PURINENUCLEOSIDE ANALOGS.

2.* 9-(1-ALKOXYETHYL-1)-6-SUBSTITUTED PURINES

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Vinyl ethers react with 6-chloro- and 6-methylthiopurines in acid medium to give 9-(1-alkoxyethyl-1)-6-chloro- and 6-methylthiopurines. The 6-chloro compounds were used to prepare 9-(1-alkoxyethyl-1)-6-mercaptopurines. All the synthesized compounds proved to be inactive against lympholeucosis P 388, and Lewis carcinoma grafted under kidney capsules in mice.

Many of the 9-substituted derivatives of 6-chloro-, 6-mercapto-, or 6-alkylthiopurines are less effective antitumor agents than the parent purines from which they are derived; however, in some cases they are superior to them in that they are more selective in their action and less toxic [2, 3].

The 9-(tetrahydro-2-furanyl)- and 9-(tetrahydro-2-pyranyl)-6-substitued purines are of this type, and are of special inerest, as they possess appreciable antitumor activity against adenocarcinoma 755, and some other types of transplanted tumors in animals [2, 4-6].

No plausible explanation of the possible mechanism of biological action of the 6,9-disubstituted purines exists in the literature. The possibility of enzymatic or chemical dealkylation of these compounds does not necessarily explain their unique biochemical properties; some authors suggest that the functional group at the 9 position can be replaced by a sugar moiety, and this nucleoside analog can than take part in certain biochemical reactions involving nucleosides [5, 7, 8].

It was also found that these compounds are highly lipohilic, which facilitates their transport through the cell membrane [3, 5].

The present work involves the synthesis of some 9-(1-alkoxyethyl-1)-6-substituted purines, i.e., compounds which are chemically similar to 9-(tetrahydro-2-furanyl)purines, but differ from them in a number of physicochemical characteristics. By analogy with the corresponding pyrimidine derivatives, it can be expected that in the 9-(1-alkoxyethyl-1)-6-substituted purines, the C–N bond will be more stable than in the corresponding tetrahydrofuran derivatives [9], and that they will also be more lipophilic.

The reaction of purines with compounds containing polarized multiple bonds, such as 2,3-dihydrofuran, 2,3-dihydropyran, acrylonitrile, and others have been reported [4-6,10,11]. For the synthesis of 9-(1-alkoxyethyl-1)-6-substituted purines, we studied the reaction of purines with vinyl ethers, since of the methods available for alkylation, this method has the advantage of being both stereospecific and easy to carry out.

The reaction of 6-chloropurine (Ia) and 6-methylthiopurine (Ib) with vinylethyl (IIa) and vinylbutyl (IIb) ethers in the presence of a catalytic amount of p-toluenesulfonic acid gave 9-(1-ethoxyethyl-1)-6-chloro-(IIIa) and 6-methylthio- (IIIc) purine, and also 9-(1-butoxyethyl-1)-6-chloro- (IIIb) and 6-methylthio- (IIId) purines.

The reaction was carried out at room temperature, and the yields of the alkylation products were high. moreover, in all cases (within the limits of accuracy of NMR) only one isomer was formed.

*For Communication 1, see [1].

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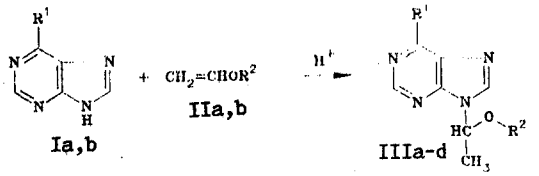
TABLE 1. Chromatographic and Spectral Data for Compounds IIIa-d and IVa and b

Compound	R_f*	UV spectrum, λ_{max}, nm (log ε)	NMR spectrum, δ, ppm †
IIIa	0,82	266 (4,01)	9,00 (1H, s, H_2), 8,83 (1H, s, H_8), 6,11 (1H, q, NCH), 3,49 (2H, m, OCH_2), 1,89 (3H, d, CH_3), 1,14 (3H, t, CH_3)
IIIb	0,89	266 (4,02)	9,01 (1H, s, H_2), 8,83 (1H, s, H_8), 6,11 (1H, q, NCH), 3,45 (2H, m, OCH_2), 1,92 (3H, d, CH_3), 1,37 (4H, m, CH_2), 0,84 (3H, m CH_3)
IIIc	0,78	285 (4,23)	8,74 (1H, s, H_2), 8,18 (1H, s, H_8), 5,99 (1H, q, NCH), 3,44 (2H, m, OCH_2), 2,74, 1,16 (3H, s, CH_3), 1,77 (3H, d, CH_3)
III d	0,87	285 (4,25)	8,74 (1H, s, H_2), 8,06 (1H, m, H_8), 5,97 (1H, q, NCH), 3,37 (2H, m, OCH_2), 2,75, 0,86 (3H, s, CH_3), 1,77 (3H, d, CH_3), 1,40 (4H, m CH_2)
IVa	0,59	325 (4,29)	8,46 (1H, s, H_2), 8,29 (1H, s, H_8), 5,87 (1H, q, NCH_2), 3,40 (2H, m, OCH_2), 1,77 (3H, d, CH_3), 1,07 (3H, t, CH_3)
IVb	0,65	326 (4,36)	8,43 (1H, s, H_2), 8,20 (1H, s, H_8), 5,81 (1H, q, NCH), 3,29 (2H, m, OCH_2), 1,73 (3H, d, CH_3), 1,31 (4H, m, CH_2), 0,78 (3H, m, CH_3)

