399. *Phosphoramidic Halides: Phosphorylating Agents Derived from Morpholine.*

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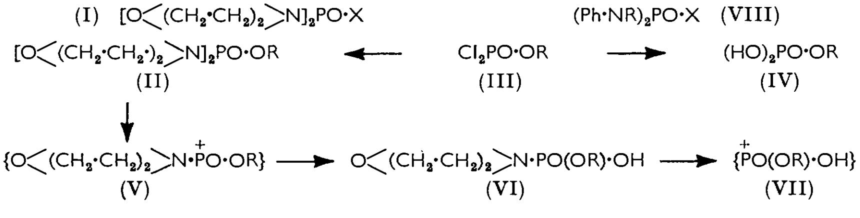
Phosphorodimorpholidic halides react with alcohols, yielding phosphoro dimorpholidates, which afford dihydrogen phosphates on mild acid hydrolysis. This method, which is particularly useful for the phosphorylation of unsaturated alcohols, has been used to synthesise ethyl, phenethyl, phenyl, *cyclo*hexyl, and the biologically important allyl and 2-(4-methyl-5-thiazolyl)-ethyl dihydrogen phosphate.

The phosphorylating properties of phosphoramidic halides may be inferred from earlier chemical studies [1] and from more recent work on the toxicity of substances of this type.[2] Attempts to utilise phosphoramidic derivatives for preparative phosphorylation, however, have hitherto met little success.[3]



We have found that phosphoramidic halides derived from morpholine are valuable reagents for the phosphorylation of alcohols.[4] Phosphorodimorpholidic bromide and chloride (I; X = Br, Cl), prepared from morpholine and the respective phosphorus

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[1] Michaelis, *Annalen*, 1903, **326**, 129; Michaelis and Schulze, *Ber.*, 1894, **27**, 2572.

[2] Saunders, " Some aspects of the chemistry and toxic action of organic compounds containing phosphorus and fluorine," Cambridge University Press, 1957, pp. 7, 87; cf. Riley, Turnbull, and Wilson, *J.*, 1957, 1373 and references cited therein.

[3] Zetzsche and Büttiker, *Ber.*, 1940, **73**, 47; Bevan, Brown, Gregory, and Malkin, *J.*, 1953, 127.

[4] Montgomery and Turnbull, *Proc. Chem. Soc.*, 1957, 178.

oxyhalide, smoothly phosphorylated alcohols in the presence of an organic base, affording the phosphorodimorpholidates [II; R = Et, $Ph{\cdot}CH_2{\cdot}CH_2$, $CH_2{:}CH{\cdot}CH_2$, $Me_2C{:}CH{\cdot}CH_2$, 2-(4-methyl-5-thiazolyl)ethyl, *cyclo*hexyl, and cholesteryl]. The morpholidic bromide phosphorylated alcohols rapidly in the cold, the less reactive chloride only on prolonged heating.

A sterically hindered tertiary base was used throughout to avoid dealkylation.[5] 2 : 6-Lutidine was generally satisfactory although tribenzylamine was preferred for the preparation of *cyclo*hexyl phosphorodimorpholidate which tended to eliminate *cyclo*hexene in the presence of other bases. Ethyl, *cyclo*hexyl, and cholesteryl phosphorodimorpholidate were prepared independently from the respective phosphorodichloridate (III; R = Et, *cyclo*hexyl, and cholesteryl).

The morpholidates were converted into their dihydrogen phosphates [IV; R = Et, $Ph{\cdot}CH_2{\cdot}CH_2$, $CH_2{:}CH{\cdot}CH_2$, 2-(4-methyl-5-thiazolyl)ethyl, and *cyclo*hexyl] by aqueous hydrolysis with a protonated ion-exchange resin, or, less smoothly, hydrochloric acid. Hydrolysis is thought to proceed by proton-attack on the morpholidate nitrogen atom, followed by P–N bond fission yielding successively the mono- and the di-hydrogen phosphates (VI and IV). The cations (V) and (VII) may be transiently involved. Consistently with this mechanism phenyl phosphorodimorpholidate (II; R = Ph), prepared from the phosphorodichloridate, afforded the intermediate phenyl hydrogen phosphoromorpholidate (VI; R = Ph) after brief contact with the resin, more prolonged treatment yielding phenyl dihydrogen phosphate (IV; R = Ph).

The phosphates were conveniently isolated as their *cyclo*hexylammonium or phenylacetamidinium salts. Allyl dihydrogen phosphate is of interest in relation to the metabolism of *Aspergillus niger*,[6] while 2-(4-methyl-5-thiazolyl)ethyl dihydrogen phosphate is an integral part of the cocarboxylase molecule.[7] Ethyl and *cyclo*hexyl dihydrogen phosphate were independently prepared from their phosphorodichloridates by hydrolysis.

