Optimization of Partial Alkylation of 3-Methyl-3,7-dihydro-1*H*-purine-2,6-dione and its 8-Alkyl Derivatives

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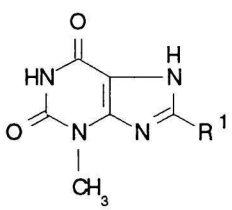
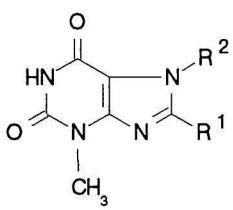
7-Alkyl-3-methyl-3,7-dihydro-1*H*-purine-2,6-diones and their 8-alkyl derivatives were obtained from 3-methyl-3,7-dihydro-1*H*-purine-2,6-dione and its 8-alkyl derivatives by partial alkylation with alkyl (C_2—C_4) bromides in the presence of potassium carbonate in dimethylformamide.

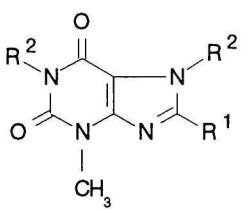
Only few papers have so far described partial alkylation of 3-methyl-3,7-dihydro-1*H*-purine-2,6-dione and its 8-substituted derivatives *I* to the corresponding 7-alkyl derivatives *II*. Thus, methylation of 3-methyl-3,7-dihydro-1*H*-purine-2,6-dione *Ia* [1], its 8-methyl derivative *Ib* [2], and 8-hydroxymethyl derivative [3] in the form of their sodium salts was reported with dimethyl sulfate in aqueous or dilute alcoholic media. A common disadvantage of these methods is the incomplete conversion of the start-



I



II



III

		a	*b*	*c*	*d*	*e*	*f*	*g*
I	R^1	H	CH_3	C_2H_5	C_3H_7			
II, *III*	R^1	H	H	H	CH_3	CH_3	CH_3	C_2H_5
	R^2	C_2H_5	C_3H_7	C_4H_9	C_2H_5	C_3H_7	C_4H_9	C_2H_5
		h	*i*	*j*	*k*	*ℓ*	*m*	
	R^1	C_2H_5	C_2H_5	C_3H_7	C_3H_7	CH_3	C_2H_5	
	R^2	C_3H_7	C_4H_9	C_3H_7	C_4H_9	CH_3	CH_3	

ing *I* to 7-alkyl derivative *II* and a concurrent formation of the 1,7-dialkyl derivative *III*. Methylation of *e.g. Ib* and *Ic* applying the method according to [3] afforded 7-methyl derivatives *IIℓ*, *IIm* (60—63 %), 1,7-dimethyl derivatives *IIIℓ*, *IIIm* (26—30 %) in addition to the unreacted starting material (7—10 %). Even the methylation with less reactive alkyl (C_2—C_4) bromides in a dilute alcoholic medium resulted in a parallel formation of monoalkyl *II* and dialkyl derivatives *III*; nonetheless, the portion of the unreacted starting *I* can make up 40 % (*e.g.* with butylation of *Id*). This was the reason why we chose the procedure *via* 5-alkylamino-6-amino-1-methyl-2,4(1*H*,3*H*)-pyrimidinediones in preparation of 7-alkyl derivatives *II* in our previous paper [4]; these pyrimidinediones furnished unequivocally derivatives *II* with the alkyl in position 7 of the purine skeleton after the imidazole ring was fused in the first step.

As found, conversion of the starting *I* to 7-alkyl derivatives *II* was substantially higher and portion of the unwanted 1,7-dialkyl compounds *III* with respect to the monoalkyl derivatives *II* lower when compared with the procedure proceeding in aqueous or dilute alcoholic media, provided the partial alkylation was carried out in an aprotic solvent, most favourably in dimethylformamide in the presence of alkali metal carbonate. The compounds *I* and *II* form such soluble salts in aqueous solutions and consequently, they can be separated from derivatives *III* by extraction of their chloroform or dichloromethane solutions or suspension of *Ia*, *Ib* with an aqueous solution of the respective alkali metal hydroxide. It was necessary to find reaction conditions to meet requirements for purity of the compound *II* (at least 98.5 % with maximum 0.8 % of the starting *I*), if the partial alkylation of compounds *I* should be an alternative method to

that described in [4]. The high resolution liquid chromatography of both the reaction mixture and products *II* showed that a 25 % excess of the alkylation agent is satisfactory when introducing methyl, ethyl or propyl group in position 7. Introduction of a butyl group according to the analogous method required an up to 40 % excess of the alkylating agent. The starting substance *I* reacted, according to our method, almost quantitatively and the monoalkylated derivative *II* was separated from the unwanted twice alkylated *III* by dissolving alkali metal salt of *II*; with only 15 % excess of the alkylating agent the content of the unreacted *I* in compound *II* rose to 2—5 %.

