N-Alkylation of Purines with Alkyl Esters of Phosphorus Oxy Acids

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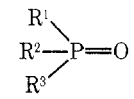
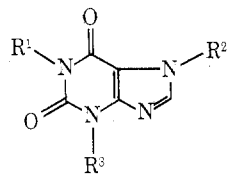
Although alkyl esters of sulfuric and sulfonic acids have been well studied and utilized as alkylating reagents,[1-3] there are few studies on alkylation reaction by alkyl esters of phosphorus oxy acids. We have previously shown that a trialkyl phosphate is an excellent reagent for the *N*-alkylation of pyrimidines[4] and imidazoles.[5] We have now extended the investigation to the *N*-alkylation of purines. Reactions were performed by heating a mixture of a purine and an excess of the ester, and the products were isolated through extraction and recrystallization. The results are summarized in Table I.

Thus, reactions of xanthine (**1**) with esters (**a, b, d, e**) brought about substitution at the 1, 3, and 7 positions to form 1,3,7-trialkyl- and 3,7-dialkylxanthines. Theophylline (**2**) was alkylated especially smoothly to furnish the corresponding 7-alkyl derivative in high yields. The reactions also revealed the following general order of alkylating power among phosphorus oxy acids; phosphate > phosphonate > phosphinate. Methylation of theobromine (**3**) and its ethyl analog (**4**) also took place easily at the 1 position to give **5** and **8**, but we were unable to ethylate these two compounds. The selective methylation at the 1-position of 3,7-dialkylxanthine may be attributed to the steric hindrance at the position or the lowered reactivity of ethyl esters.[5] Similar results in alkylation have been obtained in alkyl esters of sulfur oxy acids.[1,2]

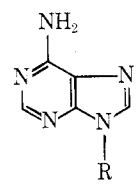
In the case of adenine (**9**), the preferential alkylation at the 3-position was observed to generate 3-alkyladenine (**10, 12**). Alkyl esters of sulfur oxy acids[2,3] and alkyl halides[6,7]



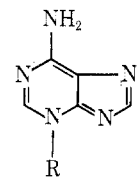
a, $R^1 = R^2 = R^3 = OMe$ **d**, $R^1 = R^2 = R^3 = OEt$
b, $R^1 = R^2 = OMe$; $R^3 = Me$ **e**, $R^1 = R^2 = OEt$; $R^3 = Et$
c, $R^1 = OMe$; $R^2 = R^3 = Me$ **f**, $R^1 = OEt$; $R^2 = Et$; $R^3 = Ph$



1, $R^1 = R^2 = R^3 = H$ **5**, $R^1 = R^2 = R^3 = Me$
2, $R^1 = R^3 = Me$; $R^2 = H$ **6**, $R^1 = R^2 = R^3 = Et$
3, $R^1 = H$; $R^2 = R^3 = Me$ **7**, $R^1 = R^3 = Me$; $R^2 = Et$
4, $R^1 = H$; $R^2 = R^3 = Et$ **8**, $R^1 = Me$; $R^2 = R^3 = Et$



9, R = H
11, R = Et



10, R = Me
12, R = Et

also have been reported to produce 3-alkyladenine preferentialy, whereas the reaction of alkyl halide with **9** in the presence of a base or with a sodium salt of **9** have been known to afford 9-alkyl derivative as a major product.

Those results indicate that the present procedure using alkyl esters of phosphorus oxy acids, especially a trialkyl phosphate, may be very useful for *N*-alkylation of purines.

Experimental Section

Uv and ir spectra were measured with Hitachi-3T, and Jasco IR-G spectrometers, respectively. Proton nmr spectra were recorded

Table I
Reactions of Purines with Alkyl Esters of Phosphorus Oxy Acids

Purine, P	Ester, E	Mole ratio, E/P	React. temp	React. time, hr	Product	Yield, %
Xanthine (**1**)	a	5	190	1.5	1,3,7-Trimethylxanthine (**5**)[a]	50
	b	5	190	2.5	**5**	51
	d	3	200	10.0	1,3,7-Triethylxanthine (**6**)	22
					3,7-Diethylxanthine (**4**)	25
	e	2	200	10.0	**6**	37
					4	39
Theophylline (**2**)	a	1.3	180	1.0	**5**	90
	b	1.3	190	5.0	**5**	98
	c	1.3	190	11.0	**5**	82
	d	3	180	1.3	7-Ethyl-1,3-dimethylxanthine (**7**)	79
	e	3	180	4.0	**7**	70
	f	3	210	2.0	**7**	90
Theobromine (**3**)	a	6	190	1.5	**5**	79
	b	3	190	11.0	**5**	77
	d	6	190	12.0	No reaction	
3,7-Diethyl-xanthine (**4**)	a	3	180	16.0	3,7-Diethyl-1-methylxanthine (**8**)	72
	b	5	190	16.0	**8**	65
	d	5	190	15.0	No reaction	
Adenine (**9**)[b]	a	1	140	2.0	3-Methyladenine (**10**)	45
	b	1	140	9.0	**10**	61
	d	1	140	4.0	3-Ethyladenine (**12**)	30
					9-Ethyladenine (**11**)	15
	e	1	140	13.0	**12**	13
					11	10

