312. *The Preparation and Physical Properties of Isopropyl Methylphosphonofluoridate (Sarin).*

By P. J. R. Bryant, (the late) A. H. Ford-Moore, B. J. Perry, A. W. H. Wardrop, and T. F. Watkins.

The preparation of pure isopropyl methylphosphonofluoridate (Sarin) is described, together with certain of its physical properties.

One of the most potent anticholinesterases[1] is isopropyl methylphosphonofluoridate[2] (III). Of the various methods for its preparation[2b,3] some were found to be tedious or to give impure products. The present communication deals with two satisfactory processes.

In the first, di-isopropyl methylphosphonate[4] (I) with carbonyl chloride yielded isopropyl methylphosphonochloridate (II), which was converted into Sarin (III) by sodium fluoride in a hot inert diluent:

$$\underset{\text{(I)}}{\mathrm{Me{\cdot}PO(OPr^i)_2}} \longrightarrow \underset{\text{(II)}}{\mathrm{Me{\cdot}POCl{\cdot}OPr^i}} \longrightarrow \underset{\text{(III)}}{\mathrm{Me{\cdot}POF{\cdot}OPr^i}}$$

In the second process, propan-2-ol was treated with an equimolar mixture of methylphosphonic dichloride[5] (IV) and methylphosphonic difluoride (V) in an inert solvent:

$$\mathrm{2Pr^iOH} + \underset{\text{(IV)}}{\mathrm{Me{\cdot}POCl_2}} + \underset{\text{(V)}}{\mathrm{Me{\cdot}POF_2}} \longrightarrow \mathrm{Me{\cdot}POF{\cdot}OPr^i}$$

Methylphosphonic difluoride was readily prepared by treating the dichloride with hydrogen fluoride.

The physical properties of Sarin were determined with exhaustively purified samples. The results tabulated lead to the following relations: $d_4^t = 1{\cdot}1182 - 0{\cdot}00118t$; $n_D^t = 1{\cdot}3917 - 0{\cdot}00043t$; the surface tension, $\gamma_t = 28{\cdot}76 - 0{\cdot}113t$; $\log_{10}\eta = 705{\cdot}4/T - 2{\cdot}219$; $\log_{10}p = 8{\cdot}5916 - 2424/T$. $[R]_D^{25} = 29{\cdot}88$. $[P]_{\text{obs.}} = 290{\cdot}2$.

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[1] Davies and Green, *Adv. Enzymology*, 1958, **20**, 283.

[2] (*a*) Sartori, *Chem. Rev.*, 1957, **48**; (*b*) Saunders, " Phosphorus and Fluorine," Cambridge Univ. Press, 1957, p. 93.

[3] Bocquet, *Ann. Soc. Roy. Sci. méd. nat. Bruxelles*, 1956, **9**, 188.

[4] Ford-Moore and Perry, *Org. Synth.*, 1951, **31**, 33.

[5] Kinnear and Perren, *J.*, 1952, 3437.

Temp.	Density (g./ml.)	n_D^{25}	Surface tension (dynes/cm.)	Viscosity (10^{-2} poise)
10°	1·1064	—	—	—
15	1·1005	1·3853	—	—
20	1·0946	1·3831	26·5	1·54
25	1·0887	1·3810	25·9	1·40
30°	1·0829	1·3789	25·4	1·28
35	1·0768	—	24·8	1·17
40	1·0710	—	—	1·08

Temp.	45°	50°	55°	60°	65°	70°	75°	80°
Vapour pressure (mm.)	9·4	12·2	16·2	20·6	26·4	33·5	42·9	53·2

Certain of the toxic symptoms of phosphonofluoridates have been previously mentioned.[6] The precautions used in handling such materials are even more important in the case of Sarin.

EXPERIMENTAL

The exits of apparatus were protected by drying tubes. Glassware which had contained phosphonofluoridates was placed in 10% aqueous sodium hydroxide for at least 6 hr. before further washing.