Experiments to separate the unreacted starting *I* by crystallization were successful using ethanol or 2-propanol only with compounds *IIa* and *IIℓ*. Compounds with longer alkyls, as *e.g. IIj* resisted separation even when employing toluene, cyclohexane, or carbon tetrachloride. Experiments to remove the unreacted *Ia* from *IIb* by a several hour stirring with a 20-fold equivalent of ammonium hydroxide resulted in *ca.* 20 % losses; the unreacted *Ia* in an amount up to 1.5 % could be removed by this procedure by approximately one half.

Lithium, sodium, potassium or calcium carbonate were tried as alkaline components of the alkylation. The best results were obtained with potassium carbonate, whilst sodium carbonate was found suitable in the presence of alkali metal iodide. The amount of the unreacted *I* exceeded the acceptable measure when applying lithium and especially calcium carbonates (*e.g.* with *IIh* up to 70 % and 90 % of *Ic* with the former and latter reagents, respectively). Calcium oxide also proved unsuitable with *IIh* leaving 27—35 % of the unreacted *Ic*. No advantages over our method brought the use of sodium salt of the starting *I* in dimethylformamide (*e.g.* by analogy with [5]).

The synthesized monoalkyl derivatives *II* were identical (as evidenced by chromatography and spectral measurements) with the corresponding compounds prepared according to [4]; they were

Table 1. Characterization, ^{1}H NMR and Mass Spectral Data of 7-Alkyl-3-methyl-3,7-dihydro-1*H*-purine-2,6-diones and Their 8-Alkyl Derivatives

Compound	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	N	Yield/% Method	M.p./°C[a]	θ/°C t/h	Chemical shifts δ	M$^+$ m/z
IIa	$C_8H_{10}N_4O_2$	49.48	5.19	28.85	79	302—303	60	1.48 (t, 3H, C—CH_3), 3.44 (s, 3H, N-3—CH_3),	194
	194.2	49.25	5.27	28.80	*A*		5	4.33 (q, 2H, N-7—CH_2), 8.16 (s, 1H, H-8),	
								11.21 (br s, 1H, H-1)	
IIb	$C_9H_{12}N_4O_2$	51.91	5.81	26.91	84, 67	268—270	100, 80	0.91 (t, 3H, C—CH_3), 1.88 (se, 2H, C—CH_2—C),	208
	208.2	51.75	5.98	26.70	*A, B*		2, 2	3.44 (s, 3H, N-3—CH_3), 4.26 (t, 2H, N-7—CH_2),	
								8.13 (s, 1H, H-8), 11.20 (br s, 1H, H-1)	
IIc	$C_{10}H_{14}N_4O_2$	54.04	6.35	25.21	85	246—248	90	0.98 (t, 3H, C—CH_3), 1.34 (se, 2H, N-7—C—C—CH_2),	222
	222.2	53.81	6.49	25.30	*B*		4	1.88 (qi, 2H, N-7—C—CH_2), 3.47 (s, 3H, N-3—CH_3),	
								4.33 (t, 2H, N-7—CH_2), 8.18 (s, 1H, H-8),	
								11.21 (br s, 1H, H-1)	
IId					61	264—266	90		208
					A	260—262[b]	5		
IIe					58	219—220	100		222
					A	218—219[b]	3		
IIf					58	229—230	100		236
					B	231—232[b]	4		
IIg					61	238—240	100		222
					A	237—238[b]	3		
IIh					72	183—185	100		236
					A	180—181[b]	4		
IIi	$C_{12}H_{18}N_4O_2$	57.58	7.25	22.39	66	205—207	100	0.99 (t, 3H, N-7—C—C—C—CH_3), 1.36 (t, 3H,	250
	250.3	57.49	7.03	22.51	*B*		5	C-8—C—CH_3), 1.38 (se, 2H, N-7—C—C—CH_2),	
								1.76 (qi, 2H, N-7—C—CH_2), 2.83 (q, 2H, C-8—CH_2),	
								3.42 (s, 3H, N-3—CH_3), 4.25 (t, 2H, N-7—CH_2),	
								11.08 (br s, 1H, H-1)	
IIj					54	175—176	100		250
					A	172—174[b]	5		
IIk	$C_{13}H_{20}N_4O_2$	59.07	7.63	21.20	40	156—159	100	0.98 (t, 3H, N-7—C—C—C—CH_3), 1.06 (t, 3H, C-8—	264
	264.3	58.85	7.77	21.45	*B*		8	C—C—CH_3), 1.38 (se, 2H, N-7—C—C—CH_2),	
								1.74 (qi, 2H, N-7—C—CH_2), 1.81 (se, 2H, C-8—C—CH_2), 2.79 (t, 2H, C-8—CH_2), 3.42 (s, 3H, N-3—CH_3),	
								4.27 (t, 2H, N-7—CH_2), 11.08 (br s, 1H, H-1)	