Cholesteryl phosphorodimorpholidate (in aqueous propanol) was not hydrolysed by prolonged treatment with the resin. The lipophilic nature of the cholesteryl group appears to prevent interaction at the resin interface in the aqueous system employed. Treatment of the phosphorodimorpholidate with acetic, formic, or hydrochloric acids resulted in (S_N1) fission of the *O*–cholesteryl bond, yielding respectively cholesteryl acetate, formate, and chloride.[8]

Phosphoramidic halides derived from aromatic amines appear to be of limited value as phosphorylating agents. Phosphorodianilidic chloride (VIII; R = H, X = Cl) easily eliminates hydrogen chloride, yielding the phosphorophenylimidate.[9] *NN*-Dimethylphosphorodianilidic chloride (VIII; R = Me, X = Cl), prepared from methylaniline and phosphorus oxychloride, was stable in this respect, and reacted smoothly with ethanolic sodium ethoxide, yielding ethyl *NN'*-dimethylphosphorodianilidate (VIII; R = Me, X = OEt). The ester was recovered unchanged after prolonged treatment with the resin, suggesting that, in derivatives of this type, delocalisation of the lone-pair electrons on nitrogen by aromatic resonance protects the P–N bond from proton attack.

EXPERIMENTAL

2 : 6-Lutidine was purified as described by Biddiscombe *et al.*[10] Phosphorus oxybromide was prepared by the method of Gerrard *et al.*[11] Phosphorylations were carried out in ethanol-free chloroform. Silica gel was washed successively with water, N-hydrochloric acid, water, and acetone, and activated at 110° for 15 hr.

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[5] Atherton, Howard, and Todd, *J.*, 1948, 1106.

[6] Shin'ichirô Baba, *J. Agric. Chem. Soc. Japan*, 1943, **19**, 651; *Chem. Abs.*, 1951, **45**, 9114.

[7] Avison and Hawkins, *Quart. Rev.*, 1951, **5**, 179, and references cited therein.

[8] Montgomery, Turnbull, and Wilson, *J.*, 1956, 4603.

[9] Caven, *J.*, 1903, **83**, 1045; Zeile and Kruckenberg, *Ber.*, 1942, **75**, 1127.

[10] Biddiscombe, Coulson, Handley, and Herington, *J.*, 1954, 1957.

[11] Gerrard, Nechvatal, and Wyvill, *Chem. and Ind.*, 1947, 437.

Phosphorodimorpholidic Bromide.—Morpholine (35 g.) was gradually added to phosphorus oxybromide (29 g.) in chloroform (120 c.c.) at 10°. The mixture was stirred at room temperature for 4 hr., filtered, and evaporated to *ca.* 50 c.c., and the resulting solution, which was moderately stable at 0° in the absence of moisture, used directly for phosphorylation

Reaction of Phosphorodimorpholidic Bromide with Alcohols.—(a) *Allyl alcohol.* The alcohol (3 c.c.), 2 : 6-lutidine (4 c.c.), and a solution (17·4 c.c.) of phosphorodimorpholidic bromide (from phosphorus oxybromide, 6·4 g.) were mixed at room temperature and set aside for 5 hr. Volatile components were removed in a vacuum, ether (40 c.c.) was added, and the solution filtered from base hydrobromide (2·9 g.), and distilled, affording *allyl phosphorodimorpholidate* (2·6 g.), b. p. 113—117°/0·002 mm., n_{D}^{17} 1·4930 (Found: N, 9·85; P, 11·55. $C_{11}H_{21}O_4N_2P$ requires N, 10·1; P, 11·2%).

(b) *Ethyl alcohol.* The alcohol similarly yielded ethyl phosphorodimorpholidate, b. p. 102—108°/0·003 mm., hygroscopic prisms, m. p. 48° (from benzene–*cyclo*hexane) undepressed on admixture with a specimen prepared from ethyl phosphorodichloridate.

(c) 2-*Phenylethanol.* The alcohol similarly yielded *phenethyl phosphorodimorpholidate,* a syrup, $n_{\text{D}}^{18\cdot5}$ 1·5231 (chromatographed on silica gel, and eluted with ethanol) (Found: N, 8·35. $C_{16}H_{25}O_4N_2P$ requires N, 8·2%).

