(ethyl acetate–heptane, 1:1). Found, %: C 81.3; H 4.6; N 14.5; M^+ 295. $C_{20}H_{13}N_3$. Calculated, %: C 81.4; H 4.4; N 14.2; M 295. Then 0.1 g (20%) of compound V was eluted, yellowish crystals, mp 188-190°C, R_f 0.33 (ethyl acetate–heptane, 1:1). Found, %: C 81.2; H 4.5; N 13.9; M^+ 295. $C_{20}H_{13}N_3$. Calculated, %: C 81.4; H 4.4; N 14.2; M 295.

6-Phenylpyrazolo[3,4-ℓ]- and -[4,3-ℓ]-4-azaphenanthrenes (VI, VII). Spiro compound III (40 mg, 0.14 mmole) was heated for 30 min at 160-165°C in a current of nitrogen (monitored by TLC). The black reaction mixture was chromatographed on a column of silica gel (h = 35 cm, d = 1.5 cm), with a mixture of hexane and ethyl acetate (5:1) as elution agent. A mixture (15 mg, 37%) of compounds VI and VII was isolated, mp 215-217°C (from heptane), R_f 0.4 (ethyl acetate–heptane, 1:1). Found, %: N 14.4; M^+ 295. $C_{20}H_{13}N_3$. Calculated, %: N 14.2; M 295.

5,6-Dimethoxycarbonylpyrazolo[3,4-ℓ]- and 6,7-Dimethoxycarbonyl pyrazolo[4,3-ℓ]-4-azaphenanthrenes (IX, X). Spiro compound VIII (0.25 g, 7 mmoles) was heated for 30 min at 120-130°C in a current of nitrogen. Chromatography on a column of silica gel (h = 40 cm, d = 1.5 cm) with a mixture of heptane and ethyl acetate (3:1) as elution agent resulted in isolation of 50 mg (20%) of a mixture of compounds IX and X, yellowish crystals, mp 148-150°C (from heptane), R_f 0.36. Found, %: N 12.3; M^+ 335. $C_{18}N_{13}N_3O_4$. Calculated, %: N 12.5; M 335.

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ALKYLATION OF ALLOPURINOL AND INOSINE WITH DIMETHYLFORMAMIDE DIMETHYLACETAL OR DIETHYLACETAL

Yu. N. Bulychev and M. N. Preobrazhenskaya

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The alkylation of allopurinol and inosine with dimethylformamide (DMF) dimethylacetal and diethylacetal was studied. Allopurinol is alkylated in both the pyrazole and pyrimidine rings. 1,5- and 2,5-Dimethyl derivatives are formed in the case of methylation. 1,5- and 2,5-Diethyl derivatives, as well as 1-ethyl-4-ethoxypyrazolo[3,4-d]pyrimidine, were obtained in the ethylation of allopurinol. The yields of the 1,5-substituted compounds are highest in both cases. The alkylation of inosine with DMF diethylacetal takes place in the 1 and 6 positions.

The N-alkylation of nitrogen heterocycles with acetals of amides in a number of cases is an effective and convenient method for obtaining the corresponding alkyl derivatives [1]. Recently we and a number of foreign authors described the use of DMF dialkylacetals for the alkylation of substituted pyrazoles [2], 1,2,3-triazoles [3], pyrazolo[3,4-d]pyrimidines [4], benzimidazoles and 1,2,4-triazoles [5], and uridine and its analogs [6]. The further development of this research seems of interest.

All-Union Oncological Science Center, Academy of Medical Sciences of the USSR, Moscow 115478.

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TABLE 1. Characteristics of Alkyl Derivatives IV-IX of Allopurinol and Inosine

