REGIOSPECIFIC ALKYLATION OF 9-BENZYL-1,3-DIMETHYL-6-HYDROXYPYRIMIDO[2,1-f]PURINE-2,4,8(1H,3H,9H)-TRIONE

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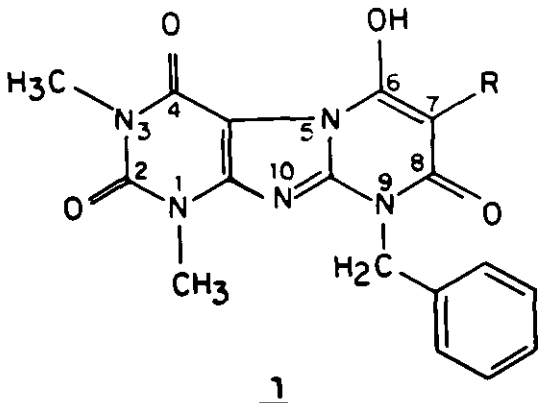
Abstract - The sodium salt of 9-benzyl-1,3-dimethyl-6-hydroxypyrimido[2,1-f]purine-2,4,8(1H,3H,9H)-trione (1a) reacted with a series of alkyl halides in N,N-dimethylformamide to yield 7-carbon alkylated products (1b-l). No O-alkylated products were detected. Isolated yields (not optimized) were in the range of approximately 15-58% for activated halides; non-activated halides were substantially less reactive and gave lower yields. The effects of reaction parameters on reactivity and site of alkylation are discussed, and it is demonstrated that the observed regiospecificity is not the result of an equilibration process.

As part of a program directed toward identification of novel therapeutic agents, the preparation of a number of pyrimidopurines (1b-l), modified at the 7-position of the tricyclic nucleus, was of interest.



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a: R = H
b-l: R = ALKYL (see Table I)

The 7-unsubstituted nucleus (1a)[1] can be prepared by the condensation of 8-benzylamino-theophylline (2)[2] with diethyl malonate (3, R = H), as shown in Scheme I. In principle, a variety of 7-substituents can be introduced by use of the appropriately substituted malonate esters. Since it was of interest to prepare a series of compounds, for which most of the requisite substituted malonate esters 3 would not be commercially available and would thus have to be prepared independently, the advantage of utilizing the 7-unsubstituted nucleus (1a) as a common intermediate in a direct alkylation process is apparent (Scheme II).

Furthermore, we had already discovered one instance in which the process described in Scheme I failed to yield the desired product: viz., wherein excess 3 with R = $CH_2CH{=}CH_2$ was reacted with 2 at 185-200°C. in the presence of catalytic sodium methoxide.

The 7-unsubstituted compound (1a) could be prepared in large (>100-gram quantities), but we anticipated that alkylation of the 6-hydroxyl group might compete to a significant extent with the desired carbon-alkylation process,[3] as illustrated in Scheme II. Compounds 1 as a class are relatively polar and insoluble materials. Thus, the necessity of separating isomeric reaction products with such physical properties could offset any advantage inherent in the common intermediate approach. However, we have observed remarkable selectivity for carbon alkylation in the tricyclic system 1a, and it is this finding, along with the concommitant limitations of the reaction, which constitutes the subject of this paper.

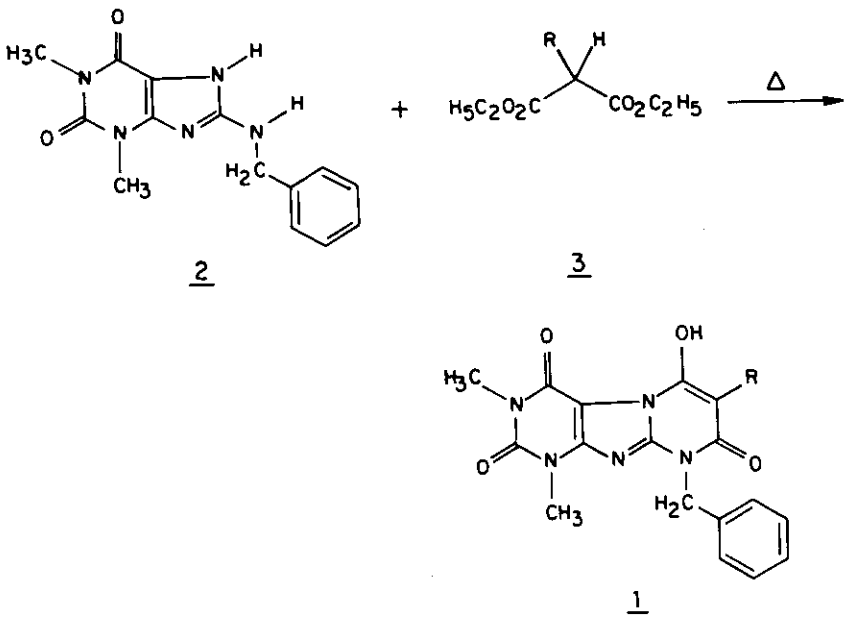
RESULTS AND DISCUSSION

N,N-Dimethylformamide was utilized as the solvent of choice in this study, mainly because of the relatively limited solubility of 1a and its salts in other solvents frequently employed in enolate anion alkylations (e.g., ethanol or benzene/toluene). Another limiting factor in the choice of solvent was the potential for solvolysis of some of the more reactive halides employed in this study. In addition, as discussed below, in an early experiment, N,N-dimethyl-formamide was found to promote allylation, which had failed when acetone was used as a solvent.

