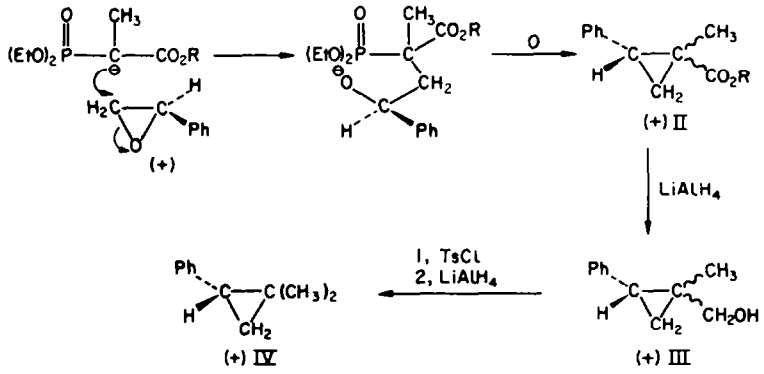

(−)-IV is preferentially formed.[12] This is assumed to be due to a difference in the configuration[13] of the carbanion in phosphonoacetates and phosphonopropionates.

TABLE 3. $[\alpha]_D$ VALUES

	(+)-*a* Series	(−)-*a* Series	*b* Series		*e* Series
II	+58°	−52·5°	+9·2°	+8·5°	+4·6°
III	+ 4·5°	− 4·1°	−0·64°	−0·60°	−0·25°
IV	+ 4·05°	− 3·9°	−0·72°	−0·75°	−0·28°

EXPERIMENTAL

Triethyl α-phosphonopropionate. A mixture of 33·2 g (0·2 mole) triethyl phosphite and 38 g (0·21 mole) ethyl α-bromopropionate was heated in a flask provided with a short fractionating column and a thermometer immersed in the reaction mixture. A slightly exothermic reaction set in at 130–140° and EtBr distilled over. After maintaining the temp at 150–160° for 4–5 hr the reaction mixture was fractionally distilled *in vacuo* yielding 30·2 g (64%) triethyl α-phosphonopropionate as a colorless liquid, b.p. 102·5–103/2 mm. (Found: C, 45·81; H, 8·23. Calc. for $C_9H_{19}O_5P$: C, 45·38; H, 8·04%.) C-(−)-Menthyl-, C-(−)-2-octyl-, C-(+)-2-octyl-, C-(−)-bornyl-P,P-diethyl α-phosphonopropionate were similarly prepared from triethyl phosphite and the corresponding α-bromopropionate (Table 1).

trans-2-*Phenyl*-1-*methylcyclopropanecarboxylic acid.* To a suspension of 1·3 g (0·054 mole) NaH in 40 ml dry DME was slowly added, with stirring, 12·3 g (0·051 mole) triethyl phosphonopropionate dissolved in 20 ml DME. After the evolution of H_2 ceased, the slightly opalescent mixture was warmed to 45–50° and treated with 6·1 g (0·051 mole) styrene oxide dissolved in 10 ml DME. The mixture was warmed to 70–75° and maintained at this temp for 5 hr and then left overnight. Most of the solvent was removed *in vacuo* and the residue treated with 200 ml water, extracted with ether, dried ($MgSO_4$), filtered and the solvent evaporated leaving a liquid (9·7 g) which was saponified by refluxing for 10 hr with a solution of 4 g NaOH in 20 ml water and 60 ml EtOH. The EtOH was evaporated under red. press., the residue diluted with water to dissolve the precipitated material and extracted with ether to remove any non-acidic contamination. The aqueous solution was then carefully acidified with dil. HCl aq. The oil which separated readily crystallized after short standing. The crystals were filtered with suction and recrystallized from aqueous EtOH to give 5·2 g (58%) 2-phenyl-1-methylcyclopropanecarboxylic acid, m.p. 78–81·5°; recrystallization from pet. ether (b.p. 40–60) yielded 4·4 g pure *trans*-2-phenyl-1-methylcyclopropanecarboxylic acid, m.p. 81·5–83° (reported[9] m.p. 81–83° and[14] 79–80°). (Found: C, 75·14; H, 6·79; Calc. for $C_{11}H_{12}O_2$: C, 74·97; H, 6·86%.) The amide, prepared *via* the acid chloride, had m.p. 201–202° (reported[9] m.p. for the *trans*-isomer 200–202° and[14] 200·5°).

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[13] A. J. Speziale and K. W. Ratts, *J. Amer. Chem. Soc.* **85**, 2790 (1963).
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(+)-2-*Phenyl*-1-*methylcyclopropanecarbocylic acid.* The condensation was carried out as above, but the styrene oxide, prepared from (−)-mandelic acid[1], was optically active, α_D +15·44° (neat, 1 dm). Saponification of the crude ester gave the acid II in 69% yield, $[\alpha]_D$ +58° (c = 2 in EtOH).