Isopropyl Methylphosphonochloridate (II).—A stream of carbonyl chloride was passed into di-isopropyl methylphosphonate (I) (270 g.) for 10 hr. with stirring at 20—30°. The mixture was left overnight, and excess of carbonyl chloride and isopropyl chloride were removed at $\ngtr$30°. Distillation gave the phosphonochloridate, b. p. 38—40°/2 mm., n_D^{25} 1·4282 (222 g.) (Found: Cl, 22·4. Calc. for $C_4H_{10}O_2ClP$: Cl, 22·65%).

Isopropyl N-*Phenylmethylphosphonamidate.*—The phosphonochloridate (10 g.) in chloroform (30 ml.) was treated dropwise with aniline (12 g.) in chloroform (10 ml.). The mixture was refluxed for 0·5 hr., cooled, filtered, shaken with dilute hydrochloric acid and then water, dried ($CaCl_2$), and evaporated. The residue crystallised on addition of light petroleum and, recrystallised from 50% aqueous ethanol, had m. p. 90—91° (Found: C, 56·6; H, 7·55. Calc. for $C_{10}H_{16}O_2NP$: C, 56·35; H, 7·5%).

Methylphosphonic Difluoride.—Methylphosphonic dichloride was melted at about 35° and treated with dry hydrogen fluoride at such a rate that the temperature rose to 75°. Hydrogen chloride was steadily evolved. If the system was completely dry, it was possible to carry out this reaction in Pyrex glass, the supply line from the gas cylinder being Polythene tubing, with a copper dip-pipe. The product was de-gassed under reduced pressure and the residue refluxed for 0·5 hr. The difluoride was then fractionated, having b. p. 98° (yield 90%). Hydrolysable chloride was not detected in carefully purified samples.

Isopropyl Methylphosphonofluoridate.—(*a*) Crude isopropyl methylphosphonochloridate (from 50 g. of diester) was refluxed in methylene chloride (50 ml.) with sodium fluoride (22 g.) for 4 hr. with stirring. After cooling, the whole was filtered and the residue washed with methylene chloride (2 × 20 ml.). The solvent was removed under reduced pressure and the product recovered at 46°/8 mm., n_D^{25} 1·3810 (Found: C, 34·2; H, 7·15; F, 13·6. Calc. for $C_4H_{10}O_2FP$: C, 34·3; H, 7·15; F, 13·6%).

(*b*) Methylphosphonic dichloride (m. p. 33°; 66·5 g.), methylphosphonic difluoride (b. p. 98°; 50 g.), and dry methylene chloride (130 ml.) were heated to reflux temperature and the source of heat removed. Propan-2-ol (59·6 g.) was then added, with stirring, at such a rate that the solvent boiled gently. Then the mixture was refluxed for a further hour, cooled somewhat, and evaporated under slightly reduced pressure. The residue was fractionated and the product collected at 49·5°/11 mm. (85%; n_D^{25} 1·3810) (Found: C, 34·3; H, 7·3; F, 13·6%). There was a small amount (*ca.* 12 g.) of high-boiling residue from which a liquid (*ca.* 4 g.), b. p. 51°/1 mm., n_D^{25} 1·4082, was isolated. Ford-Moore and Perry[4] gave b. p. 51°/1 mm., n_D^{25} 1·4081, for di-isopropyl methylphosphonate.

Physical Constants.—Isopropyl methylphosphonofluoridate, prepared by method (*b*), was twice fractionated, at a 10 : 1 reflux ratio, through a lagged 24 in. Fenske column surmounted with a Whitmore–Lux head. Head and tail portions amounting to about 10% were separated; after the second process all three fractions showed physical properties which were identical within the limits of error.

Surface tensions were determined by the maximum bubble-pressure method, viscosities

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[6] Saunders and Stacey. *J.*, 1948, 695.

according to British Standard,[7] and vapour pressures by the method of Smith and Menzies.[8] Densities were corrected and refractive indices were determined with a calibrated Abbé refractometer. Temperatures were corrected and thermostat baths were controlled within ±0·01°.

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[7] B.S.S. 188/1937, amended Jan. 1940.

[8] Smith and Menzies, *J. Amer. Chem. Soc.*, 1910, **32**, 1412.