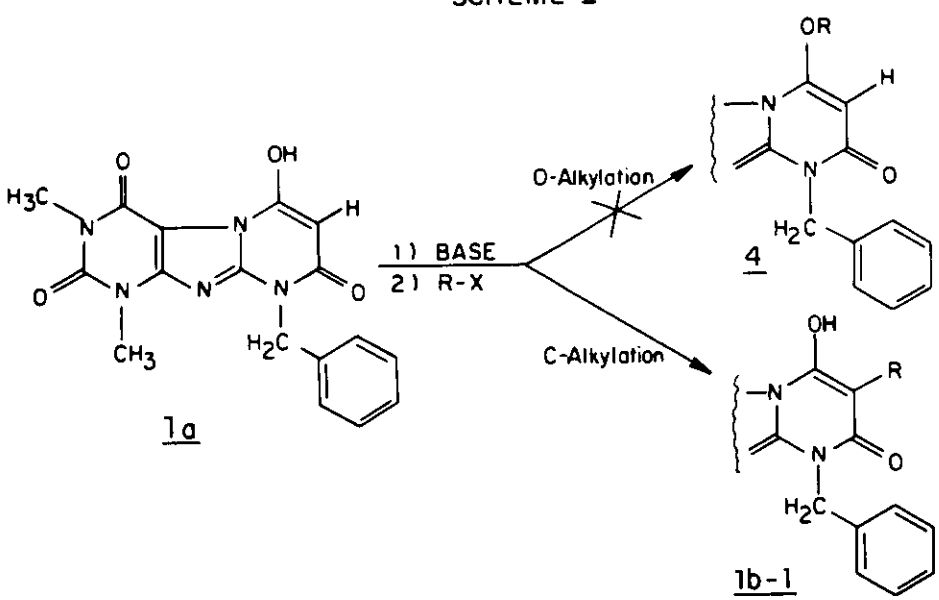
The alkylating agents employed were mainly bromides, which were preferred for their expected higher level of reactivity compared with the corresponding chlorides. The use of iodides has been suggested to be less satisfactory for the alkylation of sodium salts in N,N-dimethyl-formamide due to complexing with the solvent of the sodium iodide formed in the reaction.[4] However, we have obtained satisfactory results using iodomethane in N,N-dimethylformamide.

Both in situ enolate formation and utilization of preformed sodium salt appeared to produce comparable results with respect to the course and extent of reaction.

SCHEME I



SCHEME II



Reactivity. The nature of the alkylating agent was found to exert a significant effect on the ability to achieve reaction. As indicated in Table I, most of the substrates examined were relatively reactive primary halides (e.g., allylic, benzylic) and were capable of alkylating the enolate at room temperature. Although normally regarded as more reactive than allylic-type halides, bromoacetonitrile and methyl bromoacetate required substantial elevation of temperature to achieve a practical alkylation rate. Not unexpectedly, 1-iodopropane proved to be decidedly less reactive than the activated halides examined. It gave a poor yield of the partially purified 7-propyl product.

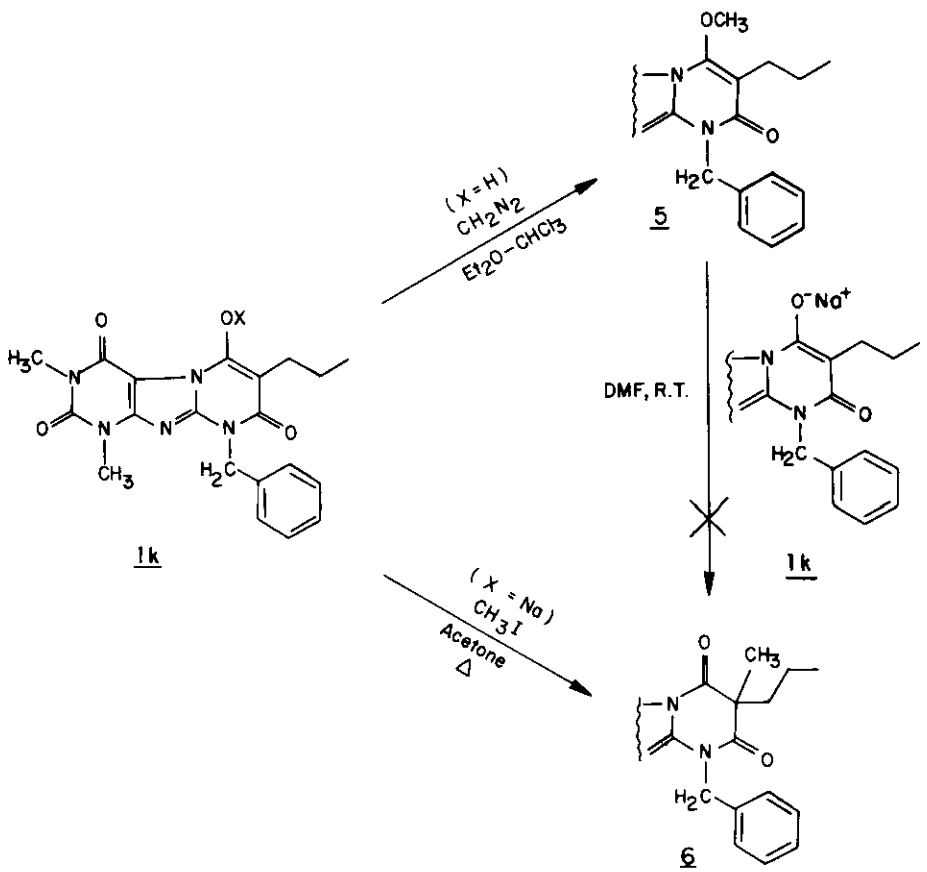
The effect of solvent must also be considered: when reaction of 1a with allyl bromide was attempted in acetone, starting pyrimidopurine was recovered unchanged, as contrasted with the results in N,N-dimethylformamide, in which the reaction proceeded readily at room temperature. Based upon this observation, as well as the solubility considerations described above, N,N-dimethylformamide was selected as the solvent of choice in subsequent alkylation experiments. Although we did not systematically explore the effect of added crown ether on the alkylation of the pyrimidopurine nucleus, in the case of propargyl bromide we observed complete recovery of unchanged starting material after 4 h at room temperature in the absence of crown ether, whereas the alkylation had proceeded to a significant extent after 16 h at room temperature in the presence of 18-crown-6.

