Stereochemistry of Nucleophilic Substitution of Menthyl Derivatives with Anion of Diphenylphosphine Oxide by an Action of Sodium Dihydridobis(2-methoxyethanolato)aluminate

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Synopsis. The reaction of an anion of diphenylphosphine oxide prepared by the action of sodium dihydridobis(2-methoxyethanolato)aluminate on the oxide with various menthyl or neomenthyl halides and sulfonates were studied to clarify the sterochemistry of the substitution. The reaction gave neomenthyl- and methyl-diphenylphosphine oxide in ratios from 100 : 0 to 0 : 100.

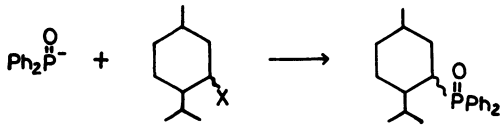
In a sequence of reactions to synthesize phosphorus-sugars, that have a phosphorus atom in the hemiacetal ring instead of an oxygen atom, the formation of a phosphorus-carbon bond was the key step. Some addition reactions of phosphorus compounds to C=C, C=N, or C=O double bond have been used to prepare a phosphorus-carbon bond on a sugar skeleton, and the process afforded usually a couple of the stereoisomeric products.[1-3] Therefore stereospecific reactions should be much more desirable for the preparation of phosphorus-carbon bond.

Preparation of phosphide anions by an action of sodium dihydridobis(2-methoxyethanolato)aluminate (SDMA) and the reaction of the anion with alkyl halides have been reported.[4,5] Stereochemistry of nucleophilic substitution reaction of metal phosphide was reported,[6] however, no report has been published concerning that of phosphorus anion prepared by SDMA from a phosphorus compound with alkyl halides or sulfonates. This note deals with the stereochemistry of nucleophilic substitution of an anion prepared by the reaction of diphenylphosphine oxide with SDMA together with the properties of leaving groups of menthyl derivatives.

Results and Discussion

The reaction of diphenylphosphine oxide with SDMA gave the phosphide anion at 0 °C. The reaction of the anion with various types of alkyl halides or *p*-toluenesulfonates gave alkyldiphenylphosphine oxide in good yield.[7] The reaction of several derivatives of menthol with the anion was carried out in order to investigate the stereochemistry of the nucleophilic substitution reaction.

$$Ph_2\overset{O}{\overset{\|}{P}}H \xrightarrow{SDMA} Ph_2\overset{O}{\overset{\|}{P}}^- \qquad (1)$$



(2)

X = OTs, OMs, OTf, Cl, Br, I

The reaction of the anion of diphenylphosphine oxide with menthyl chloride in tetrahydrofuran for 10 h at 65 °C gave a mixture of neomenthyl- and menthyl-diphenylphosphine oxide in a ratio of 10 : 1. The same reaction with menthyl iodide gave them in a ratio of 1 : 1. The reactions of the anion with menthyl *p*-toluenesulfonate and menthyl methanesulfonate gave

Table 1. Reaction of menthyl or neomenthyl derivatives (RX) with diphenylphosphine oxide in the presence of SDMA

RX		Solvent	Reaction temp/°C	Reaction time/h	Recovered RX/%	Yield of phosphines[a]/%	Ratio of neomenthyl- to menthyl-diphenylphosphine oxide
R	X						
Menthyl	Cl	THF	65	10	40	6	91 : 9
		THF	65	10	37	22	88 : 12[b]
		Toluene	111	16	—[c]	6[d]	86 : 14
	Br	THF	65	10	27	36	82 : 18
	I	THF	65	10	5	37	50 : 50
	OTs[e]	THF	65	5	75	25	100 : 0
		THF	65	10	25	55	99 : 1
	OMs[f]	THF	65	10	33	16	58 : 42
	OTf[g]	THF	65	10	0	26	88 : 12
Neomenthyl	Br	THF	65	10	73	6	0 : 100
		Toluene	111	32	71	10	0 : 100

a) Yields of neomenthyl- and menthyl-diphenylphosphine oxides isolated by preparative TLC. b) One equivalent of sodium iodide was added. c) Not determined. d) Isolated by liquid chromatography. e) *p*-Toluenesulfonate. f) Methanesulfonate. g) Trifluoromethanesulfonate.

the ratios of 99 : 1 and of 82 : 18, respectively. These results are summarized in Table 1.