a) In a sealed capillary; *b*) reported in Ref. [4].

characterized by melting points, elemental analyses, mass and ^{1}H NMR spectra (Table 1).

The prevailing majority of 1,7-dialkyl derivatives *III* ($R^1 \neq H$, reaction by-products) obtained by this reaction are low-melting and even glassy compounds crystallizing with difficulty. Due to small amounts they were characterized only by the molecular ion peaks; the values found were in accordance with the calculated ones.

EXPERIMENTAL

Melting points are uncorrected, samples for analyses were dried over phosphorus pentaoxide at 100 °C (65 Pa) for 8 h. The mass and ^{1}H NMR spectra were recorded with Jeol 100 D (70 eV, 100 μA) and Bruker AM-300 (deuterochloroform solution containing tetramethylsilane as internal reference) apparatuses, respectively. Reaction courses and purity of products were monitored by thin-layer chromatography (Silufol UV_{254} sheets, Kavalier, Votice) in chloroform—methanol (φ_r = 9 : 1), or high-performance liquid chromatography (15 cm × 0.3 cm column packed with Separon SGX RPS (Tessek, CSFR), mobile phase water—acetonitrile, φ_r = 7 : 3, flow rate 0.2 cm^3 min^{-1}, detection with UV_{278} light).

7-Alkyl-3-methyl-3,7-dihydro-1*H*-purine-2,6-diones and Their 8-Substituted Derivatives *IIa—IIk*

Method A. Alkyl bromide (12.5 mmol) was added to a stirred suspension of the respective compound *I* (10 mmol) and potassium carbonate (1.72 g; 12.5 mmol) in dimethylformamide (20 cm^3); reaction temperatures and times are listed in Table 1. Dimethylformamide was distilled off under diminished pressure and the dry residue was dissolved in dichloromethane (10 cm^3), water (15 cm^3), and 1 M aqueous sodium hydroxide (15 cm^3) with stirring. The aqueous layer was separated, extracted with dichloromethane (3 × 15 cm^3), filtered and neutralized with acetic acid or by introduction of carbon dioxide. The separated product *II* was filtered off, washed with ice-cold water and dried at 100 °C under reduced pressure.

Method B. This procedure was analogous to the preceding one with the exception that for 10 mmol of *I* 14 mmol of alkyl bromide and 14 mmol of potassium carbonate were employed.

Samples for analyses were purified either by crystallization from methanol or ethanol, or by dissolution in 1—2 M sodium hydroxide at 60—65 °C, addition of charcoal, filtration and precipitation with dilute hydrochloric acid at 60—65 °C. The melting points of purified compounds *II* are presented in Table 1. The melting points of not purified compounds were by 4—8 °C lower.

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REFERENCES

1. Bredereck, H., von Schuh, H. G., and Martini, A., *Chem. Ber. 83,* 201 (1950).
2. Golovchinskaya, E. S., *Zh. Prikl. Khim.* (Leningrad) *30,* 1374 (1957); *Chem. Abstr. 52,* 5425 (1958).
3. Bredereck, H., Siegel, E., and Föhlisch, B., *Chem. Ber. 95,* 407 (1962).
4. Rybár, A., Hesek, D., Szemes, F., Alföldi, J., and Tegza, M., *Collect. Czech. Chem. Commun. 55,* 2257 (1990).
5. Hesek, D., Tegza, M., Rybár, A., and Považanec, F., *Synthesis 1989,* 681.

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