*R_f was obtained in system B for compounds IIIa-d, and in system A for compounds IVa and b (see experimental section).
†Spectra of compounds IIIa and b and IVa and b were taken in DMSO-D_6, spectra of compounds IIIc and d in $CDCl_3$.



Ia, IIIa, b R^1=Cl, Ib, IIIc, d R^1=SCH_3; IIa, IIIa, c R^2=C_2H_5, IIb, IIIb, d R^2=C_4H_9

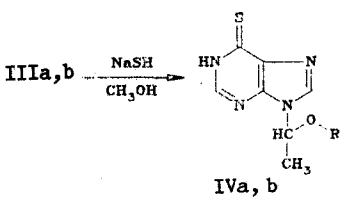
It can be assumed that IIIa-d are 9-substituted isomers, since their absorption maxima (Table 1) at 266 nm for IIIa and b, and at 285 nm for IIIc and d correspond with the absorption maximum for 6,9-disubstituted purines but differ from those of the 6,7-disubstituted purines (271 and 293 nm) [4].

During the course of the work, reports appeared in the literature [12-14] on the synthesis of 9-(1-alkoxyethyl-1)purines and 9-(1-ethoxyethyl-1)-6-substituted purines, obtained from the reaction of purines with 1-chloroethylalkyl ethers in the presence of base. The authors did not give yields of the reaction products, but noted that 7-substituted isomers were formed as by-products [14].

The 6-chloropurine derivatives IIIa and b were used for the synthesis of the corresponding 9-(1-alkoxyethyl-1)-6-mercaptopurines.

Replacement of the halogen by a mercapto group in compounds IIIa and b using thiourea in alcohol gave a single reaction product, 6-mercaptopurine, confirming that the C–N bond was hydrolyzed under these conditions.

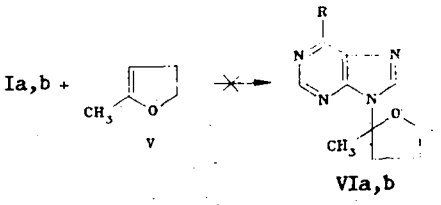
More sucessful was the use of a methanolic solution of sodium hydrogen sulfide to give 9-(1-ethoxyethyl-1)-6-mercaptopurine (IVa) and 9-(1-butoxyethyl-1)-6-mercaptopurine (IVb).



IV a R=C_2H_5, b R=C_4H_9

Structures and purity of all the compounds were confirmed from their physicochemical constants (Table 1).

An attempt was also made to synthesize the 9-(tetrahydro-2-methyl-2-furanyl) derivatives of the 6-substituted purines (VIa and b) by this method; however, the addition of Ia and b acrosss the double bond of 2-methyl-4,5-dihydrofuran (V) in the presence of p-toluenesulfonic acid or hydrogen chloride did not take place, probably because of steric hindrance.



VI a R=Cl, b R=SCH_3

A study of the antitumor activity of compounds IIIa-d, and IVa and b established that none of them were active against lympholeucosis P 388 or Lewis carcinoma grafted under kidney capsules in mice.

EXPERIMENTAL

Ultraviolet spectra were run on a Unicam Sp-1800 spectrometer (in ethanol), NMR spectra on a Bruker WH-90 (in DMSO-D_6 or $CHCl_3$), TMS was used as a reference. The purity of the compounds was checked by TLC on Silufol UV-254 plates, using the solvent systems chloroform–methanol, 10:1 (A) and ethylacetate-acetic acid, 50:1 (B).

