afforded 20 g. (84%) of di-*n*-amylaminodichloroborane, b.p. 121°/10 mm.

Anal. Calcd. for $(C_5H_{11})_2N—BCl_2$: C, 50.4; H, 9.3; B, 4.55; N, 5.9; Cl, 29.85. Found: C, 50.6; H, 9.2; B, 4.4; N, 5.9; Cl, 29.5. The reaction of this product with *n*-amyl Grignard reagent[6] resulted in the formation of the tetra-alkylated aminoborane, identical with the one described above.

Di-n-amylmethoxyborane. In a dry nitrogen atmosphere, 18.9 g. (0.1 mole) of di-*n*-amylchloroborane was added with stirring to 125 cc. of pure anhydrous methanol. The reaction mixture was slowly concentrated at room temperature *in vacuo* and the residue distilled, yielding 14.5 g. (78%) of di-*n*-amylmethoxyborane, b.p. 114–116°/8 mm.

Anal. Calcd. for $(C_5H_{11})_2BOCH_3$: C, 71.7; H, 13.7; B, 5.9. Found: C, 73.9; H, 13.7; B, 6.1.

n-Amyldihydroxyborane. Water was added dropwise to 9.2 g. (0.05 mole) of di-*n*-amylmethoxyborane in a beaker. The resultant exothermic reaction afforded 5.4 g. (93%) of white crystals of *n*-amyldihydroxyborane,[7] m.p. after recrystallization from ligroin, 92–93°. The elementary analysis corresponded to the dihydroxyborane. However, molecular weight determinations (cryoscopically in benzene) gave a value of 295, indicating the existence of a dehydrated trimeric product (calcd. for $(C_5H_{11}BO)_3$: 293.9) and illustrating the ready dehydration of an alkyldihydroxyborane.

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Synthesis and Properties of Isomeric Menthyl Phosphates.[1] Organophosphorus Compounds. III[2]

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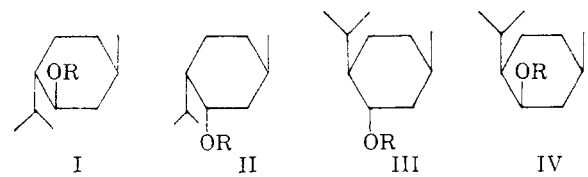
The synthesis of menthyl dihydrogen phosphate (Ib) has been reported by Milobedzki and Janczak[3] by phosphorylating (−)-menthol with phosphorus oxychloride. The same phosphate was also isolated from a reaction mixture of (−)-menthol and phosphorus pentachloride.[4] However the other isomeric menthyl phosphates have not yet been synthesized. We have synthesized the isomeric menthyl phosphates by an unequivocal method to obtain the reference compounds for the study of terpene biosynthesis. Here the syntheses and some of the properties of the phosphates are described.

Isomeric menthols employed as the starting compounds were (−)-menthol (I), (+)-neomenthol (II), (+)-isomenthol (III), and (+)-neoisomenthol (IV), and the phosphorylating agent was tetra-(*p*-nitrophenyl)pyrophosphate which was prepared by the reaction of bis(*p*-tolyl)carbodiimide with two equivalents of bis(*p*-nitrophenyl)phosphate in dioxane as described by Khorana.[5,6] Tetra(*p*-nitrophenyl)pyrophosphate was allowed to react with I, II, III, and IV in dioxane. After a reaction for approximately forty hours at room temperature, the bis(*p*-nitrophenyl)phosphates of the isomeric menthols (Ia, IIa, IIIa, and IVa) were obtained in fair yields. Among these isomeric menthyl bis(*p*-nitrophenyl)phosphates, neo- (IIa) and neoisomenthyl bis(*p*-nitrophenyl)phosphate (IVa) were unstable in polar solvents—*i.e.* they liberated bis(*p*-nitrophenyl)phosphate group on leaving the methanol solution at room temperature.