[a] Caffeine. [b] DMF was used as a solvent in the reactions.

on a Hitachi–Perkin Elmer R-20 spectrometer with a dilute solution in deuterochloroform, and tetramethylsilane as an internal standard.

Materials. Commercially available xanthine, theophylline, theobromine, and adenine, as well as trimethyl and triethyl phosphates were used without further purification. Dimethyl methyl- and diethyl ethylphosphonates were prepared quantitatively *via* Arbuzov reactions using the corresponding trialkyl phosphites and alkyl iodides.[10] Methyl dimethyl- and ethyl ethylphenylphosphinates were obtained by the procedure of Reinhardt, *et al.*,[11] and Steininger,[12] respectively. Reaction conditions are listed in Table I. The following preparations are typical.

Alkylation of Xanthine (1). A. With Trimethyl Phosphate (a). A mixture of **1** (3.0 g, 0.02 mol) and **a** (14.0 g, 0.1 mol) was refluxed with stirring. The light-boiling substances were removed from the resulting clear solution under reduced pressure to give a residue, which was then dissolved in chloroform, and the solution was neutralized with an aqueous solution of sodium hydrogen carbonate. Evaporation of the solvent from the organic solution gave caffeine (**5**) as crystals: 1.90 g (50%); mp 223–234° (tetrahydrofuran–diethyl ether) (lit.[13] mp 235°); λ_{max} (H_2O) 272 nm (log ϵ 4.04) [lit.[13] λ_{max} (H_2O) 272 nm (log ϵ 4.03)].

B. With Triethyl Phosphate (d). Compound (1) (3.25 g, 0.02 mol) and **d** (11.68 g, 0.06 mol) afforded the following two products after preparative thin layer chromatography (2-mm thickness, Silica gel G according to Stahl, E. Merck, Darmstadt, West Germany) of the chloroform extract, which was obtained from the reaction mixture in a manner similar to that mentioned above. A mixture of ether and ethanol (15:1) was employed as a developing solvent.

3,7-Diethylxanthine (4): 1.1 g (25%); R_f 0.5; mp 179–182° (H_2O) (lit.[14] mp 183°); ir (KBr) 3150 (w), 2980 (m), 1680 (s), 1540 (m), 1445 (w), 1275 (w), 1220 (w), 1030 (m), and 850 (m) cm^{-1}; nmr ($CDCl_3$) δ 8.90 (s, 1, NH), 7.50 (s, 1, ring H), 4.25 (q, 2, CH_2), 4.10 (q, 2, CH_2), 1.50 (t, 3, CH_3), and 1.32 (t, 3, CH_3).

1,3,7-Triethylxanthine (6): 1.1 g (22%); R_f 0.8; mp 108–111° (H_2O) (lit.[15] mp 111°); ir (KBr) 3100 (w), 2980 (w), 1700 (s), 1650 (s), 1545 (m), 1450 (m), 1230 (w), 1050 (w), 1020 (w), 875 (m), and 750 (m) cm^{-1}; nmr ($CDCl_3$) δ 7.45 (s, 1, ring H), 3.7–4.5 (complex m, 6, 3 CH_2) and 1.0–1.6 (complex m, 9, 3 CH_3).

Ethylation of Theophylline (2) with d. A mixture of **2** (3.46 g, 0.02 mol) and **d** (10.50 g, 0.06 mol) was heated at 180° for 1.3 hr. The reaction mixture was treated in a manner similar to the methylation of **1** to give 3.12 g (79%) of 7-ethyl-1,3-dimethylxanthine (**7**): mp 148–149° (ethanol) (lit.[2] mp 152–153°); ir (KBr) 3100 (w), 2980 (w), 1700 (s), 1650 (s), 1545 (m), 1480 (m), 1220 (m), 1190 (m), 1020 (w), 970 (m), and 740 (m) cm^{-1}; nmr ($CDCl_3$) δ 7.46 (s, 1, ring H), 4.35 (q, 2, CH_2), 3.62 (s, 3, NCH_3), 3.45 (s, 3, NCH_3) and 1.55 (t, 3, CH_3).