Compound	mp, °C	$[\alpha]_D^{20}$, deg (c, water)	R (system)	IR spectrum, $\nu_{C=O}$, cm^{-1}	UV spectrum in ethanol, λ_{max}, nm (log ε)	Found, %			Empirical formula	Calc., %			Yield, %
						C	H	N		C	H	N	
IVb	122	—	0,51 (A)	1695	255 (3,85)	55,2	6,3	28,5	$C_9H_{12}N_4O \cdot 0{,}25H_2O$	55,1	6,4	28,6	52
Vb	126...128	—	0,40 (A)	1686	260 (3,90), 267 (3,89)	55,2	6,0	28,9	$C_9H_{12}N_4O \cdot 0{,}25H_2O$	55,1	6,4	28,6	19
VI	Масло	—	0,72 (A)	—	247 (3,83), 268 (3,60)*	55,2	6,4	28,4	$C_9H_{12}N_4O \cdot 0{,}25H_2O$	55,1	6,4	28,6	14
VII	84...86	−45,9 (0,3)	0,40 (C); 0,25 (B)	1687	245 (3,93), 252 (3,94)	48,8	5,7	18,6	$C_{12}H_{16}N_4O_5$	48,7	5,5	18,9	40
VIII	133...136	−30,0 (1,0)	0,69 (C); 0,32 (B)	—	249 (3,99)	48,4	5,6	18,9	$C_{12}H_{16}N_4O_5$	48,7	5,5	18,9	26
IX	200...202†	−51,7 (0,3)**	0,28 (C); 0,13 (B)	1687	244 (3,95), 251 (3,96)	47,0	5,1	—	$C_{11}H_{14}N_4O_5$	46,9	5,0	19,9	8

*According to the data in [12], λ_{max} 247 nm (3.84) and 267 nm (3.62) for 1-methyl-4-methoxypyrazolo[3,4-d]pyrimidine; λ_{max} 259 nm (3.81) for 2-methyl-4-methoxypyrazolo[3,4-d]pyrimidine.

†According to the data in [15], 1-methylinosine has mp 210-212°C and $[\alpha]_D^{28}$ = −49.2° (c 0.5, water).

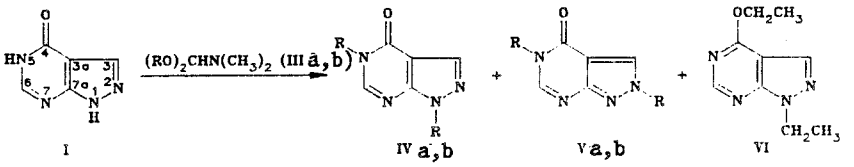
TABLE 2. PMR Spectra of Alkyl Derivatives IV-VI of Allopurinol

Compound	Chemical shift, δ, ppm							
	6-H, s		3-H, s		CH_2, q		CH_3, t	
	d_6-DMSO	$CDCl_3$	d_6-DMSO	$CDCl_3$	d_6-DMSO	$CDCl_3$	d_6-DMSO	$CDCl_3$
IVa	8,36	8,06	8,01	7,97	—	—	3,90; 3,47	3,99; 3,58
Va	8,48	8,04 (8,33)*	8,20	7,95 (8,18)*	—	—	4,00; 3,41	4,09; 3,53 (4,08; 3,53)*
IVb	8,40	8,07	8,04	7,99	4,30; 4,00	4,39; 4,08	1,39; 1,25	1,50; 1,40
Vb	8,53	8,11	8,23	7,99	4,29; 3,93	4,35; 4,02	1,44; 1,23	1,60; 1,38
VI	8,55	8,53	8,18	8,03	4,60; 4,43	4,62; 4,50	1,42; 1,42 (6H)	1,52; 1,49

*In CD_3OD.

In the present paper we describe for the first time processes involving the alkylation of the medicinal preparations pyrazolo[3,4-d]pyrimidin-4-one (allopurinol) (I) and inosine (Riboksin) (II) by DMF dimethylacetal or diethylacetal (IIIa, b, respectively). Alkyl derivatives of allopurinol are of interest as potential inhibitors of xanthine oxidase [7, 8], while alkyl derivatives of inosine are of interest as potential antimetabolites of the metabolism of nucleic acids or as minor components that enter into their composition [9].

The DMF dimethylacetal and diethylacetal were obtained by the action of the corresponding sodium alkoxides on the DMF–dimethyl sulfate complex via the method in [17]. 1,5- and 2,5-Dimethylpyrazolo[3,4-d]pyrimidin-4-ones (IVa and Va) were isolated in 37% and 27% yields in the alkylation of allopurinol (I) with acetal IIIa by heating to 100-105°C. The previously undescribed 1,5- and 2,5-diethylpyrazolo[3,4-d]pyrimidin-4-ones (IVb and Vb), as well as 1-ethyl-4-ethoxypyrazolo[3,4-d]pyrimidine (VI), were isolated in 52, 19, and 14% yields, respectively, by the action of diethylacetal IIIb on allopurinol (I) under similar conditions.



