ELECTRONIC STRUCTURE, PMR SPECTRA, AND ALKYLATING CAPACITY OF SOME 2- AND 6-ALKOXYPURINES

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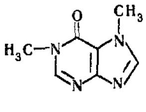
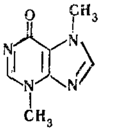
The simple MO LCAO method was used to calculate the isomeric N,N-dimethylhypoxanthines and the corresponding 2(6)-ethoxy- and 2(6)-ethoxy-8-chloro derivatives, and the PMR spectra of a number of compounds of this type were measured. A qualitative correlation was observed between changes in the π-electron densities and changes in the chemical shifts of the protons of the N-methyl groups. Factors affecting the alkylating capacity of 2(6)-alkoxypurines and the direction of the reaction of these compounds with sodiomalonic ester when the molecules contain two different reaction centers were examined. The use of the π-electron densities and orders and polarizabilities of the heterocycle–substituent bonds as reactivity indexes makes it possible to explain the highest alkylating capacity of 2-ethoxy-3,7-dimethylhypoxanthine and its 8-chloro derivative and the order of other compounds with respect to this capacity.

The ability of isomeric 2-ethoxy-8-chloro-N,N-dimethylhypoxanthines to react simultaneously with sodiomalonic ester in two directions, viz., 1) with substitution of the Cl atom in the 8-position with the formation of the corresponding 2-ethoxy-N,N-dimethylhypoxanthyl-8-malonic esters and 2) with alkylation of the sodiomalonic ester due to heterolytic cleavage of the C_2 ethoxy group, was reported in [1]. The relative reactivity of this series of compounds with respect to these two types of reactions depends on the position of the N-methyl groups and the double bonds in the purine ring. When there is only one reaction center (ethoxy groups in the 2- or 6-position) in molecules of the starting N,N-dimethylhypoxanthines, the reaction proceeds exclusively in the direction of alkylation of sodiomalonic ester, and the yield of ethylmalonic ester increases.

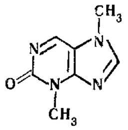
In connection with the fact that the alkylating capacity of C-alkoxy derivatives of purine under heterolytic conditions has not yet been studied, it was expedient to examine the above-listed experimental results in the light of data on the electronic structure of molecules obtained by means of quantum-chemical calculations and physical methods of investigation. In this study we have used the simple MO LCAO method* with Pullman parameters [2] to calculate 1,7-dimethylhypoxanthine (I), 3,7-dimethylhypoxanthine (II), 3,7-dimethyl-2-oxopurine (III), 1,9-dimethylhypoxanthine (IV), and the corresponding 2(6)-ethoxy- (Ia-IVa) and 2(6)-ethoxy-8-chloro derivatives (Ib-IVb), and we have measured the PMR spectra of I-III and Ia-IVa.



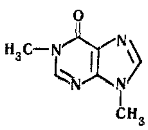
I



II



III



IV

The molecular diagrams, the free valence indexes (F_i), the diagrams of the levels, the total energies of the π electrons (E_π), and the delocalization energies (E_D) of the N,N-dimethyloxopurines (I-IV) are

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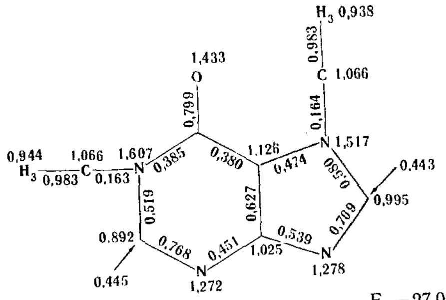
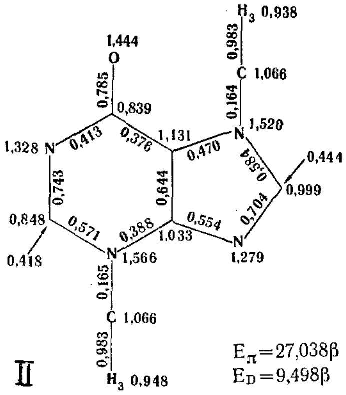
3,192
2,414
2,057
1,831
1,520
1,132
0,912
0,476
−0,835
−0,956
−1,489
−2,115
−2,416
−2,443