These findings will suggest that in the reaction the anion of diphenylphosphine oxide attacked on the carbon of menthyl chloride, bromide, and *p*-toluenesulfonate mainly in an S_N2, whereas that the anion attacked on the carbon of menthyl iodide and methanesulfonate mainly in an S_N1 manner.

The lower reactivity and the higher selectivity of inversion for neomenthyl bromide than those for menthyl bromide may attribute to the presence of an assistance by equatorial isopropyl group in breaking the equatorial carbon-bromine bond in menthyl bromide, and to the absence of it in breaking the axial carbon-bromine bond in neomethyl bromide.

Experimental

Apparatus. IR spectra were measured by Hitachi-Perkin-Elmer 337 and Japan Spectroscopic Co., Ltd. JASCO A-3 spectrophotometers, UV spectra were measured by Hitachi 340 Recording Spectrophotometer, ^{1}H-NMR spectra were run on Hitachi R-20 (60 MHz) spectrometer, mass spectra were measured by Hitachi RMU DMG GC-MS spectrometer, optical rotations were determined by Japan Spectroscopic Co., Ltd. DIP-4 digital polarimeter. Liquid chromatography and high performance liquid chromatography were carried out using Toyo Scientific Industry UVICON-540M and Japan Spectroscopic Co., Ltd. UNIFLOW-211, respectively.

Materials. Commercially available SDMA (70% benzene or toluene solution) was used. Menthyl chloride [bp 80.8 °C/8 mmHg,[8] $[\alpha]_D^{15}$ −47.7° (*c* 2.4, EtOH)],[9] menthyl bromide [bp 113 °C/22 mmHg, $[\alpha]_D^{28}$ −29.0° (*c* 1.22, EtOH)],[7] and menthyl *p*-toluenesulfonate [mp 93—95 °C, $[\alpha]_D^{25}$ −70.8° (*c* 1.0, $CHCl_3$)][10] were prepared from *l*-menthol.

Synthesis of Neomenthyl Bromide. Bromination of *l*-menthol (3.1 g) was performed by a treatment of lithium bromide (3.5 g) and chlorotrimethylsilane (5.4 g) in 40 ml of acetonitrile for 20 h under reflux. Extraction of the reaction mixture with ether followed by work-up and evaporation *in vacuo* gave neomenthyl bromide in 72% yield, bp 91 °C/7 mmHg, mp 37—40 °C, $[\alpha]_D^{15}$ −49.8° (*c* 1.04, EtOH). ^{1}H-NMR ($CDCl_3$), δ 0.78 (d, 3H, J=8.0 Hz, CH_3), 0.20—2.55 (m, 15H, C_8H_{15}), and 3.10—3.62 (m, 1H, CHBr).

Iodination of l-*Menthol.* Iodination of *l*-menthol by sodium iodide and chlorotrimethylsilane as described above gave neomenthyl iodide in 40% yield, bp 50 °C/7 mmHg, $[\alpha]_D^{15}$ 0.48° (*c* 1.1, EtOH), ^{1}H-NMR ($CDCl_3$) δ 1.01 [d, 6H, J=4.3 Hz, $CH(C\underline{H}_3)_2$], 0.30—2.77 (m, 12H, C_7H_{12}), and 4.65—5.47 (m, 1H, CHI), and menthyl iodide in 46% yield, bp 93 °C/7 mmHg, $[\alpha]_D^{15}$ −0.58° (*c* 1.0, EtOH), ^{1}H-NMR ($CDCl_3$) δ 0.88 (d, 3H, J=3.8 Hz, CH_3), 0.26—2.85 (m, 9H, C_6H_9), and 3.78—5.39 (m, 1H, CHI).

