Esters of Phosphorus Oxy-acids as Alkylating Agents. Part II.[1] *N*-Alkylation of Imidazole and Related Heterocyclic Compounds with Trialkyl Phosphates

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A new method for *N*-alkylation of imidazole, benzimidazole, pyrazole, 1,2,4-triazole, and benzotriazole using trimethyl, triethyl, and tri-n-butyl phosphates as alkylating agents is described. All these heterocycles are easily converted into the corresponding *N*-alkyl derivatives in 45—90% yields. Predominant alkylation at N-1 was observed in both triazoles.

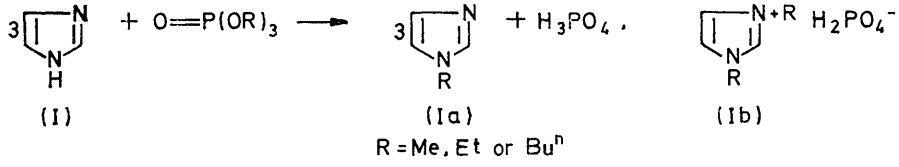
PREVIOUSLY, we described the *N*-alkylation of thymine and uracil with a trialkyl phosphate.[1] Anilines [2] and phenothiazines [3] have been similarly *N*-alkylated. Todd and his co-workers [4] reported that tertiary amines such as pyridine and *N*-methylmorpholine reacted with benzyl esters of phosphorus oxy-acids to give the quaternary salts in which one benzyl group was attached to the nitrogen atom.

We studied reactions of a trialkyl phosphate with imidazole and related heterocyclic compounds, and now report a convenient method for *N*-alkylation of this class of heterocycle.

The general procedure consists in heating a mixture of a trialkyl phosphate and 3 mol. equiv. of a heterocycle. The products may be isolated by alkaline treatment of the reaction mixture, and subsequent distillation or crystallization.

Alkylation of imidazole (I) took place quickly to produce 1-alkylimidazole (Ia) along with 1,3-dialkylimidazolium dihydrogen phosphate (Ib) as a by-product; reaction of imidazole (I) with trimethyl phosphate was complete in 30 min, and afforded 1-methylimidazole (61%) and 1,3-dimethylimidazolium dihydrogen phosphate (15%). Triethyl and tri-n-butyl phosphates were also effective for alkylation of (I), though activity as an alkylating agent decreased in the following order; methyl > ethyl > n-butyl.

A quaternary salt (Ib) may be produced by reaction of (Ia) with remaining tri-, di-, or mono-alkyl phosphate. Since (Ib) did not liberate (Ia) upon alkaline treatment, the formation of (Ib) tends to decrease the yield of (Ia). The yield of (Ia), however, increased considerably when the reaction was carried out in the presence of a tertiary amine, probably because the added base was effective in surpressing the formation of (Ib).



(I) (Ia) (Ib)

R = Me, Et or Bu^n

Reactions of a trialkyl phosphate with ring compounds analogous to (I) such as benzimidazole, pyrazole, 1,2,4-triazole, and benzotriazole were next performed. The reaction conditions and the results obtained are

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[2] D. G. Thomas, J. H. Billman, and C. E. Davis, *J. Amer. Chem. Soc.*, 1946, **68**, 895.

[3] J. I. G. Cadogan, S. Kulik, C. Thomson, and M. J. Todd, *J. Chem. Soc.* (*C*), 1970, 2437.

[4] J. Baddiley, V. M. Clark, J. J. Michalski, and A. R. Todd, *J. Chem. Soc.*, 1949, 815; V. M. Clark and A. R. Todd, *ibid.*, 1950, 2023, 2030.

shown in the Table. All these heterocycles underwent alkylation in a similar fashion to (I) to form the corresponding *N*-alkyl derivatives (II)—(V).‡ Yields were comparable with or higher than those of the usual methods for alkylation of the heterocycles, which employ alkyl halides,[5] dialkyl sulphates,[6] diazomethane,[7] *etc.*[8] In particular, the present method has advantages over the previous procedures in the preparation of 1-alkylbenzotriazole (V); a trialkyl phosphate give (V) predominantly, whereas dialkyl sulphate, alkyl halide, and diazomethane produce 1- and 2-alkyl derivatives in a ratio of 2 : 1, 3 : 2, and 1 : 3, respectively.[5]

These results suggest that alkylation by means of a trialkyl phosphate takes place easily only in a heterocycle which is as basic as imidazole, pyrazole, and triazoles.

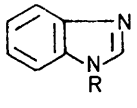
EXPERIMENTAL

U.v. and i.r. spectra were measured with Hitachi-3T and Jasco IR-G spectrometers, respectively. N.m.r. spectra were recorded on a Hitachi–Perkin-Elmer R-20 spectrometer with a dilute solution in deuteriochloroform or deuterium oxide, and tetramethylsilane as an internal or an external standard. Commercially available imidazole, benzimidazole, pyrazole, and indole, and trimethyl, triethyl and tri-n-butyl phosphates were used without further purification. Reaction temperatures and times are given in the Table.