I

$E_\pi=27{,}070\beta$
$E_D=9{,}599\beta$

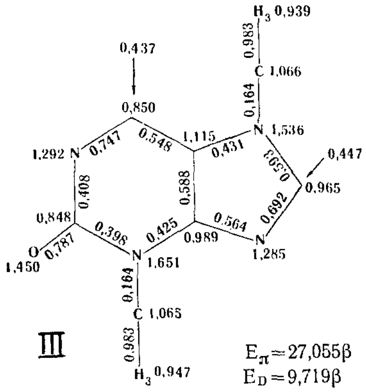
3,154
2,467
2,169
1,700
1,503
1,115
0,899
0,512
−0,835
−0,970
−1,398
−2,186
−2,417
−2,436



II

$E_\pi=27{,}038\beta$
$E_D=9{,}498\beta$

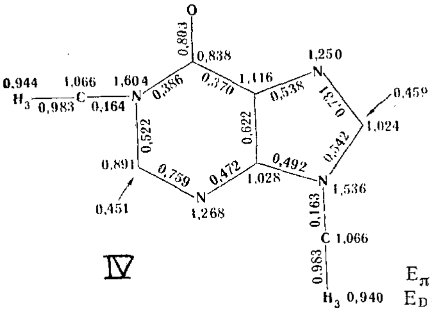
3,194
2,530
1,982
1,723
1,476
1,264
0,844
0,515
−0,595
−1,244
−1,528
−2,026
−2,418
−2,437



III

$E_\pi=27{,}055\beta$
$E_D=9{,}719\beta$

3,186
2,462
2,028
1,742
1,582
1,117
0,978
0,447
−0,786
−1,131
−1,338
−2,148
−2,418
−2,440



IV

$E_\pi=27{,}083\beta$
$E_D=9{,}589\beta$

Fig. 1. Molecular diagrams and schemes of the energy levels of 1,7-dimethylhypoxanthine (I), 3,7-dimethylhypoxanthine (II), 3,7-dimethyl-2-oxopurine (III), and 1,9-dimethylhypoxanthine (IV). (The arrows indicate the free valence indexes.)

presented in Fig. 1. In compounds I and II, which differ only with respect to the relative position of the N-methyl and exocyclic carbonyl group in the pyrimidine ring, considerable differences are observed in the distribution of the π-electron density within this ring, while such differences are extremely small in the imidazole portion of these molecules. It is important to point out that on passing from I to II the electron density and the free valence index in the 2-position decrease appreciably and, consequently, the difference in the electron densities localized on the $C_{(2)}$ and $C_{(8)}$ atoms increases. A change in the position of the exocyclic carbonyl group in the pyrimidine ring (from comparison of molecular diagrams of II and III) leads to a redistribution of the π-electron density which affects the entire purine system. The electron density in the 6-position (q_π^6) of III is close to q_π^2 in II, but $F_6^{III} > F_2^{II}$. In addition, in contrast to II, the q_π^8 value decreases in III. A comparison of the molecular diagrams of I and IV indicates that the q_π^8, F_2, and F_8 values change as a function of the nitrogen atom of the imidazole ring to which the methyl group is attached [to $N_{(7)}$ or to $N_{(9)}$]. It might be expected that the noted changes in the indexes of the electron structure in the 2- and 8-positions of molecules of isomeric N,N-dimethylhypoxanthines affect the character of the interaction of the substituent [for example, the OC_2H_5 groups attached to the $C_{(2)}$ atom] with the heteroaromatic system and, consequently, the reactivity of this substituent. However, considering the limitedness of the Hückel approximation for systems of such complexity as purines, it is expedient, even for a qualitative examination of the relative magnitudes of the electronic indexes in a series of similar molecules, to compare the results of the calculation with the results of physical methods of investigation, primarily with the PMR chemical shifts.

Two singlets of the $H_{(2)}$ [or $H_{(6)}$] protons and the $H_{(8)}$ protons and two singlets of the protons of the N-methyl group are observed in the PMR spectra of I-III (Table 1). Assignment of the signals to the protons of the purine ring was made on the basis of a comparison with the spectra of the corresponding 2(6)-ethoxy derivatives (Ia-IIIa) which contain only a signal from the $H_{(8)}$ proton.