Synthesis of Menthyl Methanesulfonate. Methanesulfonyl chloride (5.7 g) in pyridine was added to a pyridine solution of *l*-menthol (7.8 g). The work-up of chloroform solution of the product followed by sublimation gave the methanesulfonate in 77% yield, mp 32—36 °C, $[\alpha]_D^{15}$ −63.5° (*c* 1.0, EtOH). ^{1}H-NMR ($CDCl_3$) δ 0.77 (d, 3H, J=3.0 Hz, CH_3), 0.93 (d, 6H, J=7.3 Hz, $CH(C\underline{H}_3)_2$), 2.99 (s, 3H, CH_3SO_2), 0.25—3.64 (m, 9H, C_6H_9), and 4.28—4.88 (m, 1H, CH–O).

Synthesis of Menthyl Trifluoromethanesulfonate. The trifluoromethanesulfonate was prepared by *l*-menthol and trifluoromethanesulfonic anhydride in 32% yield, $[\alpha]_D^{15}$ −6.3° (*c* 1.2, EtOH).

Reaction of Menthyl Derivatives with Diphenylphosphine Oxide in the Presence of SDMA. To a solution of a mixture of diphenylphosphine oxide (1.5 mmol) and SDMA (3.5 mmol) menthyl derivatives (1.5 mmol) were added, and then the solution was allowed to react for several hours. The work-up (addition of water and activated carbon to the reaction mixture followed by filtration, extraction with chloroform, dehydration, and evaporation of the solvent *in vacuo*) of the reaction mixture followed by analysis of the product by HPLC, spectra, and optical rotation revealed that the product consisted of neomenthyldiphenylphosphine oxide and menthyldiphenylphosphine oxide in various ratios. The reaction condition, recovered starting materials, and isolated yields and ratios of the produced phosphine oxides were summarized in Table 1.

Neomenthyldiphenylphosphine oxide showed spectra as follows: ^{1}H-NMR ($CDCl_3$), δ 0.25—3.05 (m, 19H, Me, CH-$(CH_3)_2$, and ring protons) and 7.01—8.02 (m, 10H, 2×Ph); MS, 340 (M^+) and 201 [$P(O)Ph_2$]; IR ν_{max}^{KBr} 1440 (P–Ph), 1193 (P=O), and 720 cm^{-1} (P–C). Menthyldiphenylphosphine oxide showed the similar spectra. HPLC with JASCO SS-05 column eluted by chloroform–hexane (1 : 1) under 100 kg/cm^2 pressure showed peaks of menthyldiphenylphosphine oxide at 15.6 min and of neomenthyldiphenylphosphine oxide at 23.6 min, which were detected by JASCO UVIDEC-100 II UV detector at a wave length of 260.4 nm.

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References

1) H. Takayanagi, M. Yamashita, K. Seo, H. Yoshida, T. Ogata, and S. Inokawa, *Carbohydr. Res.*, **38**, C19 (1974).

2) M. Yamashita, Y. Nakatsukasa, M. Yoshikane, H. Yoshida, T. Ogata, and S. Inokawa, *Carbohydr. Res.*, **59**, C12 (1977).

3) P. T. Long, M. Yamashita, and S. Inokawa, *Carbohydr. Res.*, **76**, C4 (1979).

4) R. B. Wetzel and G. L. Kenyon, *J. Am. Chem. Soc.*, **94**, 1774 (1972).

5) R. B. Wetzel and G. L. Kenyon, *J. Org. Chem.*, **39**, 1531 (1974).

6) J. D. Morrison and W. F. Masler, *J. Org. Chem.*, **39**, 270 (1974).

7) M. Yamashita, N. Suzuki, M. Yamada, Y. Soeda, H. Yamashita, K. Nakatani, T. Oshikawa, and S. Inokawa, *Bull. Chem. Soc. Jpn.*, **56**, 219 (1983).

8) 1 mmHg=133.322 Pa.

9) R. B. King, J. Bakos, C. D. Hoff, and L. Markó, *J. Org. Chem.*, **44**, 3095 (1979).

10) H. Phillips, *J. Chem. Soc.*, **127**, 2566 (1925).