The alkylation failed decisively with the beta-oxygenated primary bromides 2-bromoethanol and 2-bromo-1,1-dimethoxyethane. Under mild conditions (to 50°C.), the pyrimidopurine 1a was recovered unchanged; as reaction temperatures were raised above 50°C., formation of complex mixtures was observed. Isolation of the components of these mixtures was not pursued. 2-Bromoethyl ether was found to react slowly at elevated temperature (80-100°C.) in the presence of 15-crown-5. As a class, beta-oxygenated halides are known to be significantly less reactive in nucleophilic displacements than are the activated halides used in this study. Surprisingly, however, even the relatively reactive epibromohydrin gave no evidence of alkylation after overnight treatment of 1a at room temperature in the presence of 18-crown-6. Higher reaction temperatures were not investigated.

It should be noted that the isolated yields reported in Table I have not been optimized. Indeed, in many instances, the reactions were not carried out to complete disappearance of starting pyrimidopurine, implying that longer reaction times or a modest elevation of reaction temperature might enhance the yield of alkylation product.

Regiospecificity. In all the reactions of the sodium enolate of 1a summarized in Table I, only C-alkylation products were observed. No O-alkylation products were detected. In two instances,

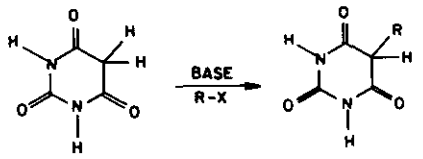
SCHEME III


OCH3
(X=H)
CH2N2
Et2O-CHCl3
5
O⁻Na⁺
DMF, R.T.
1k
1k
(X=Na)
CH3I
Acetone
Δ
CH3
6

prenylation (1j) and carbomethoxymethylation (1h), as noted in Table I, bisalkylation on carbon was observed.

We ascertained that under the reaction conditions no isomerization of O-alkylated to C-alkylated product would occur (Scheme III). Methyl iodide treatment of the sodium enolate of 1k gave the C-methylation product (6) only, consistent with the results obtained with the sodium enolate of 7-unsubstituted 1a.[5] In contrast, we found that diazomethane treatment of the free acid form of 1k gave exclusively O-methylation with no evidence of alkylation on carbon. A solution of the O-methylated product 5 in dimethylformamide was treated with a molar equivalent of the sodium salt of 1k, and the mixture was stirred overnight at room temperature. No C-methylated isomer 6 was detected.[6] We find the regiospecificity of this alkylation process to be noteworthy, particularly in view of the fact that the pyrimidopurine 1a appears to be completely enolized in solution: the proton NMR spectrum of 1a in DMF-d_7 shows the 7-H as an exchangeable one-proton singlet at δ5.55. Alkylation of barbituric acid (7), which may be regarded as a monocyclic analog of our fused pyrimidinedione system, takes place on carbon[7] (Scheme IV). However, it is known that in the solid state barbituric acid prefers the non-enolized triketo structure shown.[8] Furthermore, the PMR spectrum of barbituric acid in DMF-d_7 shows two broad 2-proton singlets at δ11.07 (NH) and 3.61 (C-5 protons), respectively, which supports the existence of structure 7 in solution. This significant difference between the enol 1a and the superficially analogous barbituric acid might have been expected to result in substantially different C-versus O-alkylation behavior by the two systems.