Of the two methyl group signals observed in the spectra of I-III, the position of one signal is comparatively slightly dependent on the structure of the pyrimidine portion of the molecule. (The chemical shifts measured in D_2O range from 3.80 to 3.91 ppm.) This signal apparently can be assigned to the protons of the N-methyl group of the imidazole ring. The structure of the pyrimidine portion of the molecule has a much more appreciable effect on the position of the second signal, which is found at stronger field. (Under the same conditions of measurement, the chemical shifts range from 3.42 to 3.76 ppm.) It is, therefore, natural to assign the second signal to the protons of the CH_3 group attached to $N_{(1)}$ or $N_{(3)}$. This assignment is confirmed by an examination of the spectra of Ia-IVa. The introduction of an ethoxy group into the 2- or 6-position leads to a shift in the signal of the $N-CH_3$ group of the pyrimidine ring of 0.26-0.37 ppm to strong field, while, as would be expected, the corresponding effect on the position of the signal of the $N-CH_3$ group of the imidazole ring is comparatively small (the change in the chemical shift does not exceed 0.1 ppm).

Difficulties associated with allowing for the effect of steric intramolecular factors (effects of magnetic anisotropy and electrical fields far removed from the examined nucleus of atoms) on the shielding of protons in complex heterocyclic systems render extremely problematical the possibility of obtaining a

TABLE 1. Proton Chemical Shifts and π-Electron Densities in Isomeric N,N-Dimethylhypoxanthines

Compound	Solvent	Chemical shifts, δ_i, ppm*							π-Electron densities						
		$H_{(2)}$	$H_{(6)}$	$H_{(8)}$	$N_{(1)}-CH_3$	$N_{(3)}-CH_3$	$N_{(7)}-CH_3$	$N_{(9)}-CH_3$	$C_{(2)}$	$C_{(6)}$	$C_{(8)}$	$N_{(1)}$	$N_{(3)}$	$N_{(7)}$	$N_{(9)}$
I	D_2O	8,01	—	7,89	3,42	—	3,80	—	0,892	0,840	0,995	1,607	1,272	1,517	1,278
Ia	D_2O	—	—	7,72	3,16	—	3,72	—	0,919	0,840	0,997	1,623	1,313	1,519	1,283
	$CDCl_3$	—	—	7,62	3,44	—	3,98	—							
II	D_2O	8,12	—	7,99	—	3,76	3,86	—	0,848	0,839	0,999	1,328	1,566	1,520	1,279
IIa	D_2O	—	—	7,79	—	3,39	3,79	—	0,882	0,840	1,001	1,365	1,588	1,520	1.280
	$CDCl_3$	—	—	7,50	—	3,60	3,99	—							
III	D_2O	—	8,76	8,16	—	3,54	3,91	—	0,848	0,850	0,965	1,292	1,651	1,536	1,285
IIIa	$CDCl_3$	—	—	7,49	—	3,59	3,87	—	0,849	0,881	0,971	1,334	1,662	1,534	1,285
IV	$CDCl_3$	—	—	7,51	3,44	—	—	3,65	0,916	0,837	1,031	1,621	1,307	1.250	1,543

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* The PMR spectra of the compounds were measured with a JNM-4H-100 spectrometer. The chemical shifts were measured in the δ scale relative to the signals of the protons in $(CH_3)_4Si$.

TABLE 2. $C_{(2\ or\ 6)}-OC_2H_5$ Bond Parameters and Alkylating Ability of Isomeric 2(6)-Ethoxy-N,N-dimethylhypoxanthines

Compound	$q_\pi^{2(6)}$*	ρ_{CO}	$\pi_{CO,O}$	Yield of ethylmalonic ester (P_{11}), %
Ia	0,892	0,329	−0,098	32,5
IIa	0,848	0,342	−0,069	92,5
IIIa	0,850	0,337	−0,090	50,0
IVa	0,891	0,333	−0,102	75,0

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* $q_\pi^{2(6)}$ is the electron density on the $C_{(2)}[C_{(6)}]$ atom in unsubstituted heterocycles I-IV (Fig. 1).

sufficiently rigorous correlation between the π-electron densities and the PMR chemical shifts. However, if the task is restricted to an examination of the relative changes in the chemical shifts in a number of monotypic molecules, the effect of a number of steric intramolecular factors can, to a first approximation, be excluded as a certain constant value [3, 4]. This sort of approach makes it possible to obtain from the PMR spectra information regarding the relative magnitudes of the π-electron densities; this information can be used to check theoretical calculations at least qualitatively.