I IVa,b Va,b VI

IIIa—Va R=CH_3; IIIb—Vb R=C_2H_5

With respect to their melting points, IVa and Va are identical to the compounds described in the literature [10, 11]. According to the UV spectral data, they are extremely similar to allopurinol 1,5- and 2,5-diribosides [10] (Table 1). The similarity in the UV spectra of IVb and Vb and dimethyl derivatives IVa and Va, respectively, made it possible to classify IVb and Vb as 1,5- and 2,5-diethyl derivatives of allopurinol. The UV spectrum of VI is similar to the UV spectrum of 1-methyl-4-methoxypyrazolo[3,4-d]pyrimidine and differs substantially from the spectrum of the 2,4-dimethyl derivative of allopurinol [12]; this provides a basis for assuming that it is the 1,4 isomer. Intense ν_{CO} absorption bands at 1685-1700 cm^{-1}, which are absent in the spectrum of VI, are observed in the IR spectra of IVa, b and Va, b (Table 1).

The PMR spectra (Table 2) also confirm the structures of IV-VI. Signals of 3-H and 6-H protons in the form of singlets are situated at weak field at 7.9-8.6 ppm; according to the data in [12], the weaker-field signals should be considered to be signals of the 6-H protons of the pyrimidine ring. Signals of N-methyl groups in the form of singlets are found at 3.5-4.6 ppm in the spectra of IVa and Va, while signals of N–CH_2 or O–CH_2 groups in the form of two-proton quartets are found in the spectra of IVb, Vb, and VI. Signals of CH_3 groups in the form of triplets are located at strong field in the spectra of IVb, Vb, and VI. The character of the change in the position of the signals of the 3-H protons of the pyrazole ring with a change in the polarity of the solvent leads to the same conclusions regarding the direction of alkylation of allopurinol that were drawn on the basis of UV and IR spectroscopic data. It is known that in the spectra of N-substituted pyrazoles and condensed pyrazoles the signal of the proton attached to the carbon atom in the α position with

TABLE 3. PMR Spectra of Alkyl Derivatives VII-IX of Inosine

Compound	Chemical shift, δ, ppm (SSCC, Hz)*									
	2-H, s	8-H, s	1′-H, d ($J_{1',2'}$)	2′-H, dd ($J_{2',3'}$)	3′-H, m	4′-H, m	5′-H, m	5″-H, m	CH_2, q	CH_3, t
VII	8,40	8,32	5,90 (5,7)	4,49 (5,2)	4,17	3,99	3,69	3,58	4,07	1,30
VIII	8,28	8,06	5,90 (5,9)	5,13	4,54	4,33	3,93	3,78	4,52	1,48
IX	8,38	8,32	5,88 (5,7)	4,48 (5,0)	4,16	3,98	3,69	3,59	—	3,53

*The PMR spectra of VII and IX were recorded in d_6-DMSO, while the spectrum of VIII was recorded in $CDCl_3$.

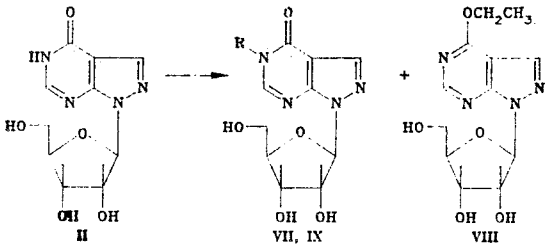
respect to the substituted nitrogen atom [the =CH–N(R)–N= fragment] is located at weaker field and is more sensitive to a change in the polarity of the solvent than the proton of the β-C atom [the –CH=N–N(R) fragment] [13]. The weaker-field position of the signals of the 3-H atoms in d_6-DMSO in the spectra of Va and Vb as compared with the spectra of IVa and IVb and the $\Delta\delta = \delta_{d_6\text{-DMSO}} - \delta_{CDCl_3}$ values, which are 0.25 (Va), 0.24 (Vb), 0.04 (IVa), and 0.05 ppm (IVb), make it possible to assume that alkyl groups in Va and Vb are in the α position and that the alkyl groups in IVa and IVb are in the β position with respect to the $C_{(3)}$ atom.