SCHEME IV



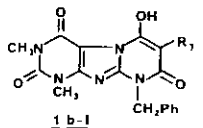
7 8

Analysis of the anticipated effects of the reaction parameters on regioselectivity[9] provides no insight into the observed predisposition of 1a to carbon alkylation exclusively. With respect to the influence of solvent, N,N-dimethylformamide might have been expected to promote alkylation of the more electronegative oxygen atom of the ambident nucleophile. Similarly, crown ether (used in propargylation (1c), benzylation (1g), and carbomethoxymethylation (1h), as noted in Table I) might have been expected to promote production of a "naked" enolate with attendant charge localization and consequent alkylation on oxygen. On the other hand, the

relatively "soft" electrophiles (allylic, benzylic, etc.) employed in this study should tend to favor the observed C-alkylation. The combined regiodirective effect of the sodium cation of the enolate and the bromide leaving group of the alkylating agents employed is probably modest, but might also have been expected to favor C-alkylation.

Our empirical observation that the net effect of these opposing factors is to render alkylation on carbon exclusively is a result not unequivocally predictable on theoretical grounds.

TABLE 1 Summary of Reaction and Purification Parameters, Melting Points, and Yield Data for Alkylation of 9-Benzyl-1,3-Dimethyl-6-hydroxypyrimido-[2,1-f]purine-2,4,8(1H,3H,9H)-trione



1 b-l

Compound No.	R_7	Crown Ether	Na Salt Preformed	Temp. °C.	Time Hr.	Equivalents of Alkyl Halide[a]	M.P., °C. (Rexal. Solvent) 6-OH	M.P., °C. 6-O⁻Na⁺	Processing Method	Chromatography Solvent	Isolated Yield,%
1b	$-CH_2CH{=}CH_2$	-	+	R.T.	5	2.7	220-222 (not rexal.)	280-300	A	MeOH-$CHCl_3$-NH_4OH (1:1:0.01)	35
1c	$-CH_2C{\equiv}CH$	18-C-6	+	R.T.	≥16	3.4	236-238 ($CHCl_3$-EtOAc)	[not prepared]	A	$CHCl_3$-MeOH (95:5)	16
1d	$-E-CH_2CH{=}CHCH_3$	-	-	R.T.	≥16	1.7	203-205 ($CHCl_3$-EtOAc)	260-280	A	Not chromatographed	36
1e	2-cyclohexen-1-yl	-	-	R.T.	18	1.5	160-162 ($CHCl_3$-Et_2O)	280-300	A	$CHCl_3$-MeOH (98:2)	46
1f	$-CH_2CH{=}C(CH_3)_2$	-	-	R.T.	20	1.4	185-187 ($CHCl_3$-Et_2O)	240-260	A	$CHCl_3$-MeOH (95:5)	31[b]
1g	$-CH_2Ph$	18-C-6	+	R.T.	≥16	2.1	190-195 (not rexal.)	[not prepared]	A	$CHCl_3$-MeOH (95:5)	27
1h	$-CH_2CO_2CH_3$	15-C-5	-	80	10	1.2	211-214.5 (not rexal.)	227-230 (dec)	B	$CHCl_3$-MeOH-NH_4OH (84:14:1)	58[c]
1i	$-CH_2C{\equiv}N$	-	+	*80*	*18*	1.1	dec >195 (MeOH-CH_3CN)	*[not prepared]*	B	$CHCl_3$-MeOH-NH_4OH (85:14:1)	50 (chromatog.) 17 (rexal.)
1j	$-CH_3$[d]	-	-	R.T.	18	1.1	208-210 ($CHCl_3$-EtOAc)	[not prepared]	A	Not chromatographed	>22
1k	$-CH_2CH_2CH_3$[d]	15-C-5	-	50-95	60	3.6	191-210[e] (not rexal.)	[not prepared]	C	Acetone-CH_2Cl_2-AcOH (1:1:0.002)	6
1l	$-(CH_2)_2-OC_2H_5$	15-C-5	-	80-100	30.5	6.0	156.5-167.5	>300	C	$CHCl_3$-MeOH (99:1)	11

a. *The alkyl bromide was used unless otherwise noted.*

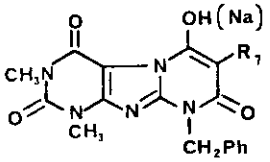
b. The 7,7-bisprenylated product (1f'; mp 154-156°C.) was also isolated (28% yield).

c. The 7,7-biscarbomethoxymethylated product (1h'; mp 205-206°C.) was also isolated (7% yield).

d. The alkylation was carried out with the corresponding alkyl iodide.

e. Isolated sample was contaminated with the 7,7-dipropylated product. A pure sample, prepared by the method illustrated in Scheme I, had mp 208-210°C.