I II III IV

I, II, III, and IV. R = H.
Ia, IIa, IIIa, and IVa. R = $—PO(OC_6H_4NO_2)_2$.
Ib, IIb, IIIb, and IVb. R = $—PO_3H_2$.
Ic. R = $—PO(OC_6H_4NO_2)OH$.

On the hydrogenation over Adams' platinum catalyst, Ia, IIa, IIIa and IVa were hydrogenolyzed to the corresponding menthyl dihydrogen phosphates, (Ib), (IIb), (IIIb), and (IVb), liberating cyclohexylamine as the hydrochloride. In this case, the addition of hydrochloric acid was necessary for smooth absorption of fourteen moles of hydrogen. If the acid was not added, the absorption of hydrogen ceased at ten moles. The necessity for the addition of acid was also pointed out by Mofatt and Khorana,[5] but the isolation of cyclohexylamine salt was not described. The role of acid may be the detoxication of toxic free amine by converting it to nontoxic ammonium ion as observed in the hydrogenation of aromatic amines.[7]

The hydrolysis of Ia with 1*N* sodium hydroxide in dioxane solution yielded menthyl mono(*p*-nitrophenyl)phosphate (Ic), liberating quantitatively one of the two *p*-nitrophenyl groups which could be determined spectrophotometrically. The solubilities of isomeric dihydrogen phosphates in water, either in the free state or as the salts, were low. Melting points of the phosphates are summarized in Table I.

(1) Presented at the 153th meeting of the Kansai Section of the Agricultural Chemical Society of Japan, Kyoto, October 18, 1958.

(2) For a previous paper in this series, see T. Hashizume, K. Fujimoto, H. Unuma, K. Takinami, and K. Morimoto, *Bull. Inst. Chem. Res. Kyoto Univ.*, **38**, 70 (1960).

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TABLE I

MELTING POINTS OF ISOMERIC MENTHYL PHOSPHATES

	Series a[a]	Series b[b]	Series c[c]	Salt[d]
Menthyl	57–58	133–134[e]	123–124	224–225
Neomenthyl	93–94	65–70	—	232–233
Isomenthyl	91–92	Sirup	—	225–226
Neoisomenthyl	Sirup	Sirup	—	232–233

[a] Bis(*p*-nitrophenyl)phosphates. [b] Dihydrogen phosphates. [c] Mono(*p*-nitrophenyl)phosphates. [d] Bis(cyclohexylammonium) salts of dihydrogen phosphates. [e] Melting point of anhydrous state (lit., m.p. 124.5°[3]); monohydrate, m.p. 82–84° (lit., m.p. 82.5°[3], 84°[4]).

EXPERIMENTAL[8]

(−)-*Menthol* (I) was purified from a commercial product, m.p. 42–43°, $[\alpha]_D$ −47° (*c*, 4 in methanol). *3,5-Dinitrobenzoate*, m.p. 154–155° (lit., m.p. 154°[9]).

(+)-*Neomenthol* (II) was prepared from (+)-menthofuran,[10] b.p. 102° (19 mm.), $[\alpha]_D$ +22° (*c*, 4 in methanol). *3,5-Dinitrobenzoate*, m.p. 154–155° (lit., m.p. 154° [9]).

(+)-*Isomenthol* (III),[11] m.p. 82–83°, $[\alpha]_D$ +27° (*c*, 4 in benzene). *3,5-Dinitrobenzoate*, m.p. 146° (lit., m.p. 147° [9]).

(+)-*Neoisomenthol* (*IV*) was prepared from (+)-menthofuran,[10] b.p. 105° (12 mm.), $[\alpha]_D$ +1° (homogeneous). *3,5-Dinitrobenzoate*, m.p. 99–100° (lit., m.p. 101° [9]).

Bis(p-nitrophenyl)phosphate was prepared by the methods reported previously,[2,12] m.p. 176.6–177.4°.

