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N-Alkylation of Nitrogen Heterocyclic Compounds with Dialkyl Phosphites

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Dialkyl phosphites were found to be efficient alkylating agents for various nitrogen heterocyclic compounds, especially for imidazole analogs and pyridones, producing the corresponding *N*-alkyl derivatives.

Generally, *N*-alkylation of nitrogen heterocyclic compounds has been attempted with dialkyl sulfates or alkyl halides. Recently, trialkyl phosphate, dialkyl phosphonate, and alkyl phosphinate were found to alkylate nitrogen heterocyclic compounds to give the corresponding *N*-alkyl derivatives in good yields.[1-4]

On the other hand, there are a few reports which show the addition of a dialkyl phosphite to the carbonyl groups of various heterocyclic compounds[5,6] and to etherify cholesterols.[7] However, there has been no report on the use of a dialkyl phosphite as an alkylating agent. The present paper shows a new method for the alkylation of imidazoles, 2,4-pyrimidinediols, and pyridones by means of a dialkyl phosphite.

Results and Discussion

Reactions were carried out by heating a mixture of a heterocyclic compound and a dimethyl, diethyl, diisopropyl, or dibutyl ester of phosphorus acid. The products were isolated by distillation or extraction after neutralization of the reaction mixtures. In the reaction

TABLE 1. REACTIONS OF NITROGEN HETEROCYCLIC COMPOUNDS WITH DIALKYL PHOSPHITES

Heterocyclic Compd	R of $(RO)_2P(O)H$	Time (h)	Temp (°C)	Product	Yield (%)
Imidazole (Im, Ia)	Me	1	155	1-Methyl-Im (Ib)	58
Benzotriazole (Bztri, IIa)	Me	1	165	1-Methyl-Bztri (IIb) 2-Methyl-Bztri (III)	46 4
Pyrazole (Pyra, IVa)	Me	1	130	1-Methyl-Pyra (IVb)	69
Theophylline (TP, Va)	Me	4.5	130	7-Methyl-TP (Vb) (Caffeine)	71
	Et	7	180	7-Ethyl-TP	60
Uracil (U, VIa)	Me	4	170	1,3-Dimethyl-U (VIb) 3-Methyl-U (VIc) 1-Methyl-U (VId)	12 29 11
	Me	11[a]	140	1,3-Dimethyl-U (VIb) 3-Methyl-U (VIc) 1-Methyl-U (VId)	19 13 26
	Et	5	196	1,3-Diethyl-U 3-Ethyl-U	7 4
Thymine (T, VIIa)	Me	4	172	1,3-Dimethyl-T (VIIb) 3-Methyl-T (VIIc) 1-Methyl-T (VIId)	10 4 35
	Me	11[a]	140	1,3-Dimethyl-T (VIIb) 1-Methyl-T (VIId)	6 25
	Et	12	176	1,3-Diethyl-T 3-Ethyl-T 1-Ethyl-T	2 1 30
	Isopropyl	13	182	1-Isopropyl-T	1
	Bu	13	180	3-Butyl-T 1-Butyl-T	1 4
2-Pyridone (2-Py, VIIIa)	Me	6	171	*N*-Methyl-2-Py (VIIIb)	81
	Me	11.5	100	*N*-Methyl-2-Py (VIIIb) 2-Methoxypyridine (IX)	52 5
	Et	6	171	*N*-Ethyl-2-Py	80
	Et	44.5	100	*N*-Ethyl-2-Py 2-Ethoxypyridine	5 10
4-Pyridone (4-Py, Xa)	Me	5.5	169	*N*-Methyl-4-Py (Xb)	98
	Et	5.75	173	*N*-Ethyl-4-Py	86

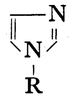
a) Tributylamine was added.

of uracil and thymine, the yields of products were obtained spectrometrically. The results are summarized in Table 1.