An examination of the experimental values of the chemical shifts (Table 1) in the light of the above concepts leads to the following results. A shift of the $H_{(2)}$ signals to weak field indicates a decrease in q_π^2 on passing from I to II. A comparison of the spectra of Ia and IVa, measured in $CDCl_3$, makes it possible to conclude that the electron density on $C_{(8)}$ in compounds which contain a methyl group attached to $N_{(9)}$ is higher than in the corresponding isomers which contain a methyl group attached to $N_{(7)}$. In the spectra of I-III the chemical shifts of the protons of the $N-CH_3$ groups increase (the signals are shifted to weak field) $\delta\ N_{(1)}-CH_3 < \delta\ N_{(3)}-CH_3 < \delta\ N_{(7)}-CH_3$, which corresponds to a decrease in the π-electron density on the nitrogen atoms in the indicated sequence. A comparison of the $\delta\ N_{(3)}-CH_3$ values in II and III (solutions in D_2O) and the $\delta\ N_{(7)}-CH_3$ and $\delta\ N_{(9)}-CH_3$ values in Ia and IVa (solutions in $CDCl_3$), respectively leads to the expressions $q_\pi^{N_{(3)}}$ (III) $> q_\pi^{N_{(3)}}$(II) and $q_\pi^{N_{(9)}} > q_\pi^{N_{(7)}}$. The influence of the electron-donating effect of conjugation of the OC_2H_5 group in the 2-position on the difference in the chemical shifts of $N_{(3)}-CH_3$ in II and IIa ($\Delta\delta\ N_{(3)}-CH_3 =$ 0.37 ppm) exceeds a similar influence on $\Delta\delta\ N_{(5)}-CH_3$ in I and Ia (0.26 ppm). Consequently,

$$\Delta q_\pi^{N_{(3)}} = q_\pi^{N_{(3)}}(\mathrm{IIa}) - q_\pi^{N_{(3)}}(\mathrm{II}) > \Delta q_\pi^{N_{(1)}} = q_\pi^{N_{(1)}}(\mathrm{Ia}) - q_\pi^{N_{(1)}}(\mathrm{I}).$$

It is apparent from the data in Table 1 that all of the enumerated expressions are in complete qualitative agreement with the results of calculations of the π-electron densities by the simple MO LCAO method. The presence of such a correlation is, in our opinion, a definite experimental basis for the possibility of using the simple Hückel method for discussion of the regularities in the reactivity of the series of compounds under study.

From a practical point of view, the clarification of two fundamental questions is of interest: 1) which electron structure indexes can characterize, at least qualitatively, the comparative alkylating ability of 2(6)-ethoxy derivatives of the I-IV systems; and 2) what are the factors which affect the direction of the reaction of the compounds with sodiomalonic ester when the molecule contains two possible reaction centers (OC_2H_5 groups in the 2- or 6-positions and a Cl atom in the 8-position)?

The alkylating capacity of the compounds with respect to sodiomalonic ester should be associated with the relative ease of heterocyclic cleavage of an ethoxy group attached to $C_{(2)}[C_{(6)}]$. It might be assumed that this ability increases with an increase in the effect of conjugation of the unshared pair of the oxygen atom of the OC_2H_5 group with the heterocyclic system, since this effect should lead to an increase in polarization and loosening of the $O-C_2H_5$ bond. The effect of conjugation of the same substituent with various heteroaromatic systems depends on the peculiarities of the electron structure of each such system and can, therefore, to a certain degree, be characterized by the electronic parameters of the carbon atom of the starting heterocycle to which a given substituent is attached [for example, the $q_\pi^{2(6)}$ value] and also by the order of the heterocycle−substituent bond (ρ_{CX}). A criterion of the reactivity of the substituent in this reaction may also be the change in the heterocycle−substituent bond order induced by the action of the approaching reagent. For small perturbations of the conjugated system this change is characterized by the bond−atom polarizability ($\pi_{CX,X} = \partial\rho_{CX}/\partial\alpha_X$). Extending the analogy between the conjugation effect

TABLE 3. Relative Changes in the Heterocycle–Substituent Bond Parameters and "Effective" Alkylating Ability of Isomeric 2(6)-Ethoxy-8-chloro-N,N-dimethylhypoxanthines