TABLE II Summary of Spectroscopic Data for 7-Alkylated and 7,7-Dialkylated-9-benzyl-1,3-dimethyl-6-hydroxypyrimido[2,1-f]purine-2,4,8(1H,3H,9H)-triones



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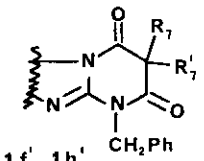

1f', 1h'

Compound No.	R_7 [R_7']	Molecular Formula	Elemental Analysis	C	H	N	Na	PMR Chemical Shifts, δ Solvent		Mass Spectrum m/e (rel. int.)	Infrared Spectrum, cm^{-1}
1b	$-CH_2CH=CH_2$	$C_{20}H_{18}N_5O_4Na\cdot H_2O$	Calcd.:	55.42	4.65	16.16	5.30	DMSO-d_6	3.05 (d, 2H, J≈6Hz), 3.2 (s, 3H), 3.4 (s, 3H), 4.6-5.1 (m, 2H, 5.6-6.0 (m, 1H), 7.3 (m, 5H)	393 (8), 91 (100)	3400, 1705, 1650, 1620, 1590, 1550
			Found:	55.04	4.33	16.42	5.54				
1c	$-CH_2C\equiv CH$	$C_{20}H_{16}N_5O_4Na\cdot 1/2H_2O$	Calcd.:	56.87	4.06	16.58	5.45	DMSO-d_6	2.35 (m, 1H), 3.2 (s, 3H), 3.4 (s, 3H), 3.4-3.5 (m, 2H), 5.2 (s, 2H), 7.2-7.4 (m, 5H)	391 (4), 285 (16), 91 (100)	3400, 3300, 1710, 1660, 1625, 1595, 1550, 1515
			Found:	56.73	4.26	16.31	4.98				
1d	$-E-CH_2CH=CHCH_3$	$C_{21}H_{20}N_5O_4Na\cdot H_2O$	Calcd.:	56.37	4.96	15.66	5.14	DMSO-d_6	1.55 (d, 3H, J≈7Hz), 3.0 (m, 2H), 3.2 (s, 3H), 3.4 (s, 3H), 5.2 (s, 2H), 5.3-5.5 (m, 2H), 7.3 (m, 5H)	407 (2), 91 (100)	3440, 1705, 1650, 1620, 1590, 1550, 1515
			Found:	56.52	4.59	16.01	5.19				
1e	2-cyclohexen-1-yl	$C_{23}H_{22}N_5O_4Na\cdot 2/3H_2O$	Calcd.:	59.09	5.03	14.98	4.92	DMSO-d_6	1.4-2.2 (m, 6H), 3.2 (s, 3H), 3.4 (s, 3H), 3.4-3.8 (m, 1H), 5.2 (s, 2H), 5.5 (br s, 2H), 7.3 (m, 5H)	433 (11), 342 (20), 91 (19), 87 (100)	3400, 1705, 1650, 1620, 1585, 1545, 1515
			Found:	59.17	4.68	15.05	4.93				
1f	$-CH_2CH=(CH_3)_2$	$C_{22}H_{22}N_5O_4Na\cdot H_2O$	Calcd:	57.26	5.24	15.18	4.98	DMSO-d_6	1.55 (s, 3H), 1.65 (s, 3H), 3.0 (d, 2H, J≈7.5Hz), 3.2 (s, 3H), 3.4 (s, 3H), 5.2 (s, 2H), 5.1-5.3 (m, 1H), 7.3 (m, 5H)	421 (3), 91 (98), 44 (100)	3400, 1705, 1650, 1620, 1590, 1550, 1510
			Found:	56.86	4.95	15.26	5.00				

(Continued)

TABLE II Summary of Spectroscopic Data for 7-Alkylated and 7,7-Dialkylated-9-benzyl-1,3-dimethyl-6-hydroxypyrimido[2,1-f]purine-2,4,8(1H,3H,9H)-triones

Compound No.	R_7 [R_7']	Molecular Formula	Elemental Analysis	C	H	N	Na	PMR Chemical Shifts, δ Solvent		Mass Spectrum m/e (rel. int.)	Infrared Spectrum, cm^{-1}
1f'	$-CH_2CH=C(CH_3)_2$ [$-CH_2CH=C(CH_3)_2$]	$C_{27}H_{31}N_5O_4$	Calcd.:	66.24	6.38	14.31	-	$CDCl_3$	1.47 (s, 6H), 1.52 (s, 6H), 2.8 (d, 4H, J≈7.5Hz), 3.4 (s, 3H), 3.6 (s, 3H), 4.8 (m, 2H), 5.2 (s, 2H), 7.2-7.5 (m, 5H)	489 (4), 421 (95), 366 (87), 330 (100), 91 (97)	1760, 1710, 1695, 1665, 1625, 1580, 1510
			Found:	66.39	6.25	14.12	-				
1g	$-CH_2Ph$	$C_{24}H_{21}N_5O_4$	Calcd.:	65.00	4.77	15.80	-	$CDCl_3$	3.45 (s, 3H), 3.65 (s, 3H), 3.8 (s, 2H), 5.35 (s, 2H), 7.1-7.6 (m, 10H), 14.4 (exchangeable s, 1H)	443 (27), 352 (96), 91 (100)	1705, 1680, 1660, 1600, 1500
			Found:	65.16	4.80	15.99	-				
1h	$-CH_2CO_2CH_3$	$C_{20}H_{19}N_5O_6$	Calcd.:	56.47	4.50	16.46	-	$CDCl_3$	3.45 (s, 3H); 3.57 (s, 2H), 3.65 (s, 3H), 3.70 (s, 3H), 5.36 (s, 2H), 7.25, 7.50 (m, 5H), 14.64 (exchangeable s, 1H)	425 (22), 366 (100), 91 (98)	1735, 1700, 1650, 1615, 1548, 1508
			Found:	56.51	4.57	16.39	-				
1h'	$-CH_2CH_2CH_3$ [$-CH_2CO_2CH_3$]	$C_{23}H_{23}N_5O_8$	Calcd.:	55.63	4.66	14.08	-	$CDCl_3$	3.17 (s, 4H), 3.38 (s, 3H) 3.47 (s, 6H), 3.57 (s, 3H), 5.31 (s, 2H), 7.34 (m, 5H)	497 (52), 91 (100)	1763, 1736, 1709, 1672, 1631, 1577, 1508
			Found:	55.62	4.71	14.15	-				
1i	$-CH_2C\equiv N$	$C_{19}H_{16}N_6O_4$[a]	Calcd.:	58.16	4.11	21.42	-	$DMSO-d_6$	3.20 (s, 3H), 3.35 (s, 2H), 3.37 (s, 3H), 5.20 (s, 2H), 7.30 (m, 5H)	392 (33), 301 (84), 91 (100)	3480, 3220, 2240, 1705, 1655, 1615, 1590, 1555, 1515
			Found:	54.32	4.13	21.47	-				
1j	$-CH_3$	$C_{18}H_{17}N_5O_4$	Calcd.:	58.85	4.67	19.07	-	$CDCl_3$	2.00 (s, 3H), 3.43 (s, 3H), 3.61 (s, 3H), 5.34 (s, 2H), 7.15-7.60 (m, 5H), 14.12 (exchangeable s, 1H)	367 (34), 276 (100), 91 (85)	1705, 1688, 1656, 1605, 1505
			Found:	58.85	4.66	19.06	-				