The position and character of the shift of the signals of the 6-H protons depend on the position of the alkyl group in the pyrazole ring and the solvent used to record the PMR spectra. In the spectra, recorded in d_6-DMSO, of 2,5-dialkyl derivatives Va and Vb of allopurinol as compared with 1,5-dialkyl derivatives IVa and IVb the signals of the $H_{(6)}$ atoms are located at weaker field and are shifted to a greater degree to strong field with a decrease in the polarity of the solvent. The $\Delta\delta = \delta_{d_6\text{-DMSO}} - \delta_{CDCl_3}$ values for Va and Vb are 0.44 and 0.42 ppm, as compared with 0.30 and 0.33 ppm for IVa and IVb. A strong-field shift of the signals of the 6-H atoms with a decrease in the polarity of the solvent is observed only for IV-Va, b with a fixed lactam form of the pyrimidine ring, while in the case of VI, the pyrimidine ring of which has a lactim configuration, the position of the signal of the 6-H atom does not change. One cannot exclude the possibility that the indicated empirical principles are general in character and may prove to be useful in structural investigations of substituted isomeric pyrazolo[3,4-d]pyrimidine and related compounds.

Other derivatives of orthoformic acid that are capable of alkylating compounds of the pyrazole series such as methyl or ethyl orthoformate [14] do not alkylate allopurinol. The conditions of alkylation of allopurinol by acetal IIIa or IIIb (the polarity of protic or aprotic organic solvents, the reaction temperature or time, as well as the reagent ratio) do not affect the positional specificity of the reaction. Monoalkyl derivatives of allopurinol were not obtained in a single case, and only a decrease in the overall yields of the alkylation products was observed. The alkylation of allopurino with traditional aklylating agents such as dimethyl sulfate or alkyl halides in alkaline media even using the techique of interphase catalysis usually leads to a large number of isomeric and side products, the separation of which is fraught with considerable difficulties [5, 10]. The alkylation of allopurinol with DMF acetals excludes the formation of side products associated with opening of the pyrimidine ring in an alkaline medium, proceeds with satisfactory yields with minimal formation of isomeric compounds, and can be successfully used for the simultaneous introduction of substituents into the pyrazole and pyrimidine rings.

We also studied the alkylation of inosine and hypoxanthine with acetal IIIb. An extremely complex mixture of products, the separation of which presents great difficulties, is formed in the alkylation of hypoxanthine. The alkylation of inosine with acetal IIIb takes place exclusively in the pyrimidine ring; 1-N-ethylinosine (VII), 6-O-ethylinosine (VIII), and 1-N-methylinosine (IX) were obtained in 40, 26, and 8% yields, respectively (see scheme top of next page).

The formation of 1-N-methylinosine (IX) in very small amounts is evidently associated with the presence of admixed mixed DMF methylethylacetal in starting diethylacetal IIIb and is a consequence of incomplete transacetalization by sodium ethoxide of the dimethyl sulfate–DMF complex, from which acetal IIIb is usually obtained.



II VII, IX VIII

VII R=CH_2CH_3; IX R=CH_3

The isolated 1-N-methylinosine (IX) was found to be identical with respect to its melting point, specific rotation, and UV spectrum to the compound previously described in [15]. The structures of VII and VIII were established from the set of IR, UV, and PMR spectral data (Table 3) and were confirmed by the results of elementary analysis. The UV spectra of VII and IX recorded in ethanol are extremely similar (Table 1); this makes it possible to assume that VII is 1-N-ethylinosine. The assignment of VIII to the 6-O-ethyl derivative was made on the basis of IR and UV spectroscopic data. According to the data from the UV spectrum in water, VIII is closest to the described 6-O-methylinosine (Table 4). Compound VII differs from 3- and 7-methylinosine with respect to the absence of a bathochromic shift of the absorption maximum at pH 7. The IR spectrum of VIII does not contain an absorption band of a carbonyl group at 1680-1700 cm^{-1} (Table 1), while the IR spectra of 1-alkyl derivatives VII and IX, as well as inosine itself, contain an intense absorption band at 1687-1690 cm^{-1}; this constitutes evidence for a lactim form of the pyrimidine ring in VIII and, consequently, for 6-O substitution.