(d) cyclo*Hexanol.* The alcohol, phosphorylated in the presence of tribenzylamine, yielded cyclo*hexyl phosphorodimorpholidate,* hygroscopic prisms (chromatographed on silica gel and crystallised from benzene–light petroleum), m. p. 53° (Found: C, 53·2; H, 8·8. $C_{14}H_{27}O_4N_2P$ requires C, 52·8; H, 8·6%) undepressed on admixture with a specimen prepared from *cyclo*hexyl phosphorodichloridate.

(e) *Prenol* (3 : 3-*dimethylallyl alcohol*). The alcohol similarly yielded 3 : 3-*dimethylallyl phosphorodimorpholidate,* a syrup (Found: N, 8·8. $C_{13}H_{25}O_4N_2P$ requires N, 9·2%).

(f) 2-(4-*Methyl*-5-*thiazolyl*)*ethyl alcohol.* The hydrochloride of the alcohol [12] (2·0 g.) was dissolved in chloroform (6 c.c.) and 2 : 6-lutidine (6 c.c.), and a chloroform solution (15 c.c.) of phosphorodimorpholidic bromide [from phosphorus oxybromide (4·5 g.)] added. The mixture was warmed at 40° for 15 min., water (0·3 c.c.) and excess of light petroleum were added, the whole was filtered from precipitated salts, and the filtrates were evaporated. The residue was dissolved in benzene and chromatographed on silica gel, affording 2-(4-*methyl*-5-*thiazolyl*)-*ethyl phosphorodimorpholidate* as a syrup (1·5 g.) (Found: N, 10·2. $C_{14}H_{24}O_4N_3PS$ requires N, 11·6). The *dipicrolonate,* crystallised from ethanol–ether, had m. p. 181° [Found: N, 17·3%; equiv. (by titration), 406. $C_{14}H_{24}O_4N_3PS,2C_{10}H_8O_5N_4$ requires N, 17·3%; equiv., 445].

Phosphorodimorpholidic Chloride.—Morpholine (71 g.) was added slowly to phosphorus oxychloride (19 c.c.) in benzene (200 c.c.) at 10—20°. The mixture was stirred for 3 hr., filtered, and evaporated, and the residue distilled in *ca.* 10 g. portions, affording the dimorpholidic chloride (32 g.), b. p. 137—140°/0·02 mm., m. p. 81° (from *cyclo*hexane) (Found: C, 37·1; H, 6·3; N, 10·6; Cl, 13·5. $C_8H_{16}O_3N_2PCl$ requires C, 37·7; H, 6·3; N, 11·0; Cl, 13·9%).

Reaction of Phosphorodimorpholidic Chloride with Alcohols.—(a) *With ethanol.* Ethanol (7 c.c.), 2 : 6-lutidine (4·5 c.c.), and phosphorodimorpholidic chloride (8·5 g.) were refluxed for 16 hr. The solution was evaporated, the residue extracted with ether, and the extract distilled, affording ethyl phosphorodimorpholidate, b. p. 112—123°/0·002 mm. (4 g.), m. p. 48° undepressed on admixture with a specimen prepared from ethyl phosphorodichloridate.

(b) *With cholesterol.* Cholesterol (5·4 g.), pyridine (10 c.c.), and phosphorodimorpholidic chloride (3·5 g.) were heated for 17 hr. in a carbon tetrachloride vapour bath (76°). The product was diluted with water, and the precipitate collected, affording *cholesteryl phosphorodimorpholidate* (3·7 g.), m. p. 153° (from light petroleum) (Found: C, 69·9; H, 10·1; N, 4·5; P, 5·4. $C_{35}H_{61}O_4N_2P$ requires C, 69·5; H, 10·2; N, 4·6; P, 5·1%).

Phenyl Phosphorodimorpholidate.—Prepared from phenyl phosphorodichloridate (1 mol.) by treatment with morpholine (4 mols.) in benzene at 20—30°, this was obtained as prisms, m. p. 84° (from *cyclo*hexane). Audrieth and Toy [13] give m. p. 85°.

Cholesteryl Phosphorodimorpholidate.—Cholesteryl phosphorodichloridate [8] (100 mg.) was warmed with morpholine (0·07 c.c.) in benzene (0·8 c.c.) for 1 hr. at 50—60°, then filtered. Evaporation yielded the morpholidate, m. p. 159° (from light petroleum), undepressed by admixture with a specimen prepared from phosphorodimorpholidic chloride.

Ethyl Phosphorodichloridate.—Ethanol (23 g.) was stirred into phosphorus oxychloride

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[12] Williams, Waterman, Keresztesy, and Buchman, *J. Amer. Chem. Soc.*, 1935, **57**, 536.

