Esters of Phosphorus Oxy Acids as Alkylating Agents. IV. *N*-Alkylation of Imidazole and Its Analogs with Alkyl Esters of Phosphonic and Phosphinic Acids

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Methyl, ethyl esters of phosphonic and phosphinic acids were found to be efficient alkylating agents for imidazole, benzimidazole, 1,2,4-triazole, 1,2,3-benzotriazole and pyrazole, giving the corresponding *N*-methyl or *N*-ethyl derivatives.

In a previous paper a report was given on the *N*-alkylation reactions of imidazoles with trialkyl phosphates.[1] Since phosphonic and phosphinic acid esters are also considered to be potentially useful as alkylating agents, we investigated the *N*-alkylation of imidazoles with these phosphorus oxy-acid esters, and found simple methods of alkylation for this class of heterocycles.

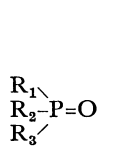
Reactions were carried out by heating a base in an ester, and the products were isolated by distillation or extraction.

Table 1 gives a summary of the alkylation reactions of imidazole (**I**, R=H), benzimidazole (**II**, R=H), 1,2,4-triazole (**III**, R=H), 1,2,3-benzotriazole (**IV**, R=H), and pyrazole (**VI**, R=H).

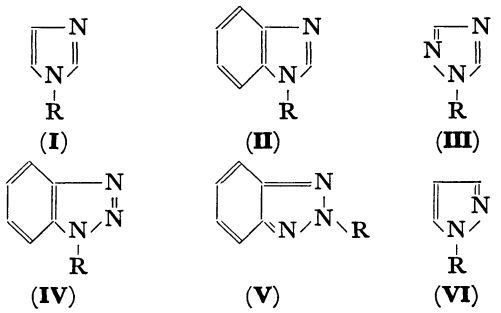
All the bases underwent *N*-alkylation to give the corresponding products in fairly good yields. Especially, in triazole, reactions brought into substitution at the N-1 position only to afford 1-alkyltriazole (**III**, R=Me, Et). In benzotriazole, the N-1 position was alkylated preferentially to the N-2 position to give 1-alkyl derivatives (**IV**, R=Me, Et) as a main product. High selective alkylation in the present method would be very useful, since other alkylating agents such as alkyl halide, diazomethane and dimethyl sulfate showed much lower selectivity,[2-8] giving a mixture of 1- and 2-alkyl isomers in approximately 5 to 3, 3 to 10, and 2 to 1 mole ratios, respectively.

Alkyl-imidazoles, benzimidazoles, triazoles and pyrazoles were isolated by direct distillation of the reaction mixtures. Separation of 1-methyl and 2-methylbenzotriazole was carried out easily through fractionating the reaction mixture between a dilute hydrochloric acid and chloroform, since the former is soluble in a dilute acid while the latter goes into the organic layer.

The results suggest that alkyl esters of phosphonic and phosphinic acids could be utilized as convenient alkylating agents for the preparation of *N*-alkyl derivatives of imidazole and its analogs.



a: $R_1=R_2=OMe$, $R_3=Me$
Dimethyl methylphosphonate
b: $R_1=R_2=OEt$, $R_3=Et$
Diethyl ethylphosphonate
c: $R_1=OMe$, $R_2=R_3=Me$
Methyl dimethylphosphinate
d: $R_1=OEt$, $R_2=Et$, $R_3=Ph$
Ethyl ethylphenylphosphinate



(**I**) (**II**) (**III**) (**IV**) (**V**) (**VI**)

Table 1. Reactions of imidazole and its analogs with esters of phosphonic and phosphinic acids

Base (B)	Ester (E)	Mole ratio (E/B)	React. temp (°C)	React. time (hr)	Product	Yield (%)
Imidazole (**I**)	**a**	0.5	200	1	1-methylimidazole	54
	c	1	200	10.5	1-methylimidazole	50
	b	0.5	200	1	1-ethylimidazole	39
	d	0.5	193	6	1-ethylimidazole	37
Benzimidazole (**II**)	**a**	1	200	5	1-methylbenzimidazole	37
	b	1	200	5	1-ethylbenzimidazole	59
	d	0.5	198	6	1-ethylbenzimidazole	34
1,2,4-Triazole (**III**)	**a**	0.5	200	2	1-methyltriazole	36
	b	0.5	200	1.3	1-ethyltriazole	32
Benzotriazole (**IV**)	**a**	0.5	200	1.5	1-methylbenzotriazole 2-methylbenzotriazole	80 7
	a	0.5	200	3	1-methylbenzotriazole 2-methylbenzotriazole	87 8
	b	0.5	200	2	1-ethylbenzotriazole	71
Pyrazole (**VI**)	**a**	0.5	150	1	1-methylpyrazole	67
	b	0.5	170	1	1-ethyltriazole	62

Experimental

IR were measured with a JASCO IR-G spectrometer. NMR spectra were recorded on a Hitachi-Perkin Elmer R-20 spectrometer with a dilute solution in deuteriochloroform using tetramethylsilane as an internal standard.

Materials. Commercial imidazole, benzimidazole, triazole, benzotriazole and pyrazole were used without further purification. Dimethyl methyl- and diethyl ethylphosphonate were synthesized *via* Arbuzov reaction of the corresponding trialkyl phosphites with alkyl iodides. Methyl dimethyl- and ethyl ethylphenylphosphinates were prepared by the procedure of Reinhardt *et al.*[9]

The following reactions are typical. Reaction conditions are listed in Table 1.