Methylation of 3,7-Diethylxanthine (4) with a. Compound **4** (1.0 g, 0.005 mol) was treated with excess of **a** to produce 0.8 g (72%) of 3,7-diethyl-1-methylxanthine (**8**): mp 96° (sublimed); ir (KBr) 3100 (w), 1700 (s), 1650 (s), 1545 (m), 1490 (m), 1230 (m), 1000 (m), and 750 (m) cm^{-1}.

Anal. Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 54.25; H, 6.18; 24.42.

Alkylation of Adenine (9). A. With a. A mixture of **9** (1.50 g, 0.01 mol) and **a** (1.40 g, 0.01 mol) in dimethylformamide (10 ml) was refluxed for 2 hr. The reaction mixture was allowed to stand overnight to yield crystals which was dissolved in aqueous sodium hydrogen carbonate and the solution was concentrated to dryness. Extraction of the residue with ethanol and evaporation of the solvent afforded 3-methyladenine (**10**) as crystals: 0.75 g (45%); mp 300° (water) (lit.[16] mp 302°); λ_{max} (H_2O) 274 nm (log ϵ 4.17) [lit.[16] λ_{max} (H_2O) 274 nm (log ϵ 4.21)].

B. With d. Adenine (1.50 g, 0.01 mol) and **d** (2.0 g, 0.01 mol) were refluxed in dimethylformamide (8 ml) for 4 hr. The solvent was evaporated under reduced pressure to give a residue, which was then dissolved in aqueous hydrogen carbonate and concentrated as much as possible. The resulting residue in ethanol was chromatographed on alumina (2 cm × 30 cm, 300 mesh, neutral). Elution with a mixture of ethyl acetate and methanol (10:1) gave 0.2 g (15%) of 9-ethyladenine (**11**): mp 193° (ethyl acetate–ether) (lit.[17] mp 194–195°); λ_{max} (H_2O) 260.0 nm (log ϵ 4.13) [lit.[17] λ_{max} (H_2O) 262 nm (log ϵ 4.15)].

Subsequent elution with the same solvent afforded 0.5 g (30%) of 3-ethyladenine (**12**): mp 229–232° (lit.[16] mp 233°); λ_{max} (H_2O) 274.5 nm (log λ 4.15) [lit.[16] λ_{max} (H_2O) 273 nm (log ϵ 4.04)].

Registry No.—**1,** 69-89-6; **2,** 58-55-9; **3,** 83-67-0; **4,** 53432-04-5; **5,** 58-08-2; **6,** 31542-50-4; **7,** 23043-88-1; **8,** 53432-05-6; **9,** 73-24-5; **10,** 5142-23-4; **11,** 2715-68-6; **12,** 43003-87-8; **a,** 512-56-1; **b,** 756-79-6; **c,** 14337-77-0; **d,** 78-40-0; **e,** 78-38-6; **f,** 2227-43-2.

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Synthesis of Furoguaiacidin Diethyl Ether

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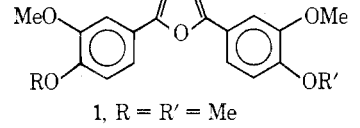
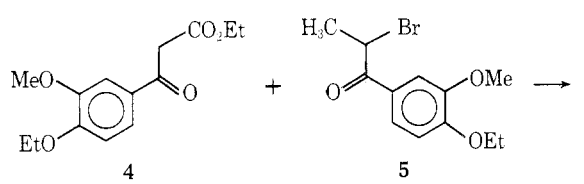
From "lignum vitae", the heartwood of *Guaiacum officinale*, King and Wilson[1] isolated and identified nine lignans including furoguaiacin [as the dimethyl ether (**1**)] and methylfuroguaiacin [as the ethyl ether (**2**)]. Until recently,



1, R = R′ = Me
2, R = Me; R′ = Et



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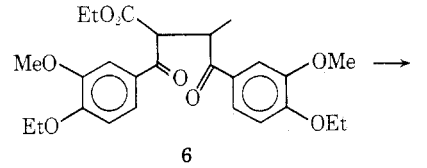

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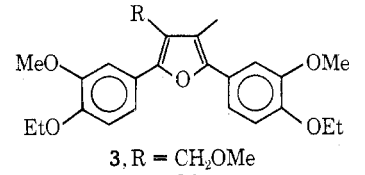

3, R = CH_2OMe
7, R = CO_2Et
8, R = CH_2OH