[13] Audrieth and Toy, *ibid.*, 1942, **64**, 1337.

(153 g.) at 0°, and the product distilled after 30 min., affording the dichloridate (41 g.), b. p. 62—65°/12 mm. Walczynska [14] gives b. p. 64—65°/10 mm.

Reaction of Ethyl Phosphorodichloridate with Morpholine.—Morpholine (27 g.) was gradually added to ethyl phosphorodichloridate (13 g.) in ether (200 c.c.) at 10—15°, and the product filtered, and evaporated to dryness affording *ethyl phosphorodimorpholidate* (7·2 g.), hygroscopic prisms, m. p. 48° (from benzene–*cyclo*hexane) (Found: N, 10·1. $C_{10}H_{21}O_4N_2P$ requires N, 10·6%).

cyclo*Hexyl Phosphorodichloridate.*—*cyclo*Hexanol (10 g.) and 2 : 6-lutidine (11 g.) in carbon tetrachloride (20 c.c.) were added to phosphorus oxychloride (15 g.) in carbon tetrachloride (100 c.c.) at 0—10°. After a further hour the product was filtered from base hydrochloride (17 g.) and evaporated, yielding the dichloridate as a colourless oil (20 g.) which decomposed on attempted distillation in a vacuum, with the production of *cyclo*hexene (b. p. 81°).

cyclo*Hexyl Phosphorodimorpholidate.*—The foregoing oil (10 g.) was mixed with carbon tetrachloride (160 c.c.), and morpholine (17 g.) added at 0—10°. The mixture was stirred for 2 hr. at room temperature, filtered, and evaporated, yielding the phosphorodimorpholidate (10 g.), hygroscopic prisms, m. p. 57° (from benzene–light petroleum) (Found: N, 8·9. Calc. for $C_{14}H_{27}O_4N_2P$: N, 8·8%).

Hydrolysis of Phosphorodimorpholidates.—Solutions of the foregoing phosphorodimorpholidates (500 mg.) in water (5 c.c.) were percolated slowly (1—2 hr.) through Amberlite IR-120 resin (H^+ form) at 60°. The following dihydrogen phosphates were obtained by evaporation:

(a) Ethyl dihydrogen phosphate, syrup (230 mg.). This gave a bis*cyclo*hexylammonium salt, m. p. 188° (from aqueous acetone), undepressed on admixture with a specimen prepared by hydrolysis of ethyl phosphorodichloridate (Found: N, 8.1. Calc. for $C_2H_7O_4P,2C_6H_{13}N$: N, 8·6%), and a *bis(phenylacetamidinium) salt*, plates (from ethereal ethanol), m. p. 157° (Found: N, 14·7. $C_2H_7O_4P,2C_8H_{10}N_2$ requires N, 14·2%).

(b) Phenyl dihydrogen phosphate (260 mg.) (from chloroform), m. p. 94°. This gave a bis(*cyclo*hexylammonium) salt, m. p. 211° undepressed on admixture with authentic specimens.

(c) *cyclo*Hexyl dihydrogen phosphate (240 mg.) (from benzene–*cyclo*hexane), m. p. 86°, identical with a specimen prepared by hydrolysis of *cyclo*hexyl phosphorodichloridate. Its *bis*cyclo*hexylammonium salt* had m. p. 212° (from ethanol) (Found: N, 7·5. $C_6H_{13}O_4P,2C_6H_3N$ requires N, 7·4%).

(d) *Allyl dihydrogen phosphate*, a syrup (250 mg.) [Equiv. (by titration), 75. $C_3H_7O_4P$ requires equiv., 69]. It gave a *bis*cyclo*hexylammonium salt*, m. p. 175° (decomp.) (from aqueous acetone) (Found: N, 7·9. $C_3H_7O_4P$, $2C_6H_{13}N$ requires N, 8·3%). We were unable to confirm the properties of allyl dihydrogen phosphate reported by Shin'ichirô Baba.[6]

(e) *Phenethyl dihydrogen phosphate*, a syrup (225 mg.) (Equiv., 103. $C_8H_{11}O_4P$ requires equiv., 101). It gave a *mono*cyclo*hexylammonium salt*, m. p. 177° (from aqueous acetone) (Found: N, 4·0%; equiv., 300. $C_8H_{11}O_4P,C_6H_{13}N$ requires N, 4·65%; equiv., 301).

(f) 2-(*4-Methyl-5-thiazolyl)ethyl dihydrogen phosphate* (105 mg.) (Equiv., 134. $C_6H_{10}O_4PNS$ requires equiv., 112). It gave an *acid* cyclo*hexylammonium salt*, m. p. 190° (from aqueous acetone) (Found: N, 7·2. $2C_6H_{10}O_4NSP,C_6H_{13}N,H_2O$ requires N, 7·45%).