Reactions of imidazole and related heterocyclic compounds with trialkyl phosphates

Heterocycle	Trialkyl phosphate $(RO)_3PO$ R	Base * added	Reaction temperature (°)	Reaction time (h)	Product	Yield (%)
Imidazole	Me		165	0·5	1-Me-imidazole	61
	Me	a	85	5	1-Me-imidazole	74
	Et	a	85	5	1-Et-imidazole	63
	Bu^n	b	160	1	1-Bu^n-imidazole	55
Benzimidazole	Me	a	85	5	1-Me-benzimidazole	60
	Et	a	85	5	1-Et-benzimidazole	68
	Bu^n	b	160	1	1-Bu^n-benzimidazole	56
Pyrazole	Me		150	0·5	1-Me-pyrazole	74
	Me	b	150	0·5	1-Me-pyrazole	90
	Et	b	150	0·5	1-Et-pyrazole	89
	Bu^n	b	150	0·5	1-Bu^n-pyrazole	80
1,2,4-Triazole	Me		160	1	1-Me-1,2,4-triazole	41
	Me	a	85	5	1-Me-1,2,4-triazole	54
	Et	a	85	5	1-Et-1,2,4-triazole	55
	Bu^n	b	150	2	1-Bu^n-1,2,4-triazole	36
Benzotriazole	Me		170	1	1-Me-benzotriazole	69
					2-Me-benzotriazole	10
	Et		170	1	1-Et-benzotriazole	88
	Bu^n		170	1	1-Bu^n-benzotriazole	50
Pyrrole	Me		130	10	†	
Indole	Me		180	2	1-Me-Indole	38
	Et		180	5	†	

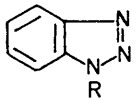
* a = Triethylamine; b = tri-n-butylamine. † Starting materials recovered.



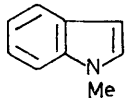
(II)

(III)

(IV)



(V)



R = Me, Et, or Bu^n

(VI)

Pyrrole and indole, on the other hand, were unreactive towards a trialkyl phosphate, allowing only slow methylation of the latter to 1-methylindole (VI) (see Table).

1-Methylimidazole.—A mixture of imidazole (7·0 g, 0·10 mol) and trimethyl phosphate (6·0 g, 0·04 mol) was heated with stirring. The resulting mixture was dissolved in benzene (50 ml) and the solution was stirred with 30% aqueous potassium hydroxide. Evaporation of the solvent from the organic layer and distillation of the residue afforded 1-methylimidazole as a liquid (5·0 g, 61%), b.p. 81° at 11 mmHg (lit.,[9] 94—95° at 14 mmHg). Spectroscopic data of the product were identical with those of an authentic sample.

The following preparations are typical. Other compounds in the Table were prepared similarly, and their physical constants agreed with the literature values.

‡ Quaternary salts analogous to (Ib) were also obtained, but their oily and hygroscopic nature prevented their definite identification.

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[6] O. Brewere, *Annalen*, 1938, **539**, 276; M. A. Phillips, *J. Chem. Soc.*, 1929, 2820; C. A. Rajahn, *Ber.*, 1926, **59**, 607.

[7] M. R. Atkinson and J. B. Polya, *J. Chem. Soc.*, 1954, 141.

[8] R. H. Wiley, N. R. Smith, and J. Moffat, *J. Amer. Chem. Soc.*, 1954, **76**, 4933; P. Brookes and P. D. Lawley, *J. Chem. Soc.*, 1961, 3923.

[9] L. P. Kyrides, F. B. Zienty, G. W. Stehly, and H. L. Morrill, *J. Org. Chem.*, 1947, **12**, 577.

When the reaction was carried out in the presence of triethylamine (10·0 g, 0·10 mol), the yield of 1-methylimidazole increased to 6·1 g (74%).

1,3-*Dimethylimidazolium Dihydrogen Phosphate*.—The mixture obtained by the reaction of imidazole and trimethyl phosphate as above was distilled under reduced pressure to afford 1-methylimidazole (4·1 g, 50%). The residue gave the *imidazolium salt* (Ib; R = Me) as crystals, m.p. 250° (from ethanol), $\nu_{max.}$ (KBr) 3100m, 2750m, 2300m, 1575m, 1090s, 930s, 625m, and 540m cm^{-1}, $\lambda_{max.}$ (H_2O) 208·5 nm (ε 3200), τ (D_2O) 1·35br (1H, s), 2·55 (2H, s), and 6·10 (6H, s) (Found: C, 28·3; H, 5·7; N, 13·3; P, 14·2. $C_5H_{11}N_2P,H_2O$ requires C, 28·3; H, 6·15; N, 13·2; P, 14·6%).

