The *N*-Alkylation of Xanthine Derivatives with Trialkyl Phosphates

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The *N*-alkylation of xanthine, theophylline, and theobromine with trimethyl, triethyl, and triallyl phosphates in a weak alkaline aqueous solution is described. Especially, trimethyl phosphate converted these heterocycles to the corresponding *N*-methyl derivatives in good yields.

Xanthine and its methylated derivatives, such as theophylline and theobromine, occur in living systems, especially in plants. Since these methylated purines and other alkyl analogs are biologically and physiologically important, the *N*-alkylation of this class of heterocycles has been studied actively.

Various alkylating agents, such as dialkyl sulfate,[1-3] alkyl *p*-toluenesulfonate,[3] and alkyl halide,[4,5] have been used for the *N*-alkylation of xanthine and its derivatives. Although the site of alkylation is influenced by various conditions, it has been generally established that, under alkaline conditions, alkylation takes place in the following order, that of the decreasing acidity of the replaced proton: N-3, N-7, and then N-1. Under neutral or acidic conditions, on the other hand, only imidazole ring-nitrogens are alkylated, converting the purine into quaternised or betaine forms.

In previous papers, we reported the *N*-alkylation of purines,[6] imidazoles,[7,8] and pyrimidines[9] by heating with alkyl esters of phosphoric acid at about 200 °C. Since this procedure would be too vigorous for many natural products, however, we continued our search for mild conditions, using xanthine, theophylline, and theobromine. This paper will show a facile *N*-alkylation of this class of heterocycles in a weak alkaline aqueous solution at 25—60 °C. Unlike reactions with other alkylating agents, which in most cases are insoluble in water, the present reaction can be carried out successfully in an aqueous environment because of the water-soluble property of a trialkyl phosphate.

Results and Discussion

The reactions were carried out by stirring a mixture of a purine and a 2—5 molar excess of trialkyl phosphate in water (pH 9—10) at 25—60 °C. The products were isolated through extraction and recrystallization. The results are summarized in Table 1.

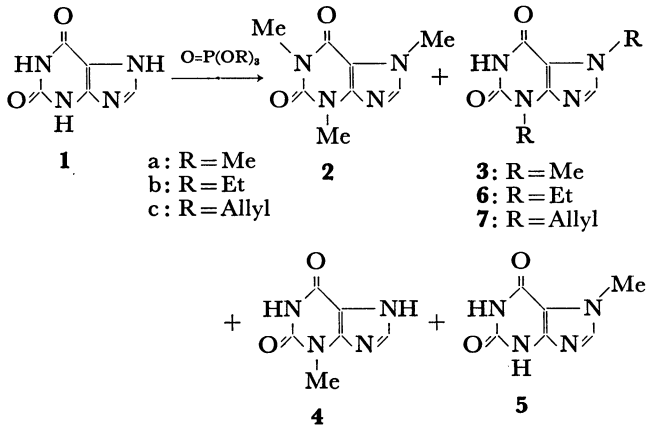
The reaction of xanthine (**1**) with trimethyl phosphate (**a**) at 25 °C for 48 h afforded four ultraviolet absorbing products (**2**—**5**). The **2** and **3** products were produced mainly, and identified as caffeine and theobromine respectively through their physical constants. Compounds **4** and **5** were identified as 3-methylxanthine and 7-methylxanthine respectively according to their ultraviolet absorption spectra. With an increase in the reaction temperature and the reaction time, **1** tends to be methylated effectively at the N-1, N-3, and N-7 positions to produce 1,3,7-trimethylxanthine (**2**, caffeine), while at low temperatures and short reaction times **3** is isolated as the only product. Ethylation and allylation took place also in **1** to give 3,7-dialkyl derivatives (**6**, **7**). These results suggest that the N-1 position of **1** is less reactive than the N-3 and N-7 positions.

This trend was observed also in the alkylation of theobromine (**3**) and theophylline (**10**). Thus, although **10** was alkylated with triethyl phosphate (**b**) or triallyl phosphate (**c**) to give the corresponding 7-alkyl derivatives (**11** and **12**) quantitatively, **3** was transformed to the 1-alkyl derivatives (**8** and **9**) in only low yields.