Phenyl Hydrogen Phosphoromorpholidate.—Phenyl phosphorodimorpholidate (530 mg.) was treated in water (5 c.c.) with Amberlite IR-120 resin (H^+ form) during 30 min., and the solution evaporated, affording the hydrogen phosphoromorpholidate (290 mg.). The cyclo*hexylammonium salt*, m. p. 202° (from aqueous acetone), depressed the m. p. of bis(*cyclo*hexylammonium) phenyl phosphate (Found: N, 8·6. $C_{10}H_{14}O_4NP,C_6H_{13}N$ requires N, 8·2%).

cyclo*Hexyl Dihydrogen Phosphate.*—*cyclo*Hexyl phosphorodichloridate (10 g.) in carbon tetrachloride (50 c.c.) was treated with *tert.*-butyl alcohol (8·5 g.) and water (1·0 c.c.) for 30 min. at 50°. Removal of the solvent left an oil which was dissolved in a slight excess of saturated sodium hydrogen carbonate solution, filtered through Amberlite resin IR-120 (H^+ form), and evaporated to dryness, affording the *dihydrogen phosphate* (4·8 g.), m. p. 85° (from chloroform–*cyclo*hexane) (Found: C, 39·7; H, 7·5. $C_6H_{13}O_4P$ requires C, 40·0; H, 7·3%).

cyclo*Hexylammonium Di*cyclo*hexyl Phosphate.*—*cyclo*Hexanol (20 g.) and 2 : 6-lutidine (21 g.) in carbon tetrachloride (40 c.c.) were gradually added at 0° to phosphorus oxychloride (15 g.) and 2 : 6-lutidine (2 g.) in carbon tetrachloride (200 c.c.). The solution was set aside overnight, filtered, shaken with M-potassium hydrogen sulphate at 0°, and dried (Na_2SO_4),

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[14] Walczynska, *Roczniki Chem.*, 1926, **6**, 110; *Chem. Abs.*, 1927, **21**, 2457.

and the solvent removed. The residue was heated with *tert.*-butyl alcohol (10·5 g.) at 90° for 30 min., evaporated at room temperature, extracted with 2·5N-sodium hydroxide (80 c.c.), acidified with acetic acid, and treated with *cyclo*hexylamine, affording the cyclo*hexylammonium salt*, needles (4·7 g.), m. p. 211° (from ethanol–ether) (Found: C, 59·9; H, 10·2; N, 3·9. $C_{12}H_{23}O_4P,C_6H_{13}N$ requires C, 59·8; H, 10·0; N, 3·9%).

Solvolysis of Cholesteryl Phosphorodimorpholidate.—(a) *With acetic acid.* The dimorpholidate (180 mg.) was refluxed with acetic acid for 50 hr. The product was diluted with water affording 3β-acetoxycholest-5-ene [8] (105 mg.; m. p. 112°).

(b) *With formic acid.* The dimorpholidate, heated with 90% formic acid at 100° for 20 min., similarly yielded 3β-formyloxycholest-5-ene, m. p. 94° (from ethanol), $[\alpha]_D$ −56°.

(c) *With hydrogen chloride.* The dimorpholidate, heated at 90° for 15 min. with 2N-hydrogen chloride in 80% aqueous acetic acid, similarly afforded 3β-chlorocholest-5-ene,[8] m. p. 88°.

NN′-*Dimethylphosphorodianilidic Chloride.*—Methylaniline (214 g.) was added to phosphorus oxychloride (77 g.) in toluene (220 c.c.), the mixture refluxed for 1 hr., cooled, filtered, and evaporated, and the residue distilled, affording the *phosphorodianilidic chloride* (90 g.), b. p. 149—151°/0·03 mm., n_D^{20} 1·5851 (Found: N, 9·9. $C_{14}H_{16}ON_2PCl$ requires N, 9·5%).

Ethyl NN′-*Dimethylphosphorodianilidate.*—Ethanol (8 c.c.), the foregoing chloride (9·8 g.), and 2 : 6-lutidine (4·5 c.c.) were refluxed for 16 hr., then evaporated, the residue was extracted with ether, and the extracts were distilled, yielding the *phosphorodianilidate* (5·3 g.), b. p. 145—148°/0·03 mm., n_D^{18} 1·5631 (Found: N, 9·2. $C_{16}H_{21}O_2N_2P$ requires N, 9·2%).

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