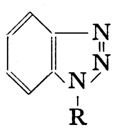
The reaction of imidazole (Ia) with dimethyl phosphite proceeded smoothly at 155 °C to give 1-methylimidazole (Ib) as a liquid with the coformation of monomethyl phosphite or phosphorus acid. Facile alkylations were also observed in theophylline (Va) and pyrazole (VIa) giving 7-alkyl and 1-alkyl derivatives, respectively. Selective alkylation took place in benzotriazole (IIa) in which alkylation occurred at the N-1 position preferentially to the N-2 position producing 1-methylbenzotriazole (IIb) and 2-methylbenzotriazole (III) at an approximately 11 to 1 molar ratio. Other alkylating agents, such as dialkyl sulfates, alkyl halides, and diazomethane, are known to give N-1 and N-2 derivatives at less selective ratios (2: 1, 5: 3, and 3: 10, respectively).[8-14]

In 2,4-pyrimidinediols, the yields of *N*-alkyl derivatives was rather low, *e.g.*, in the reaction with uracil (VIa) at 170 °C, 1,3-dimethyluracil (VIb), 3-methyluracil (VIc), and 1-methyluracil (VId) were obtained in 12, 29, and 11% yields, respectively. But when a large amount of a tertiary amine was used in the reaction, the conversion of uracil to methylated derivatives increased even at low reaction temperature (140 °C), *e.g.*, for tributylamine, 1,3-dimethyluracil (VIb), 3-methyluracil (VIc), and 1-methyluracil (VId) were obtained in 19, 13, and 26% yields, respectively, with no other product. The employment of solvents, such as *N,N*-dimethylformamide, ethanol, and diglyme, lowered the yield of the *N*-alkyl derivatives by about one-third, but tended to increase the relative yield of the 1-alkyl derivatives produced. In the reaction of thymine (VIIa), alkylation occurred mainly at the N-1 position giving 1-alkyl derivatives along with small amounts of 3-alkyl and 1,3-dialkyl derivatives. In this case, the reaction was not appreciably affected by the addition of a tertiary amine. The yield of the 1,3-dialkyl derivative increased with the reaction temperature and no *O*-alkylation was observed for these 2,4-pyrimidinediols (VIa, VIIa). At higher temperature (about 200 °C), the yields of alkylated products from VIa and VIIa decreased and relatively large amounts of unknown products were obtained, which appeared to be derived from decomposition of the pyrimidine ring, since no absorption was observed in the aromatic region of complex NMR spectra.

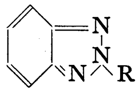
$(RO)_2P(O)H$ Dialkyl phosphite
R=Me, Et, Isopropyl, Bu



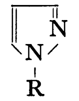
R=H (Ia)
Me (Ib)



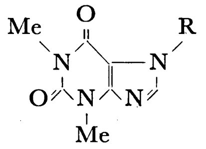
R=H (IIa)
Me (IIb)



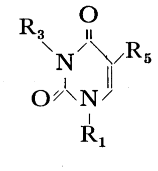
R=Me (III)



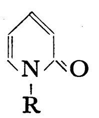
R=H (IVa)
Me (IVb)



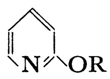
R=H (Va)
Me (Vb)



$R_1=R_3=R_5=H$ (VIa)
$R_1=R_3=Me, R_5=H$ (VIb)
$R_1=R_5=H, R_3=Me$ (VIc)
$R_1=Me, R_3=R_5=H$ (VId)
$R_1=R_3=H, R_5=Me$ (VIIa)
$R_1=R_3=R_5=Me$ (VIIb)
$R_1=H, R_3=R_5=Me$ (VIIc)
$R_1=R_5=Me, R_3=H$ (VIId)



R=H (VIIIa)
Me (VIIIb)



R=Me (IX)

R=H (Xa)
Me (Xb)

However, for 2-pyridone (VIIIa), alkylation occurred very smoothly giving the corresponding *N*-alkyl derivative. Here, the *O*-alkyl derivative was isolated only when the reaction was carried out at low temperature and was found to undergo rapid thermal rearrangement to the corresponding *N*-alkyl derivative upon heating at high temperature. Similar facile alkylation was observed in 4-pyridone (Xa) although the *O*-alkyl derivative was neither isolated nor detected even at low temperature (97 °C).