Thus, $N_{(1)}$- and $O_{(6)}$-alkyl derivatives are formed in the alkylation of inosine with acetal IIIb. The methylation of inosine with the usual methylating agents takes place in the $N_{(1)}$, $N_{(7)}$, and $O_{(6)}$ positions [16]. The absence of substitution in the 7 position constitutes evidence for more selective alkylation of inosine with diethylacetal IIIb in the pyrimidine ring primarily in the 1 position.

EXPERIMENTAL

The PMR spectra were recorded with a Bruker WH-360 spectrometer with tetramethylsilane (TMS) as the internal standard. The UV spectra of solutions of IV-IX in ethanol (Table 1) and VII-IX in water (Table 4) were recorded with a Unicam SP-800 recording spectrophotometer. The IR spectra of KBr pellets were obtained with a Perkin–Elmer 283 spectrometer. The specific rotation was determined by means of a Perkin–Elmer 241 polarimeter. Analytical TLC was carried out on Silufol UV-254 plates in chloroform–methanol systems [98:2 (a), 9:1 (B), 4:1 (C)]. Preparative chromatography was carried out on plates with a loose layer of LSL 5/40 silica gel (Czechoslovakian SSR) with dimensions of 20 × 20 cm (layer thickness 1.5 mm) in the same solvent system.

Acetals IIIa, b were obtained by the action of the corresponding sodium alkoxides on the DMF–dimethyl sulfate complex by the method in [17].

The physicochemical and spectral characteristics of the compounds are presented in Tables 1-4.

TABLE 4. UV Spectra of Alkyl Derivatives VII-IX of Inosine and Some Known Alkyl-Substituted Inosines in Water

Compound	λ_{max}, nm (lg ε)		
	pH 1	pH 7	pH 12
VII	250 (4,01)	250 (4,01)	247 (4,11)
IX	250 (4,02)	250 (4,02)	248 (4,12)
1-Methylinosine [15]	250 (4,02)	249 (4,02)	249 (4,03)
VIII	252 (4,02)	251 (4,04)	248 (4,13)
Inosine [15]	251 (4,04)	248,5 (4,09)	253 (4,12)
6-O-Methylinosine [15]	250 (—)	—	250 (—)
7-Methylinosine [15]	252 (—)	264 (—)	Unstable
3-Methylinosine [9]	Unstable	259 (4,12)	Unstable

1,5- and 2,5-Dimethylpyrazolo[3,4-d]pyrimidin-4-one (IVa and Va). A 0.52-g (3.8 mmoles) sample of allopurinol (I) was heated in 5 ml of acetal IIIa for 7 h at 110°C with monitoring of the course of the reaction by means of data from TLC in system B. The mixture was cooled and filtered, and the filtrate was evaporated. The residue was evaporated twice with 5-ml portions of toluene, the residual oil was dissolved in 4 ml of chloroform, and the solution was applied to plates for preparative chromatography and chromatographed in system B with collection of the zones with R_f 0.50 (IVa) and 0.43 (Va). The substances obtained were subjected to repeated preparative chromatography on silica gel in system B with collection of the zones with the same R_f values. The compounds formed after removal of the solvent were recrystallized from methanol to give 0.23 g (37%) of IVa [mp 188°C (mp 187-189°C [11]). UV spectrum (in alcohol): λ_{max} 254 nm ($\log \varepsilon$ 3.78)] and 0.17 g (27%) of Va [mp 288-289°C (mp 291-292°C [11]). UV spectrum (in alcohol), λ_{max} ($\log \varepsilon$): 260 (3.88), 267 nm (3.87)]. According to the data in [10], UV spectrum (in alcohol) of the 1,5-diribofuranoside, λ_{max} ($\log \varepsilon$): 254 nm (3.85); UV spectrum of the 2,5-diribofuranoside: 261 nm (3.89). The remaining alkyl derivatives IVb, Vb, and VI-IX were obtained via a similar method.

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