9-(1-Ethoxyethyl-1)-6-chloropurine (IIIa). To a suspension of 2.0 g (13 mmoles) of Ia in 30 ml of dry ethyl acetate was added 100 mg of p-toluenesulfonic acid and 1.51 g (2.0 ml, 21 mmoles) of IIa. The reaction mixture was stirred at room temperature for 5 h, then diluted with 100 ml of ethyl acetate, washed with 2 × 20 ml of 15% potassium carbonate, 30 ml of water, and dried with anhydrous sodium sulfate. The solvent was evaporated, giving 2.81 g (95.9%) of an oily substance, which was twice recrystallized from a mixture of diethyl ether and petroleum ether to give 2.17 g (74%) of IIIa, mp 49°C. Found: C 47.5; H 4.7; N 24.8%. $C_9H_{11}ClN_4O$. Calculated: 47.7; H 4.9; N 24.7%.

9-(1-Butoxyethyl-1)-6-chloropurine (IIIb) was synthesized by the method described above from 2.0 g (13 mmoles) of Ia and 2.10 g (3.0 ml, 24 mmoles) of IIb. Two recrystallizations from hexane gave 2.60 g (78.5%) of IIIb, mp < 30°C. Found: C 52.2; H 6.1; N 21.7%. $C_{11}H_{15}ClN_4O$. Calculated: C 51.9; H 6.0; N 22.0%.

9-(1-Ethoxyethyl-1)-6-methylthiopurine (IIIc) was synthesized from 2.0 g (12 mmoles) of Ib and 1.87 g (2.5 ml, 26 mmoles) of IIa. The product was recrystallized from diethyl ether containing hexane to give 2.26 g (79%) of IIIc, mp 68°C. Found: C 50.5; H 5.8; N 23.3%. $C_{10}H_{14}N_4OS$. Calculated: C 50.4; H 5.9; N 23.5%.

9-(1-Butoxyethyl-1)-6-methylthiopurine (IIId) was synthesized from 2.0 g (12 mmoles) of Ib and 2.40 g (3.0 ml, 24 mmoles) of IIb. Two recrystallizations from hexane gave 2.38 g (74.5%) of IIId, mp 33°C. Found: C 53.9; H 6.7; N 20.7%. $C_{12}H_{18}N_4OS$. Calculated: C 54.1; H 6.8; N 21.0%.

9-(1-Ethoxyethyl-1)-6-mercaptopurine (IVa). To a solution of 2.27 g (10 mmoles) of IIIa in 20 ml of methanol was added 20 ml of 1 N sodium hydrogen sulfide in methanol, the mixture refluxed for 30 min, and then filtered. The filtrate was neutralized with acetic acid, the precipitated material filtered off, and precipitated from 1 N NaOH solution with acetic acid. Recrystallization from ethanol gave 1.48 g (66%) of IVa, mp 202-204°C. Found: C 48.3; H 5.4; N 25.2%. $C_9H_{12}N_4OS$. Calculated: C 48.2; H 5.4; N 25.0%.

9-(1-Butoxyethyl-1)-6-mercaptopurine (IVb) was synthesized from 2.55 g (10 mmoles) of IIIb by the method described above; 1.86 g (74%) of IVb with mp 182-184°C (decomp.) was obtained. Found: C 52.6; H 6.5; N 22.1%. $C_{11}H_{16}N_4OS$. Calculated: C 52.4; H 6.4; N 22.2%.

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CONFIGURATION OF 2-(4-PYRIDYL)-5-ARYLOXAZOLE MOLECULES IN VARIOUS STATES OF AGGREGATION

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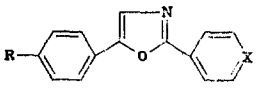
The electronic absorption and emission spectra in the crystals, solutions, vapor, and ethanol—ether (77°K) were investigated for the series of 2-(4-pyridyl)-5-aryl-substituted oxazoles at various temperatures. The conjugation between the rings of the system was investigated by mass spectrometry. The combination of spectral data shows that the configurations of such molecules both in the ground state and in the excited state depends substantially on the state of aggregation and on the temperature.

Earlier [1-3] we studied the effect of the state of aggregation and temperature on the configuration and on the conjugation between the rings in heterosystems with structures of the biphenyl type in the ground and excited states. Using a set of independent physical methods (electronic and vibrational spectroscopy, dielectric constant measurement, mass spectrometry, photoionization, and x-ray crystallography) and considering the reactivity of such compounds, we came to the conclusion that the conjugation in this case does not in fact depend on the angle of rotation (θ) of the rings forming the bis-system when $\theta < 60°$.

The aim of the present investigation was to examine the more complex system of 2-(4-pyridyl)-5-aryloxazoles in terms of the above-mentioned problems. We undertook spectral-luminescence and mass-spectrometric studies of the molecules of a series of 2-(4-pyridyl)-5-aryloxazoles (I-IV) and of the model compound 2,5-diphenyloxazole (V).



I–V

I—IV X=N, V X=CH; I, V R=H, II R=CH_3, III R=Cl, IV R=OCH_3,

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