Anal. Calcd. for $C_{12}H_9O_8N_2P$: C, 42.40; H, 2.67; N, 8.28; P, 9.10. Found: C, 42.53; H, 2.80; N, 8.10; P, 8.89.

Menthyl bis(p-nitrophenyl)phosphate (Ia) general procedure of the phosphorylation). Bis(*p*-nitrophenyl)phosphate (7.48 g., 0.022 mole) was dissolved in warm anhydrous dioxane (50 ml.). The solution was cooled rapidly to room temperature, and to this solution was added *N,N'*-bis(*p*-tolyl)carbodiimide[13] (2.44 g., 0.011 mole). Bis(*p*-tolyl)urea was instantly formed and suspended in the solution of resulting tetra(*p*-nitrophenyl)pyrophosphate. To this mixture, without removing the bis(*p*-tolyl)urea, (−)-menthol (I) (1.56 g., 0.01 mole) (I) (1.56 g., 0.01 mole) was added and the reaction mixture was shaken for 40 hr. at room temperature. Bis(*p*-tolyl)urea was removed by filtration and the filtrat was concenterated at about 40° under reduced pressure. The solid residue was extracted thrice with chloroform and the chloroform extract was washed repeatedly with water to remove the acidic bis(*p*-nitrophenyl)phosphate. The neutral chloroform layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The syrup which remained was recrystallized from methanol to give slightly pale yellow crystals, yield: 2.82 g. (59%), m.p. 57–58°, $[\alpha]_D$ +20° (*c*, 2 in chloroform).

Anal. Calcd. for $C_{22}H_{27}O_8N_2P$: C, 55.23; H, 5.69; N, 5.86; P, 6.48. Found: C, 55.48; H, 5.79; N, 6.08; P, 6.58.

Neomenthyl bis(p-nitrophenyl)phosphate (IIa) formed pale yellow needles, yield: 21%, m.p. 93–94°.

Anal. Found: C, 55.18; H, 5.81; N, 5.84; P, 6.63.

Isomenthyl bis(p-nitrophenyl)phosphate (IIIa) formed pale yellow needles, yield: 47%, m.p. 91–92°, $[\alpha]_D$ +9° (*c*, 1 in chloroform).

Anal. Found: C, 55.52; H, 5.68; N, 5.90; P, 6.31.

Neoisomenthyl bis(p-nitrophenyl)phosphate (IVa) was a syrup and not obtained in a pure state; crude yield, 4.30 g. from 1.56 g. of IV. Recrystallization of this crude phosphate from methanol caused the liberation of bis(*p*-nitrophenyl)-phosphate which was isolated, recrystallized from ethyl acetate and identified on admixture with the authentic specimen. Therefore this crude phosphate was used without further purification for the subsequent catalytic hydrogenation.

Menthyl dihydrogen phosphate (Ib) (*general procedure of the catalytic hydrogenation*). A solution of Ia (500 mg.) in ethanol (100 ml.) containing concentrated hydrochloric acid (0.5 ml.) was hydrogenated over Adams' catalyst (100 mg.). During 4 hr., hydrogen (346 ml., measured at 19°) corresponding to 14 moles was smoothly absorbed. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was extracted with water. The sirup which remained was recrystallized from water to give Ib; yield, 253 mg. (95%), m.p. 82–84°. This was the monohydrate and transformed into the anhydrous state by drying over anhydrous phosphoric acid, m.p. 133–134°, recrystallized from benzene.

Anal. Calcd. for $C_{10}H_{21}O_4P$: P, 13.11. Found: P, 12.81.

Bis(cyclohexylammonium)salt, m.p. 224–225° dec. $[\alpha]_D$ −48° (*c*, 2 in methanol) was recrystallized from ethanol.

Anal. Calcd. for $C_{22}H_{47}O_4N_2P$: N, 6.45; P, 7.13. Found: N, 6.47; P, 7.17.

The above water extract was concentrated under reduced pressure. The residue was dried and recrystallized from an ether-ethanol mixture to give cyclohexylammonium chloride; yield, 264 mg. (93%), m.p. 205° undepressed on admixture with the authentic specimen.