(Continued)

TABLE II Summary of Spectroscopic Data for 7-Alkylated and 7,7-Dialkylated-9-benzyl-1,3-dimethyl-6-hydroxypyrimido[2,1-f]purine-2,4,8(1H,3H,9H)-triones

Compound No.	R_7 [R_7']	Molecular Formula	Elemental Analysis	C	H	N	Na	PMR Chemical Shifts, δ Solvent		Mass Spectrum m/e (re. int.)	Infrared Spectrum, cm^{-1}
1k	$-CH_2CH_2CH_3$ [b]	$C_{20}H_{21}N_5O_4$	Calcd.:	60.75	5.35	17.71	-	$DMSO-d_6$	0.85 (t, 3H, J=7Hz), ~1.1-1.6 (m, 2H), ~2.2-2.5 (m, ~2H, overlaps DMSO-d_6), 3.25 (s, 3H), 3.42 (s, 3H), 5.23 (s, 2H), 7.28 (m, 5H)	395 (2), 366 (20), 159 (56), 91 (23), 58 (100)	1706, 1684, 1662, 1605, 1536, 1505
			Found:	60.91	5.57	17.70	-				
1l	$-CH_2CH_2OC_2H_5$	$C_{21}H_{23}N_5O_5$	Calcd.:	59.28	5.45	16.46	-	$CDCl_3$	1.15 (t, 3H, J=7Hz), 2.85 (t, 2H, J≈7Hz), 3.30-3.77 (m, 4H), 3.45 (s, 3H), 3.63 (s, 3H), 5.37 (s, 2H), 7.25, 7.50 (m, 5H), 1425 (exchangeable s, 1H)	425 (2), 366 (88), 91 (100)	1700, 1685, 1655, 1608, 1510
			Found:	59.23	5.40	16.44	-				

a. Carbon analysis exceeded ± 0.4% deviation from theory.

b. Isolated sample was contaminated with the 7,7-dipropylated product. Tabulated data are derived from a pure sample prepared by the method illustrated in Scheme I.

EXPERIMENTAL

General. Melting points were determined on a Thomas-Hoover or Electrothermal capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian CFT-20 (79.5 MHz) or EM-390 (90 MHz) spectrometer, and are expressed as ppm (δ) from Me_4Si internal standard. The solvents in which the spectra were obtained are specified in the text and in Table II. IR spectra were obtained on nujol mulls and were recorded on a Varian MAT CH5 spectrometer. Microanalyses were performed by the Physical Analytical Services Department of the Schering Pharmaceutical Research Division, and carbon, hydrogen and nitrogen results were within ± 0.4% of theory except as noted in Table II. Unless otherwise indicated, all reagents and chemicals were obtained commercially and were used without pretreatment or further purification.

9-BENZYL-1,3-DIMETHYL-6-HYDROXYPYRIMIDO[2,1-f]PURINE-2,4,8(1H,3H,9H)-TRIONE (1a)

A mixture of 10.0 g (0.0351 mole) of benzylaminotheophylline[2] and 60 ml of diethylmalonate was stirred under a nitrogen atmosphere for 2.5 h in an oil bath maintained at approximately 200°C. The mixture was allowed to cool to room temperature and was then diluted with approximately 150 ml of diethyl ether; the resultant off-white precipitate was collected. This crude product was dissolved in 250 ml of chloroform. The solution was washed once with 100 ml of ice-water and was dried over anhydrous magnesium sulfate. Solvent was removed in vacuo (rotavapor), the residue was triturated with ethyl acetate, and 10.3 g (83%) of off-white solid with mp 211-214°C. was collected. The title compound thus obtained was sufficiently pure to be utilized in the alkylation experiments described below without further treatment. PMR ($CDCl_3$): 14.34 (s, ≤1H), 7.2-7.6 (m, 5H), 5.55 (exchangeable s, 1H), 5.35 (s, 2H), 3.65 (s, 3H), 3.46 (s, 3H); MS: 353 (3%, M^+), 91 (100%); IR (Nujol): 1704, 1678, 1658, 1600, 1505 cm^{-1}; Anal. Calcd. for $C_{17}H_{15}N_5O_4$: C, 57.78; H, 4.28; N, 19.82. Found: C, 57.60; H, 4.25; N, 19.67.