(−)-2-*Phenyl*-1-*methylcyclopropanecarboxylic acid* was similarly prepared from styrene oxide, α_D −15·53° (neat, 1 dm) and triethyl α-phosphonopropionate. Saponification of the crude ester gave the acid II in 58% yield, $[\alpha]_D$ −52·5° (c = 3·11 in EtOH).

Partial asymmetric synthesis of 2-*phenyl*-1-*methylcyclopropanecarboxylic acid.* A typical experiment is as follows. Into a slurry of 2·5 g NaH (50% suspension in mineral oil) in 40 ml dry DME was added dropwise and under continuous stirring 17 g (0·0488 mole) C-(−)-menthyl-P,P-diethyl α-phosphonopropionate dissolved in 20 ml DME. After the evolution of H_2 ceased, the mixture was stirred for a further 30 min, warmed to 50° and treated with 5·8 g (0·0483 mole) racemic styrene oxide dissolved in 10 ml DME. The mixture was warmed to 65–70°, maintained at this temp for 5–6 hr, and allowed to stand overnight. Most of the solvent was removed under red. press., the residue treated with 200 ml water, extracted with ether and dried over $MgSO_4$. The solvent was evaporated and the residue taken up in 100 ml EtOH, then 5 g KOH dissolved in 30 ml water was introduced and the mixture refluxed for 10 hr. EtOH was completely removed under red. press., the residual solution diluted with water and thoroughly extracted with ether. The aqueous solution was acidified with HCl, extracted with ether, dried and concentrated to give an oil, 3·66 g (42%) which crystallized on standing, m.p. 70–83°, $[\alpha]_D$ +9·2° (c = 4·462 in EtOH). Recrystallization from aqueous EtOH (1:1) caused partial resolution a lower rotating mixture separating first, 2·1 g, $[\alpha]_D$ +4·6° (c, = 3·852 in EtOH), m.p. 81–83°. (Found: C, 74·93; H, 6·83; Calc. for $C_{11}H_{12}O_2$: C, 74·97; H, 6·86%.) Dilution of the warmed mother liquor with about equal volume of water gave a second crop of acid II, 1·1 g, $[\alpha]_D$ +17° (c = 2·582 in EtOH) m.p. 79–82°. (Found: C, 75·21; H, 6·95; Calc. for $C_{11}H_{12}O_2$: C, 74·97; H, 6·86%.)

trans-2-*Phenyl*-1-*methylcyclopropylcarbinol.* To a suspension of 1·1 g (0·029 mole) LAH in 100 ml dry ether was slowly added with stirring at room temp 3·6986 g (0·021 mole) *trans*-2-phenyl-1-methylcyclopropanecarboxylic acid dissolved in 75 ml dry ether. After addition was complete, the mixture was stirred for 1½ hr at room temp and then 3 hr at gentle reflux. The mixture was then cooled in ice-water and hydrolysed with dil H_2SO_4. The layers were separated, the ethereal solution was successively washed with water, 2N NaOH, water, and dried over $MgSO_4$. Evaporation of the solvent left an oil, 3·1192 g, which was fractionally distilled *in vacuo* to give the carbinol, 2·811 g, b.p. 85–87°/0·5 mm; its *p*-nitrobenzoate prepared *via* the acid chloride and recrystallized from EtOH, had m.p. 114·5–115·5°. (Found: C, 69·64; H, 5·82; $C_{18}H_{17}O_4N$ requires: C, 69·44; H, 5·50%.)

2-*Phenyl*-1,1-*dimethylcyclopropane.* An ice-cold solution of 3·1192 g (0·0192 mole) *trans*-2-phenyl-1-methylcyclopropylcarbinol in dry pyridine (20 ml) was treated portionwise with 3·9152 g (0·0205 mole) toluene-*p*-sulphonyl chloride. The mixture was let to stand in a refrigerator (4°) for 48 hr then poured into a mixture of ether (100 ml), crushed ice (200 g) and HCl (25 ml), shaken several times and separated. The ethereal solution was dried over Drierite, allowed to stand in a refrigerator for several days, then filtered still cold and added into a stirred suspension of 1 g (0·0255 mole) LAH in 50 ml dry ether. After 3 hr stirring at room temp the mixture was heated to the b.p. and refluxed for further 3 hr. After the usual working up the ethereal solution was washed successively with water, HCl, NaOH aq, water and dried. Evaporation of the solvent gave a clear liquid which distilled at 100–105°/16 mm (reported[15] b.p. 130°/40 mm), and showed an IR spectrum consistent[15] with the structure of phenyldimethylcyclopropane. (Found: C, 89·97; H, 9·65; Calc. for $C_{11}H_{14}$: C, 90·35; H, 9·65%.) Optically active 2-phenyl-1,1-dimethylcyclopropanes were similarly prepared from the active carbinols. The results are summarized in Table 3. Attempts to isolate 2-phenyl-1-methylcyclopropylcarbinyl tosylate or brosylate were unsuccessful resulting in deeply coloured decomposition products.

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