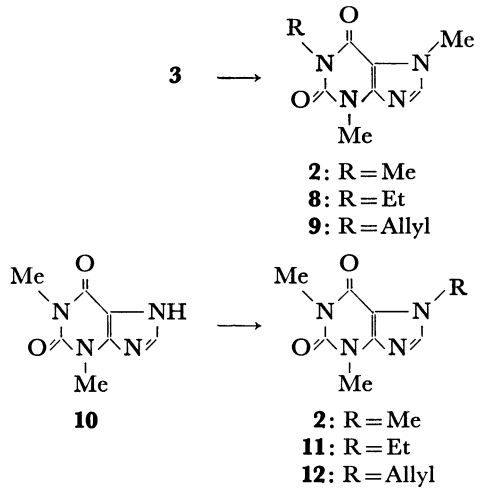
Table 1. Reactions of purines with trialkyl phosphates[a]

Purine	R of O=P $(OR)_3$	Mole ratio (Ester/Purine)	Temp (°C)	Time (h)	Product	Yield (%)
Xanthine (**1**)	Me	6	60	48	Caffeine (**2**)	73
1	Me	6	25	48	**2**	17
					3	9
					3-Methylxanthine (**4**)	Trace
					7-Methylxanthine (**5**)	Trace
1	Et	3	80	48	3,7-Diethylxanthine (**6**)	6
1	Allyl	3	60	48	3,7-Diallylxanthine (**7**)	15
Theophylline (**10**)	Me	6	25	48	**2**	83
10	Me	3	60	8	**2**	92
10	Et	3	60	48	7-Ethyltheophylline (**11**)	26
10	Allyl	3	60	48	7-Allyltheophylline (**12**)	50
Theobromine (**3**)	Me	6	25	100	**2**	87
3	Me	3	60	24	**2**	93
3	Et	3	60	48	1-Ethyltheobromine (**8**)	10
3	Allyl	3	60	48	1-Allyltheobromine (**9**)	16

a) The reactions were carried out in an aqueous solution at pH 9—10.



The low reactivity of the N-1 position towards alkylation might be attributed to the decreased nucleophilicity of the N-1 nitrogen atom and the steric hindrance around the N-1 position towards the alkyl groups of phosphate esters by two adjacent carbonyl groups at the 2 and 6 positions.



The order of the reactivity of trialkyl phosphates in aqueous solutions was $O=P(OCH_3)_3$ (**a**)>$O=P(OCH_2$–$CH=CH_2)_3$ (**c**)>$O=P(OCH_2H_5)_3$ (**b**). The high reactivity of **a** may result partly from its low steric hindrance at the reaction site. The unexpected high reactivity of **c**, in spite of its decreased solubility in water, may originate from its conjugated structure.

The above results indicate that trialkyl phosphate, especially **a**, may be a useful alkylating agent, allowing an alkylation reaction to proceed under mild conditions.

Experimental

The UV and IR spectra were measured with Hitachi EPS-3T and Jasco IR-G spectrometers respectively. The NMR spectra were recorded on a Hitachi-Perkin Elmer R-20 spectrometer, with a dilute solution in deuteriochloroform or dimethyl-d^6 sulfoxide and tetramethylsilane as the internal and outside standards. Thin-layer chromatography was performed on silica gel [GF_{254} (type 60), Merck] using a mixture of chloroform and methanol (7: 1). Commercially available xanthine, theophylline, and theobromine, as well as trimethyl and triethyl phosphates, were used without further purification. The triallyl phosphate was prepared by the procedure of Toy and Costello.[10]

The following preparations are typical. The reaction conditions are listed in Table 1.

Alkylation of Xanthine (1). *A. With Trimethyl Phosphate (a)*: *Procedure 1*: A mixture of **1** (1.38 g, 9.1 mmol) and **a** (7.50 g, 54.0 mmol) in water (10 ml) was stirred at 60 °C. The solution was maintained at pH 9—10 throughout the reaction by the occasional addition of 4 M sodium hydroxide. After 48 h of stirring, the reaction mixture was extracted with chloroform. The subsequent evaporation of the solvent from the organic extract gave caffeine (**2**) as crystals; mp 233—234 °C (from THF–ethanol) (lit,[11] mp 235 °C), (1.28 g, 73%).

Procedure 2: A mixture of **1** (1.35 g, 8.9 mmol) and **a** (7.50 g, 54.0 mmol) in water (20 ml, pH 9—10, NaOH) was stirred at 25 °C for 48 h. Thin-layer chromatography of the reaction mixture showed four ultraviolet absorbing products; R_f: **5**= 0.27, **4**=0.31, **3**=0.46, and **2**=0.69 (chloroform–methanol 7: 1). The subsequent evaporation of the solvent from the organic layer gave **2** as crystals; (0.29 g, 17%). The aqueous layer was neutralized with concentrated hydrochloric acid and extracted with chloroform. Upon the concentration of the organic layer, **3** was obtained as a white powder and was identified as theobromine by a comparison of its physical properties with those of an authentic sample (0.14 g, 9%). The ultraviolet spectra of the aqueous extract of the corresponding spots for **5** and **4** coincided with those of 7-methyl- and 3-methylxanthine respectively; 7-methylxanthine: λ_{max} (H_2O) nm: 265 (pH 1), 269 (pH 7), 283 (pH 13) [lit,[12] 266 (pH 0.8), 268 (pH 4), 268 (pH 7), 288 (pH 13)], 3-methylxanthine: λ_{max} (H_2O) nm: 269 (pH 1), 272 (pH 7), 275 (pH 13) [lit,[11] 270 (pH 6), 274 (pH 14)].