Sodium Salt of 1a: A suspension of 10.3 g (0.029 mole) of the 6-hydroxy form of 1a was suspended in 250 ml of water. To the stirred suspension was added 27 ml of 1N aqueous sodium hydroxide, and the mixture was stirred at room temperature for 30 min. (pH fell to ≤8 as measured by pH paper). Excess undissolved free acid was filtered out, and the filtrate was lyophilized. The residual solid was triturated with ether and filtered to give the sodium salt as an off-white powder with a decomposition point above 295°C. Such material could be alkylated without further purification. PMR (DMSO-d_6): 7.3 (m, 5H), 5.2 (s, 2H), 4.4 (exchangeable s, 1H), 3.4 (s, 3H), 3.15 (s, 3H); MS: 353 (3%, M^+), 285 (100%), 91 (79%); IR (Nujol): 3400, 1710, 1650, 1620, 1600, 1550, 1515 cm^{-1}; Anal Calcd. for $C_{17}H_{14}N_5O_4Na \cdot 0.5H_2O$: C, 53.23; H, 3.93; N, 18.22; Na, 5.98. Found: C, 52.96; H, 3.78; N, 17.94; Na, 5.56.

ALKYLATION OF 9-BENZYL-1,3-DIMETHYL-6-HYDROXYPYRIMIDO[2,1-f]PURINE-2,4,8(1H,3H,9H)-TRIONE (1a): GENERAL METHOD

The sodium salt of 1a was prepared *in situ* as described below. Alternatively, in some cases, the preformed sodium salt (isolation described above) was utilized. Reaction parameters, as well as details of product purification, are summarized in Table I.

To a suspension of 1a in N,N-dimethylformamide (12-15 ml per gram of 1a) was added ≥1.2 molar equivalents of sodium hydride (a commercial oil dispersion [Alfa] was generally prewashed with petroleum ether, but in some cases was used without washing), and the resultant mixture was stirred in an inert atmosphere at room temperature for 15-30 min. An excess (10 to 500 molar%) of the alkyl halide was then added and the reaction mixture allowed to stir under inert gas at the temperature and for the time interval indicated in Table I.

At the end of the reaction period, the mixture was processed according to one of the three following methods.

Processing Method A. The reaction mixture was poured into a stirred ice-water mixture. The resultant moist precipitate was collected and dissolved in chloroform. The chloroform solution was washed with water and dried (anhydrous magnesium sulfate). Solvent was removed *in vacuo*, and the residue was chromatographed on silica gel, eluting with the solvent system indicated in Table I. In some cases, the chromatographically isolated products were further purified by *recrystallization*.

Processing Method B. Dimethylformamide was removed from the reaction mixture under vacuum, and the residue was triturated with ether. The mixture was filtered, and the solid thus collected was dissolved in the eluting solvent and chromatographed on silica gel.

Processing Method C. Dimethylformamide was removed from the reaction mixture under vacuum. The residue was partitioned between methylene chloride and dilute aqueous hydrochloric acid. The organic extract was washed successively with water and brine, dried (anhydrous magnesium sulfate), and evaporated under reduced pressure. The residue thus obtained was chromatographed on silica gel.

Characterization of Alkylation Products. Spectroscopic data for alkylation products 1b-1, 1f', and 1h' in either 6-hydroxy or sodium salt form, as indicated, are summarized in Table II.

9-BENZYL-1,3-DIMETHYL-6-METHOXY-7-(1-PROPYL)PYRIMIDO[2,1-f]PURINE-2,4,8(1H,3H,9H)-TRIONE (5)

To an ice-cooled solution of 3.0 g (7.59 mmoles) of 9-benzyl-1,3-dimethyl-6-hydroxy-7-(1-propyl)-pyrimido[2,1-f]purine-2,4,8(1H,3H,9H)-trione in 200 ml of chloroform was added an ether solution of diazomethane (prepared from an approximately equivalent amount of Diazald [Aldrich]). The

resultant solution was stirred at 0°C. for 15 h. Then, 10 ml of glacial acetic acid was added, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 5 min. Solvent was removed under reduced pressure, and the residue was redissolved in chloroform and washed with aqueous sodium bicarbonate. The chloroform solution was concentrated under reduced pressure to a slurry, which was diluted with ether and filtered to obtain a crude white solid. The crude product was chromatographed on silica gel, eluting with chloroform-methanol (9:1), and yielded a partially purified product that was recrystallized from chloroform-hexane to obtain 0.40 g (13% yield) of the title compound with mp 199-201°C. PMR ($CDCl_3$): 0.99 (t, 3H J≈7Hz), 1.60 (m, 2H), 2.58 (br t, 2H), 3.41 (s, 3H), 3.61 (s, 3H), 4.08 (s, 3H), 5.43 (s, 2H), 7.2-7.7 (m, 5H); MS: 409 (78%, M^+), 394 (25%), 318 (21%), 91 (100%); IR (Nujol): 1710, 1678, 1660, 1608, 1509 cm^{-1}; Anal. Calcd. for $C_{21}H_{23}N_5O_4$: C, 61.60; H, 5.66; N, 17.11. Found: C, 61.65; H, 5.66; N, 17.28.