For the above reactions, the reactivities of the dialkyl phosphites were found to be in the following general order; methyl>ethyl>butyl>isopropyl as shown in Table 1. The present results suggest that dialkyl phosphites may be utilized as covenient alkylating agents, especially for imidazole analogs and pyridones.

Experimental

UV and IR spectra were measured with Hitachi 3-T and Jasco IR-G spectrometers, respectively. NMR spectra were recorded on a Hitachi-Perkin Elmer R-20 spectrometer with a dilute solution in deuterochloroform and deuterium oxide using tetramethylsilane as an internal and external standard.

Preparative thin-layer chromatography (aluminium oxide, Merck Art 1064) was used to analyze the reaction products.

All materials are commercially available and were used without further purification. The reaction conditions are given in Table 1. The following experiments are typical. Other compounds in the table were prepared similarly and their physical constants agreed with the literature values.

Methylation of Imidazole (Ia). A mixture of Ia (1.00 g, 0.015 mol) and dimethyl phosphite (0.81 g, 0.70 mol) was heated at 155 °C with stirring for 1 h. After the reaction mixture had been neutralized by aqueous sodium hydrogencarbonate, it was extracted with tetrahydrofuran. Upon concentration of the organic extract, 1-methylimidazole (Ib) was obtained as a liquid; (0.70 g, 58%). bp 76—77 °C/11 Torr (lit,[11] 94—95 °C/13 Torr). IR and NMR spectra of the product are identical with those of an authentic sample.

Methylation of Theophylline (Va). 1.01 g (0.0056 mol) of Va and 1.20 g (0.0109 mol) of dimethyl phosphite were heated at 130 °C for 4.5 h with stirring. The reaction mixture was neutralized and extracted with chloroform. The organic layer gave 7-methyltheophylline (Vb, caffeine, 0.775 g, 71%). IR, NMR, UV, and mp measurements were consistent with those of an authentic sample.

Methylation of Pyrazole (IVa). A mixture of IVa (1.00 g, 0.0147 mol) and dimethyl phosphite (0.81 g, 0.0073 mol) was heated at 130 °C for one hour with stirring. 1-Methylpyrazole (IVb) was distilled at 127 °C during the reaction through a distillation column; (0.85 g, 69%). bp 127 °C (lit,[15] 127 °C); NMR: τ(CDCl$_3$): 2.60 (d, J=3 Hz, 2H, ring), 3.81 (t, J=3 Hz, 1H, ring), and 6.20 (s, 3H, –CH$_3$).

Methylation of Benzotriazole (IIa). A mixture of IIa (2.00 g, 0.0168 mol) and dimethyl phosphite (0.93 g, 0.0084 mol) was heated at 165 °C with stirring for one hour. The reaction mixture was neutralized with aqueous sodium hydrogencarbonate and extracted with chloroform. The organic layer was concentrated to give the residue (1.44 g), the NMR spectrum of which showed only peaks attributable to 1-methylbenzotriazole (IIb), 2-methylbenzotriazole (III), and benzotriazole (IIa). From the area ratio (34: 3: 4) of the singlet peaks of the CH$_3$ groups of both isomers (τ=5.83 for IIb and τ=5.60 for III), and the NH group of IIa (τ=−5.50), the yields of IIb, III, and IIa were calculated to be 46, 4, and 16%, respectively. Isolation of these products was carried out in a manner similar to that mentioned in a previous paper.[4] The values of the physical constants agree with those of authentic samples.