B. With Triallyl Phosphate (c): The treatment of **1** (1.52 g, 10.0 mmol) with **c** (5.10 g, 30 mmol) in water (10 ml, pH 9—10, NaOH) gave 3,7-diallylxanthine (**7**, 0.38 g, 15%) after the reaction mixture had been stirred at 60 °C for 48 h; mp 182.5—184 °C (from ethanol); IR (KBr): 3000 (m), 2800 (w), 1680 (s), 1585 (m), 1540 (m), 1375 (m), 1295 (w), 1265 (m), 1130 (m), 990 (s), 920 (s), 840 (m), 750 (w), and 620 cm^{-1} (m); NMR (DMSO-d^6): 4.43 (complex m, 2H, $-CH_2$–CH=CH_2), 4.60—5.30 (complex m, 2H, $-CH_2$–CH=CH_2), 5.45—6.25 (complex m, 1H, $-CH_2$–CH=CH_2), and 7.92 ppm (δ) (s, 1H, H[8]); UV, λ_{max} (H_2O) nm: pH 1, 269 (log ε 4.13), pH 7, 273 (log ε 3.96), pH 13, 275 (log ε 4.00); Found: C, 56.54; H, 5.08; N, 23.74%. Calcd for $C_{11}H_{12}N_4O_2 \cdot 0.1H_2O$: C, 56.54; H, 5.22; N, 23.95%.

Alkylation of Theophylline (10). *A. With Trimethyl Phosphate (a)*: A mixture of **10** (1.54 g, 8.6 mmol) and **a** (3.75 g, 27.0 mmol) was stirred in water (10 ml, pH 9—10, NaOH) at 60 °C for 8 h. After the reaction mixture had then been allowed to stand at room temperature, **2** appeared as crystals from the solution (1.28 g, 79%). The organic layer was concentrated to give another crop of **2** (0.20 g, 12%).

B. With Triallyl Phosphate (c): A reaction of **10** (1.81 g, 10.0 mmol) with **c** (5.10 g, 30.0 mmol) in water (10 ml, pH 9—10, NaOH) at 60 °C for 48 h afforded 7-allyltheophylline (**9**, 1.11 g, 50%) after a procedure similar to that described above; mp 101—103 °C (from hexane) (lit,[13] 101—102 °C); IR (KBr): 3100 (m), 2950 (w), 1700 (s), 1655 (s), 1550 (m), 1480(m), 1370 (w), 1230 (m), 1030 (m), 940 (w), 760 (s), 750 (s), and 620 cm^{-1} (m); NMR ($CDCl_3$): 3.48 (s, 3H, $-CH_3$), 3.67 (s, 3H, $-CH_3$), 5.03 (complex m, 2H, $-CH_2$–CH=CH_2), 5.20—5.53 (complex m, 2H, $-CH_2$–CH=CH_2), 5.70—6.45 (complex m, 1H, $-CH_2$–CH=CH_2), and 7.65 ppm (δ) (s, 1H, H[8]); UV, λ_{max} (H_2O) nm: pH 1, 273 (log ε 3.98), pH 7, 275 (log ε 3.94), pH 13, 275 (log ε 3.94); Found: C, 54.47; H, 5.43; N, 26.00%. Calcd for $C_8H_{10}N_4O_2$: C, 54.54;

H, 5.49; N, 25.44%.

Alkylation of Theobromine (3) with Triallyl Phosphate (c). A reaction of **3** (1.81 g, 10.0 mmol) with **c** (5.20 g, 30.0 mmol) in water (10 ml, pH 9—10, NaOH) at 60 °C for 48 h afforded 1-allyltheobromine (**9**, 0.29 g, 16%) upon the treatment of the reaction mixture in a manner similar to that described above; mp 139—142 °C (sublime); IR (KBr): 3200 (m), 2900 (w), 1700(s), 1640 (s), 1540 (m), 1450 (m), 1360 (m), 1275 (w), 1230 (m), 1100 (w), 920 (s), 860 (w), 760 (s), 740 (s), 650 (w), and 620 cm^{-1} (m); NMR ($CDCl_3$): 3.58 (s, 3H, $-CH_3$), 4.00 (s, 3H, $-CH_3$), 4.63 (complex m, 2H, $-CH_2-CH=CH_2$), 5.03—5.47 (complex m, 2H, $-CH_2-CH=CH_2$), 5.48—5.96 (complex m, 1H, $-CH_2-CH=CH_2$), and 7.53 ppm (δ) (s, 1H, H^8); UV, λ_{max} (H_2O) nm: pH 1, 274 (log ε 4.03), pH 7, 275 (log ε 4.01), pH 13, 275 (log ε 4.01); Found: C, 54.77; H, 5.40; N, 25.88%. Calcd for $C_8H_{10}N_4O_2$: C, 54.54; H, 5.49; N, 25.44%.

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