9-BENZYL-7-(1-PROPYL)-1,3,7-TRIMETHYLPYRIMIDO[2,1-f]PURINE-2,4,6,8(1H,3H,7H,9H)-TETRONE (6)

A mixture of 1.0 g (2.40 mmoles) of the sodium salt of 9-benzyl-1,3-dimethyl-6-hydroxy-7-(1-propyl)pyrimido[2,1-f]purine-2,4,8(1H,3H,9H)-trione (prepared in a manner analogous to that described above for the sodium salt of 1a), 0.50 g (3.62 mmoles) of potassium carbonate, and 2.0 g (14.1 mmoles) of methyl iodide in 50 ml of acetone was refluxed under argon for 16 h. Acetone was removed under reduced pressure, and the residue was partitioned between water and chloroform. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to a slurry. The slurry was diluted with ether and filtered to give a crude white solid. The crude product was dissolved in 200 ml of ethyl acetate and was washed with dilute aqueous hydrochloric acid. The ethyl acetate solution was dried (anhydrous magnesium sulfate), filtered, and concentrated under reduced pressure to a slurry which was diluted with ether and filtered to obtain 0.5 g (51% yield) of the product as a white solid with mp 175-180°C. PMR ($CDCl_3$): 0.79 (t, 3H, J≈7Hz), 0.95-1.4 (m, 2H), 1.63 (s, 3H), 1.85-2.15 (m, 2H), 3.40 (s, 3H), 3.60 (s, 3H), 5.28 (s, 2H), 7.3-7.6 (m, 5H); MS: 409 (100%, M^+), 311 (39%); IR (Nujol): 1775, 1715, 1675, 1618, 1580, 1515, 1501 cm^{-1}; Anal. Calcd. for $C_{21}H_{23}N_5O_4$: C, 61.60; H, 5.66; N, 17.11. Found: C, 61.71; H, 5.89; N, 17.16.

ATTEMPTED ISOMERIZATION OF 5 TO 6

A solution of approximately 6 mg (ca. 0.014 mmole) of 9-benzyl-1,3-dimethyl-6-methoxy-7-(1-propyl)pyrimido[2,1-f]purine-2,4,8(1H,3H,9H)-trione (5) and approximately 6 mg (ca. 0.014 mmole) of the sodium salt of 9-benzyl-1,3-dimethyl-6-hydroxy-7-(1-propyl)pyrimido[2,1-f]purine-

2,4,8(1H,3H,9H)-trione (1k) in 400 ml of N,N-dimethylformamide (dried over type 3Å molecular sieves) was stirred at room temperature under nitrogen for 23 h. An aliquot was evaporated (in vacuo; 35°C.) to dryness, the residue was dissolved in methylene chloride-methanol, and the solution was examined by thin-layer chromatography on Analtech silica gel GF plates (250-micron layer). Detection of spots was effected by ultraviolet light and iodine staining. Elution with chloroform-methanol (98:2) and comparison with an authentic sample of 9-benzyl-7-(1-propyl)-1,3,7-trimethylpyrimido[2,1-f]purine-2,4,6,8(1H,3H,7H,9H)-tetrone (6) [$R_f \approx 0.26$] showed only the starting materials [approximate R_f's: 5, 0.44; 1k, 0.00]. No trace of compound 6 was detected. Elution with chloroform-methanol-acetic acid (95:5:0.1) further substantiated the identities of the reaction constituents as the starting materials [approximate R_f's: 5, 0.74; 1k, 0.34] and corroborated the absence of compound 6 [$R_f \approx 0.68$].

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5. As shown, the C-methylation of enolate 1k was performed in refluxing acetone. As Table I indicates, methyl iodide reacts similarly to the alkyl bromides in alkylating the 7-carbon of 1a at room temperature in N,N-dimethylformamide. Thus, the regiochemical outcome of the methylation of 1k would be expected to be the same had dimethylformamide been used.
6. The results of this experiment demonstrate that O-alkylated products are not intermediates in the alkylation of 1a. It is interesting to note that MNDO/2 calculations suggest that, in general, the 7-C-alkylated products are thermodynamically more stable than their 6-O-alkylated isomers. In the specific case discussed above, the 7-carbon-dialkylated product 6 is calculated to be more stable than 5 by some 10 kcal./mole. Details of these calculations will be discussed in a future publication.

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10. We have recently found that more satisfactory mass spectra of the sodium salts can be obtained by fast atom bombardment techniques.

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