Methylation of Uracil (VIa). A mixture of VIa (3.01 g, 0.0268 mol), dimethyl phosphite (6.00 g, 0.0545 mol), and tributylamine (10.0 g) was heated at 140 °C for 11 h with stirring. After one hour of heating, VIa was a thoroughly mixed solution. The reaction mixture was diluted with water to 50 ml, then separated using preparative aluminium oxide thin-layer chromatography (eluted with CHCl$_3$: MeOH=10: 1). This gave four ultraviolet absorbing spots [R_f and λ_{max} (mμ): **a**=0.97, 267.5, **b**=0.57, 260.0, **c**=0.38, 268.0, and **d**=0.10, 259.5], which were identified to be **a**=1,3-dimethyluracil (VIb), **b**=3-methyluracil (VIc), **c**=1-methyluracil (VId), and **d**=uracil (VIa), from a comparison of the physical constants (from IR, UV, NMR, and mp determinations) with literature values[7,16,17] and authentic samples. The yields for the reaction products were calculated to be VIb=19, VIc=26, and VId=30%.

Methylation of Thymine (VIIa). A mixture of VIIa (0.50 g, 0.0039 mol) and dimethyl phosphite (2.40 g, 0.0218 mol) was heated at 172 °C for 4 h with stirring. The reaction mixture was neutralized with sodium hydrogencarbonate and diluted to 80 ml and then separated in a manner similar to that described above. The following products were obtained (their physical constants are consistent with those of authentic samples and literature values): *N*-Alkyl derivatives, yield, R_f (CHCl$_3$: MeOH=10: 1), and λ_{max}(H$_2$O): 1,3-dimethylthymine (VIIb), 10, 0.98, 272, 3-methylthymine (VIIc), 4, 0.72, 265, and 1-methylthymine (VIId), 35%, 0.47, 273 mμ, respectively; (lit,[18] VIIb, 272, VIIc, 264.5, and VIId, 273 mμ).

Methylation of 2-Pyridone (VIIIa). A mixture of VIIIa (3.00 g, 0.0316 mol) and dimethyl phosphite (3.60 g, 0.0327 mol) was heated at 100 °C for 11.5 h. Then the mixture was made alkaline with aqueous sodium hydroxide and then extracted with chloroform. Thin-layer chromatography (eluted with CHCl$_3$: MeOH=10: 1) showed three spots (R_f, **e**=0.77, **f**=0.44, **g**=0.33). The spots **e** and **g** were identified from authentic samples to be *N*-methyl-2-pyridone (VIIIb) and 2-pyridone (VIIIa), respectively. The residue (1.97 g) from the organic layer dissolved with deuterochloroform in order to obtaine the NMR spectrum. From the area ratio (20: 2.1) of the singlet peaks of the CH$_3$ groups of both isomers [τ=6.62 for VIIIb and τ=6.27 for 2-methoxypyridine (IX)], the yield of *N*-methyl and *O*-methyl derivatives were calculated to be 52 and 5%, respectively. Distillation of this mixture gave IX (trace) and VIIIb (1.44 g, 42%): 2-methoxypyridine (IX); bp 60 °C/50 Torr (lit,[20] 142.4 °C), picrate (acetone–H$_2$O); mp 141—143 °C (lit,[20] 145—146 °C): *N*-methyl-2-pyridone (VIIIb); bp 92 °C/4 Torr (lit,[19] 250 °C).

Methylation of 4-Pyridone (Xa). 1.74 g (0.0183 mol) of Xa and 2.04 g (0.0185 mol) of dimethyl phosphite reacted at 169 °C for 5.5 h. The reaction mixture produced only one thin-layer chromatographic product; R_f=0.72 (Xb) and R_f=0.41 (Xa) (eluted with CHCl$_3$: MeOH=10: 1). Making the solution alkaline with aqueous sodium hydroxide and extracting with chloroform gave *N*-methyl-4-pyridone (Xb, 1.95 g, 98%); picrate (acetone–H$_2$O), mp 183.5—184.5 °C, NMR; τ (CDCl$_3$) 2.49 (d, J=7 Hz, 2H, ring), 3.77 (d, J=7 Hz, 2H, ring), and 6.36 (s, 3H, –CH$_3$).

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