Compound	q_π^8	ρ_{CCl}	$\pi_{CCl,Cl}$	$q_\pi^8 - q_\pi^2$	$\rho_{CO} - \rho_{CCl}$	$\pi_{CO,O} - \pi_{CCl,Cl}$	P_I*, %	P_{II}, %	$\frac{P_{II}}{P_I + P_{II}}$
Ib	0,995	0,124	−0,035	0,103	0,205	−0,063	53	14	0,21
IIb	0,999	0,123	−0,039	0,151	0,219	−0,030	50	42	0,46
IIIb	0,965	0,130	−0,043	0,115	0,207	−0,057	80	0,0	0,00
IVb	1,024	0,118	−0,038	0,133	0,215	−0,064	70	27	0,28

* P_I is the yield of purinylmalonic ester, and P_{II} is the yield of ethylmalonic ester [1].

and the alkylating ability of the ethoxy group in this series of compounds, it can be assumed that this ability increases with increasing ρ_{CO} and decreasing q_π^C and $\pi_{CO,O}$.

The results of the calculation (Table 2) indicated that all three considered indexes correspond to the maximum alkylating ability of 2-ethoxy-3,7-dimethylhypoxanthine; this agrees with the experimental data obtained in [1]. However, the order of decrease in the reactivity in the series of remaining compounds does not agree with the indexes since, in all cases, IIIa, the experimental reactivity of which is less than that predicted by any index, deviates from the expected order. It can be assumed that this is a consequence of the steric shielding in this compound of the reaction center (the 6-ethoxy group) of the closely situated methyl group (7-CH_3). Attesting to such an assumption is the significant effect of this methyl group on the shielding of $H_{(8)}$, whose signal in III is considerably shifted to weak field (to 8.72 ppm). If IIIa is excluded from consideration for the indicated reason, such indexes as q_π and, especially, ρ_{CO} correctly convey the order of the change in the alkylating properties in the investigated series of compounds.

The alkylation of sodiomalonic ester by compounds containing Cl in the 8-position (Ib-IVb) proceeds with considerably lower yields since these compounds are capable of entering into a competitive heterocyclic substitution of the Cl atom. The lability of the chlorine atom increases with a decrease in the conjugation effect of this atom with the heteroaromatic system. The reactivity of these compounds in the heterolytic substitution of the chlorine should therefore increase with an increase in the π-electron density in the 8-position of the starting heterocycle (q_π^8), with a decrease in the $C_{(8)}-Cl$ bond order (ρ_{CCl}), and with an increase in the polarizability of this bond ($\pi_{CCl,Cl}$). From this it can be assumed that the "effective" alkylating ability of Ib-IVb, characterized by the ratio of the yield of ethylmalonic ester to the overall yield of products of both competing reactions, depends on both the above-examined changes in the electronic parameters of the $C_{(2\text{ or }6)}-OC_2H_5$ bond and on changes in the analogous parameters of the $C_{(8)}-Cl$ bond. In the process, it should increase with a decrease in the π-electron density in the 2(6)-position as compared with the q_π^8 value in the starting heterocycle, with an increase in the $C-OC_2H_5$ bond order (ρ_{CO}) as compared with the $C_{(8)}-Cl$ bond order (ρ_{CCl}), and with a decrease in the polarizability ($\pi_{CO,O}$) as compared with $\pi_{CCl,Cl}$. A comparison of the results of calculation of all three parameters with experimental data (presented in Table 3) indicates that this sort of dependence is actually observed, at least qualitatively. The calculation results in the following order of increase in the relative yield of ethylmalonic ester: Ib < IIIb < IVb < IIb; the experimental results correspond to the order: IIIb < Ib < IVb < IIb. The compound containing 6-ethoxy and 7-methyl groups (IIIb) again deviates from this correlation and forms only the corresponding purinylmalonic ester (alkylation does not occur) with sodiomalonic ester.

As for the above examined IIIa, the decrease in the alkylating ability of IIIb is apparently associated with the additional effect of a steric factor due to the $N_{(7)}-CH_3$ group, which is in the peri position to the reaction center in these compounds. The steric factor may become decisive when the molecule contains a second possible reaction center (the Cl atom in the 8-position), and the reaction proceeds almost completely in the direction of heterolytic substitution of the chlorine atom. Considering this circumstance, it can be supposed that the "effective" alkylating ability of 2(6)-ethoxy-8-chloro-N,N-dimethylhypoxanthines is qualitatively accurately characterized by the difference in the q_π and ρ_{C-A} indexes for the 8- and 2-positions of the investigated molecules.

The bond–atom polarizabilities ($\pi_{CO,O}$) in both the Ia-IVa series and Ib-IVb series less satisfactorily characterize the alkylating ability of the compounds.

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