1-Methylimidazole. A mixture of **I** (6.35 g, 0.092 mol) and **a** (5.80 g, 0.047 mol) was heated at 200 °C with stirring for 1 hr. The reaction mixture was treated with aqueous sodium bicarbonate and extracted with chloroform. The organic solution was concentrated and the residue was distilled under diminished pressure to give 1-methylimidazole as a liquid; (4.14 g, 54%), bp 75—76 °C/11 mmHg (lit,[5] 94—95 °C/14 mmHg). The IR spectrum of the product was identical with that of an authentic sample.

1-Ethylbenzimidazole. A mixture of **II** (3.00 g, 0.025 mol) and **d** (2.52 g, 0.014 mol) was heated at 198 °C for 6 hr. The reaction mixture was treated in a manner similar to the alkylation of **I** to give 1.27 g (34%) of 1-ethylbenzimidazole; bp 90—98 °C/1 mmHg (lit,[10] 160—162 °C/12 mmHg); picrate mp 216—217 °C (from ethanol) (lit,[10] 219 °C); IR (neat): 3300 (broad s), 3050 (m), 2970 (s), 2920 (s), 1610 (m), 1500 (s), 1460 (s), 1330 (s), 740 (s), and 700 cm^{-1} (m); NMR: τ 2.43 (complex m, 2H, ring), 2.70 (complex m, 3H, ring), 6.27 (q, J=7 Hz, 2H, $-CH_2-$), and 9.00 (t, J=8 Hz, 3H, $-CH_3$).

1-Methyl-1,2,4-Triazole. *1,2,4*-Triazole (III) (0.95 g, 0.0138 mol) was allowed to react with **a** (0.85 g, 0.0069 mol) to give 0.41 g (46%) of 1-methyl-1,2,4-triazole; bp 60 °C/10 mmHg (lit,[11] 175—176 °C); IR (neat): 3350 (broad s), 3100 (m), 2950 (w), 1520 (s), 1280 (s), 1220 (m), 1140 (s), 1010(m), 990 (m), and 680 cm^{-1} (s); NMR: τ 1.90 (s, 1H, ring) 2.12 (s, 1H, ring), and 6.10 (s, 3H, $-CH_3$).

Methylation of 1,2,3-Benzotriazole. A mixture of **IV** (5.75 g, 0.0482 mol) and **a** (2.99 g, 0.024 mol) was refluxed for 1.5 hr. The reaction mixture was subsequently made alkaline with aqueous sodium bicarbonate and extracted with chloroform (40 ml). The organic layer showed the presence of only two products in thin-layer chromatography (R_f=0.82 and 0.45, $CHCl_3$: CH_3OH=9: 1, Silica-Gel Merck Art-7730). The residue (5.5 g) obtained after evaporation of the solvent was dissolved in deuteriochloroform for study of the NMR spectrum. Only peaks, which are attributed to those of 1-methyl- and 2-methyl-benzotriazoles, were observed. From the area ratio (35: 3) of singlet peaks of CH_3 groups of both isomers (τ 5.74 for 1-methyl- and τ 5.50 for 2-methyl derivative, respectively), the yields of 1-methyl- and 2-methylbenzotriazole were calculated to be 80% and 7%, respectively. The residue (5.5 g) was then dissolved in benzene and fractionated with dilute hydrochloric acid. Neutralization of the acid layer, extraction with chloroform and subsequent recrystallization with hexane gave pure 1-methylbenzotriazole, 3.85 g (60%); mp 64 °C (from hexane) (lit,[12] 65 °C); IR (KBr): 3050 (m), 2950 (m), 1620 (m), 1590 (m), 1500 (s), 1450 (s), 1300 (s), 1270 (s), 1200 (s), 1030 (s), 740 (s), and 660 cm^{-1} (s); NMR: τ 1.95—2.00 (complex m, 1H, ring), 2.50—2.90 (complex m, 3H, ring), and 5.74 (s, 3H, $-CH_3$). Evaporation of benzene gave 2-methylbenzotriazole; 0.32 g (5%): bp 90—95 °C/10 mmHg (lit,[12] 104 °C/15 mmHg); NMR: τ 1.85—2.10 (complex m, 2H, ring), 2.43—2.60 (complex m, 2H, ring), and 5.50 (s, 3H, $-CH_3$).

Ethylation of 1,2,3-Benzotriazole. Benzotriazole (2.97 g, 0.0234 mol) was heated with **b** (2.07 g, 0.0125 mol) at 200 °C for 2 hr. The reaction mixture was neutralized with aqueous sodium bicarbonate and the solution was extracted with chloroform (10 ml×3). The organic layer was concentrated and the residue was distilled to give the product. The NMR spectrum of the distillate showed a set of signals consistent with the expected structure; bp 117 °C/2 mmHg (lit,[11] 150—151 °C/13 mmHg); IR (neat) 3300 (broad s), 3050 (s), 2970 (s), 2920 (s), 1610 (m), 1495 (s), 1469 (s), 1230 (s), 740 (s), and 700 cm^{-1} (m); NMR: τ 1.95—2.30 (complex m, 1H, ring), 2.50—2.90 (complex m, 3H, ring), 5.45 (q, J=8 Hz, 2H, $-CH_2-$), and 8.53 (t, J=8 Hz, 3H, $-CH_3$).

1-Methylpyrazole. 1-Methylpyrazole was distilled at 127 °C during heating of the reaction mixture through a distillating column as a clear liquid; 0.81 g (67%), bp (lit,[13] 127 °C); IR (neat): 3350 (broad s), 3100 (s), 2920 (s), 1515 (s), 1440 (m), 1390 (s), 1275 (s), 1205 (s), 1085 (s), 1065 (m), 1025 (s), 960 (s), 875 (m), 750 (broad s), 675 (s), and 605 cm^{-1} (s); NMR: τ 2.40 −2.80 (complex m, 2H, ring), 3.75—3.85 (complex m, 1H, ring), and 6.22 (s, 3H, $-CH_3$).

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