Neomenthyl dihydrogen phosphate (IIb), yield: 73%, m.p. 65–70°. *Bis(cyclohexylammonium)salt*, m.p. 232–233° dec.

Anal. Found: P, 7.30.

Isomenthyl dihydrogen phosphate (IIIb), a syrup, yield: 95%. *Bis(cyclohexylammonium)salt*, m.p. 225–226° dec.

Anal. Found: N, 6.74; P, 7.33.

Neoisomenthyl dihydrogen phosphate (IVb). Crude IVa (85% purity, calculated from the absorption of hydrogen) (1.00 g.) yielded bis(cyclohexylammonium) salt of IVb; yield, 490 mg., m.p. 232–233° dec. $[\alpha]_D$ ±0 (*c*, 1 in methanol).

Anal. Found: N, 6.60; P, 7.34.

Hydrolysis of menthyl bis(p-nitrophenyl)phosphate (Ia). a). *Determination of liberated p-nitrophenol.* To a solution of Ia (9.812 mg.) in dioxane (5 ml.) was added 1*N* sodium hydroxide (2 ml.) resulting in a yellow coloration. Aliquots (0.3 ml.) of this reaction mixture were successively poured into a solution of dioxane-borate buffer (1:1 v/v, *p*H 8.6) (10 ml.) and those absorbances were measured spectrophotometrically at 440 mμ. A constant absorbance (0.625) was attained after 45 min. at room temperature, corresponding to the liberation of 1 mole of *p*-nitrophenol (calcd. absorbance = 0.623).

b). *Menthyl mono(p-nitrophenyl)phosphate* (Ic). Into a solution of Ia (500 mg.) in dioxane (50 ml.) was added 1*N* sodium hydroxide (30 ml.). This reaction mixture was shaken for 2 hr. at room temperature, then neutralized with 1*N* hydrochloric acid, concentrated to a few milliliters under reduced pressure, and finally acidified with concentrated hydrochloric acid to give a pasty precipitate. This precipitate was washed with water by decantation, dried and recrystallized from *n*-hexane-benzene to give colorless needles; yield, 310 mg. (83%), m.p. 123–124°, $[\alpha]_D$ −58° (*c*, 1 in chloroform).

(8) All melting and boiling points were uncorrected. Analyses were undertaken by the Microchemical Laboratory, Department of Agricultural Chemistry, Kyoto University, and by Mr. Kurihara, the Institute of Infectious Diseases, Tokyo University.

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(13) The compound was freshly synthesized before use from N,N'-bis-(*p*-tolyl)thiourea.[12]

Anal. Calcd. for $C_{16}H_{24}O_6NP$: C, 53.69; H, 6.75; P, 8.67. Found: C, 53.47; H, 7.06; P, 8.68.

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Organic Phosphorus Compounds. VII.[1] The Preparation of Methylphosphonic Chlorofluoride

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For a study of preparative methods for isopropyl methylphosphonofluoridate, Sarin, a sample of the previously unknown methylphosphonic chlorofluoride, $CH_3P(O)ClF$ (I), was required. Although the complete replacement of chlorine by fluorine in methylphosphonic dichloride (II) by means of anhydrous hydrogen fluoride proceeds readily with the formation of methylphosphonic difluoride (III),[3] all attempts to replace only one of the chlorine atoms in II by fluorine under a variety of conditions were unsuccessful. The resulting reaction product yielded in all cases by distillation only II and III in varying ratios depending on the molar ratio of II to hydrogen fluoride employed. The desired I was obtained, however, from methylphosphonofluoridic acid, $CH_3P(O)(F)OH$ (IV), which gave the desired I by treatment with thionyl chloride.