1-*Methylpyrazole*.—A mixture of pyrazole (1·92 g, 0·28 mol) and trimethyl phosphate (2·0 g, 0·14 mol) was heated, and 1-methylpyrazole was distilled off as an oil (1·70 g, 73%), b.p. 128° (lit.,[10] 127°); its i.r. and n.m.r. spectra were identical with those of an authentic sample.

The yield of 1-methylpyrazole increased to 2·1 g (90%) when the reaction was carried out in the presence of tri-n-butylamine (2·70 g, 0·15 mol).

1-*Methyl*-1,2,4-*triazole*.—Trimethyl phosphate (4·14 g, 0·03 mol) was treated with 1,2,4-triazole (5·10 g, 0·074 mol) to give a solution which was mixed with benzene (50 ml) and 30% aqueous potassium hydroxide. The solvent was removed from the organic portion, and distillation of the residue gave the product (2·5 g, 41%), b.p. 60° at 10 mmHg (lit.,[11] 175—176°).

Reaction in the presence of triethylamine (7·5 g, 0·075 mol) afforded 1-methyl-1,2,4-triazole (3·3 g, 54%) on distillation of the reaction mixture.

1- *and* 2-*Methylbenzotriazoles*.—A mixture of benzotriazole (7·13 g, 0·06 mol) and trimethyl phosphate (3·1 g, 0·02 mol) was heated with stirring. The resulting solution consisted of two layers. The upper layer was dissolved in chloroform (50 ml) and the solution was washed with 10% aqueous sodium hydrogen carbonate. Evaporation of the solvent gave crystals (5·26 g), which according to their n.m.r. spectrum consisted of 1-methylbenzotriazole (4·44 g) and 2-methylbenzotriazole (0·82 g). The lower layer was similarly processed to give 1-methylbenzotriazole (1·0 g).

1-Methylbenzotriazole was easily separated from the 2-methyl isomer by dissolving the mixture in benzene and washing the solution with dilute HCl (the former is soluble in acid whereas the latter is not). Neutralization of the acid layer, extraction with chloroform, and recrystallization gave pure 1-methylbenzotriazole, m.p. 64° (from n-hexane) (lit.,[12] 65°), τ ($CDCl_3$) 2·1—2·45 (1H, complex m), 2·60—3·10 (3H, complex m), and 5·90 (3H, s). 2-Methylbenzotriazole had b.p. 110° at 20 mmHg (lit.,[12] 104° at 15 mmHg), τ ($CDCl_3$) 2·10—2·50 (2H, complex m), 2·60—3·00 (2H, complex m), and 5·65 (3H, s).

1-*Ethylbenzotriazole*.—The mixture obtained after heating benzotriazole (6·0 g, 0·05 mol) with triethyl phosphate (3·40 g, 0·18 mol) was worked up as described above to give 1-ethylbenzotriazole (6·45 g, 88%) as a liquid, one spot on t.l.c., b.p. 120—122° at 4 mmHg (lit.,[11] 150—151° at 13 mmHg); τ ($CDCl_3$) 2·50—3·00 (1H, complex m), 3·05—3·65 (3H, complex m), 6·05 (2H, q), and 9·10 (3H, t).

1-*n-Butylbenzotriazole*.—Reaction of benzotriazole (2·76 g, 0·023 mol) and tri-n-butyl phosphate (2·50 g, 0·009 mol) afforded 1-n-butylbenzotriazole (2·0 g, 50%) after treatment as described above, b.p. 170—172° at 17 mmHg (lit.,[13] 170—172° at 17 mmHg), τ ($CDCl_3$) 2·00—2·40 (1H, complex m), 2·50—3·05 (3H, complex m), 5·50 (2H, t), 8·12 (2H, quint), and 8·50—9·30 (5H, complex m).

1-*Methylindole*.—A mixture of indole (7·10 g, 0·06 mol) and trimethyl phosphate (8·60 g, 0·06 mol) was heated at *ca.* 180° for 2 h. The cooled reaction mixture was dissolved in chloroform (50 ml) and the solution was neutralized with sodium hydrogen carbonate. The organic solution was concentrated and the residue distilled under reduced pressure to give 1-methylindole (3·0 g, 38%), b.p. 98° at 3 mmHg (lit.,[14] 70—75° at 2 mmHg); picrate, m.p. 150° (from aqueous methanol) (lit.,[14] 150°).

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[13] F. Krollpfeiffer, H. Pots, and A. Rosenberg, *Ber.*, 1938, **71***B*, 596.
[14] E. Fisher and O. Hess, *Ber.*, 1884, **17**, 562.