While the hydrolysis of Sarin and of its chlorine analog, $CH_3P(O)(Cl)OCH(CH_3)_2$, proceeds with the formation of isopropyl methylphosphonate, $CH_3P(O)(OH)OCH(CH_3)_2$, IV was obtained readily by the thermal decomposition of Sarin at its boiling point by elimination of propene. Treatment of IV with refluxing thionyl chloride and subsequent fractionation of the reaction mixture yielded I as a relatively stable compound boiling at 126.0–126.5° under atmospheric pressure.

One of the fluorine atoms of III can be estimated as fluoride ion by the method of Sass *et al.*[4] while the P-to-F bond of I is stable under the conditions of this method. It is thus possible to determine III in the presence of I. The presence of small amounts of fluorine which can be detected as fluoride ion, even in carefully fractionated I, indicates that under the conditions of the distillation disproportionation of the I occurs to a small extent. A fractionated sample of I containing 0.83% fluoride ion, corresponding to 4.37% III, was found to undergo a slow disproportionation reaction at 60° with a further increase of 6.74% in the III content during a period of seventy hours.

EXPERIMENTAL

Thermal decomposition of isopropyl methylphosphonofluoridate. Isopropyl methylphosphonofluoridate[5] (46.7 g., 0.33 mole) in a 100-cc. round bottom flask, equipped with a reflux condenser and an attached Dry Ice–acetone trap, was immersed in an oil bath at 160–165°. After an induction period of about 30 min., the decomposition of I began with the evolution of a gas. During the decomposition the pot temperature dropped to 141° and remained steady until the gas evolution ceased after a total heating period of 50 min. The condensate in the attached cold trap consisted of 14.1 g. propene (14.03 g. corresponds to a quantitative yield) which was identified by its conversion to 1,2-dibromopropane, b.p. 139–140°; lit.,[6] b.p. 140.7–140.8°/740 mm. Hg.

After the removal of a small forerun at 30–33°/5 mm., distillation of the viscous oily pot residue (31.0 g.) of crude IV under reduced pressure gave the bulk of the methylphosphonofluoridic acid IV as a colorless oily liquid, b.p. 69–72°/2 mm.

Anal. Calcd. for CH_4PFO_2: P, 31,61; total F, 19.38. Found: P, 31.46; total F, 20.28.

A small amount of solid distillation residue was recrystallized from a 1:5 mixture of absolute ethanol and acetone to yield methylphosphonic acid, m. 105°; lit.[7], m.p. 105°.

Preparation of methylphosphonic chlorofluoride (I). Crude, undistilled IV (438.5 g.) from the thermal decomposition of Sarin was mixed in a 2-l. round bottom flask with 500 g. thionyl chloride, and the mixture refluxed for 6 hr. until the pot temperature rose to 80°. An additional 50 g. of thionyl chloride was then added, and the mixture heated for another 3 hr. during which the pot temperature finally reached 127°. Distillation of the crude reaction mixture through a 15-cm. column packed with glass helices at 68 mm. pressure yielded 389 g. of crude chlorofluoride I boiling at 52–67°. The product was redistilled through a 30-cm. helix-packed column to give 240 g. of a constant boiling fraction at 41°/30 mm. containing 1.77% of ionic fluorine. On the basis of the fluoride ion analysis, the chlorofluoride contained 9.3% of methylphosphonic difluoride.

The distilled I (230 g.) was solidified by cooling with a Dry Ice–acetone bath and then slowly thawed. The portion which was liquid at −23° was filtered from the crystal sludge, and the part of the filter residue melting at −23 to −19° separated by filtration. The residue melting above −19° was discarded. Estimation of fluoride ion in the fraction melting at −23 to −19° showed a content of 1.56% fluoride ion. Since further fractional crystallization did not lower the difluoride content markedly, 190 g. of recrystallized product was redistilled through a 30-cm. helix-packed column to yield 127 g. of distillate, b.p. 34–35°/14 mm. The fluoride ion content of 0.5% in this batch of I corresponded to 2.7% methylphosphonic difluoride.

A sample of I prepared as described above, but purified only by repeated distillation under reduced pressure was analyzed.

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