SYNTHESIS AND ANTIVIRAL ACTIVITY OF S-ALKYNYL DERIVATIVES OF MERCAPTOPURINES

E. V. Ratsino, S. I. Radchenko
E. B. Shtil'bans, L. A. Rachkovskaya,
L. B. Sokolov, G. E. Alekseeva, and
M. A. Shneider

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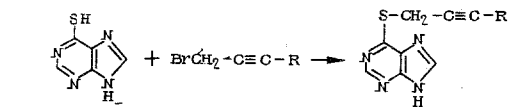
Some analogs of nucleic acid bases, for example, mercaptopurines, possess considerable antiviral activity [1].

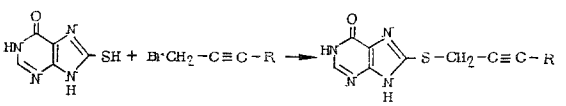
S-Alkynyl derivatives of purines are not well known and little work has been done on their antiviral activity.

We have synthesized some propargyl and vinylacetone derivatives of S-substituted 6-mercaptopurine and 8-mercaptohypoxanthine.

The reaction was carried out in liquid ammonia by mixing equivalent amounts of the mercaptopurine with propargyl bromide or 1-bromo-4-penten-2-yne in the presence of sodamide.



I, II
I: R=H
II: R=CH=CH$_2$



III: R=H
IV: R=CH=CH$_2$

III, IV

The UV spectra of compounds (I-IV), taken in 0.1 N sodium hydroxide showed a hypsochromic shift of 10-18 nm in comparison with the original 6-mercaptopurine and 8-mercaptohypoxanthine, confirming that S-alkylation of the mercaptopurine had occurred [2].

NMR spectra confirmed the retention of the propargyl or vinylacetyl group (Table 1).

The IR spectra of compounds (I) and (III) contained bands at 3230-3270 and 2120 cm^{-1} corresponding to the monosubstituted triple bond; spectra of compounds (II) and (IV) showed a triple bond characteristic of 1-alkylthio-4-buten-2-ynes [4].

EXPERIMENTAL (PHARMACOLOGICAL)

The study of the virus-inhibiting activity of the compounds was carried out on 10-11 day chick embryos, using the most common type of virus — type A and B influenza virus [A/Leningrad/110/72 (H3N2) and B/USSR/69 strains], and also the Rauscher virus (VSR) [RSV (RAV = 1) and RSV (RAV = 50) strains], a sarcoma-causing RNA-containing virus.

In the first case, the drug (1 mg/embryo) was introduced into the embryonic allantoic cavity in 0.2 ml one hour before inoculation with the virus. The presence of the virus was determined by the standard hemagglutination reaction on a 1% solution of chick erythrocytes after 48 hours for influenza A and after 72 hours for influenza B.

The effect of the compounds on Rauscher virus was studied using both prophylactic and curative treatments. In prophylaxis, the drug was injected into the chorioallantoic cavity 1 hour before the introduction of the virus; Rauscher virus ($10^{-3.5}\cdot OD_{50}$ in 0.1 ml) was in-

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TABLE 1. Physicochemical Properties of S-alkynyl Derivatives of Mercaptopurines

Compound	Name	Found, % S	Empirical formula	Calculated, % S	UV spectrum, nm	IR spectrum, ν C≡CH, cm⁻¹	NMR spectrum, δ, ppm	R_f*
I	6-(2-Propynylthio)purine [3]	16.28	$C_8H_6N_4S$	16.85	291	2120 3230	8.7 s (H, C_8—H), 8.40 s (H, C_2—H), 4.24 (2H, I 2Hz S—CH_2), 2.88 (H, I 1.5Hz≡CH)	0.68
II	6-(4-Penten-2-ynylthio)purine	14.35	$C_{10}H_{10}N_4S$	14.80	295	—	8.71 s (H, C_8—H), 8.36 s (H, C_2—H) 5.3—5.8 m (3H, —CH=CH_2), 4.38 s (2H, —S—CH_2—)	0.70
III	8-(2-Propynylthio)hypoxanthine	15.05	$C_8H_6H_4OS$	15.52	280	2120 3270	7.90 s (H, C_2—H) 4.21 d (2H, I2 Hz —S—CH_2), 2.82 t (H, I1.5Hz≡CH)	0.67
IV	8-(4-Penten-2-ynylthio)hypoxanthine	13.35	$C_{10}H_8H_4OS$	13.80	285	—	7.96 s (H, C_2—H), 5.35—5.8m (3H, —CH=CH_2), 4.30 s (2H, —S—CH_2—)	0.65

*TLC system, butyl alcohol—ethanol—water, 4:1:5 (upper layer).

TABLE 2. Antiviral Activity of S-Alkynyl Derivatives of Mercaptopurines

Compound	Antiviral activity (protective index), %					
	prophylactic method				curative method	
	A/Leningrad/110/72	B/USSR/69	RSV (RAV=1)	RSV (RAV=50)	RSV (RAV=1)	RSV (RAV=50)
I	68,3	16,2	58,3	52,5	73,3	70,0
II	35,7	48,6	—	20,6	—	0
III	21,24	0	—	—	24,0	—
IV	26,6	0	25,6	—	64,7	—

oculated into an artificial air pocket through the same aperture as the drug.

To study the medicinal effect, the drug was introduced in the same way 1.5-2 h after the injection of the virus. In all cases, the results were assessed after 7 days, from the average number of points of infection in the chorioallantoic cavities caused by the Rauscher virus. The test was carried out three times with each compound and the protection index calculated.

The results of the study of the antiviral activity of S-alkynyl derivatives of mercaptopurines are given in Table 2 and it can be seen that compound (I) was the most effective antiviral agent with respect to both infectious virus and oncogenic virus. However, in prophylactic treatment, compound (II) was more active against type B influenza virus than type A but had virtually no effect on the tumor virus. Compound (IV) had very little effect on influenza virus but was very effective in the treatment of virus-induced tumors.

Thus, although the mercaptopurine S-alkynyl derivatives possess some antiviral activity, they are less active than remantadine and other adamantane derivatives.

EXPERIMENTAL (CHEMICAL)

IR spectra of the compounds in KBr pellets were taken on an IR-10 (GDR) spectrophotometer, NMR spectra on a Tesla (ChSSR) instrument using DMSO as solvent and tetramethylsilane as internal standard.

General Method for the Preparation of S-Alkynyl Derivatives of Mercaptopurines. To a suspension of 0.01 mole of sodamide in 50 ml of liquid ammonia was added 0.01 mole of 6-mercaptopurine (or 8-mercaptohypoxanthine), the solution mixed for 10 minutes, and 0.011 mole of propargyl bromide (or 1-bromo-4-penten-2-yne) added [5]. After mixing for 30 minutes, the ammonia was evaporated off, the residue dissolved in 2 N ammonium hydroxide, and the product precipitated by neutralization with 10% acetic acid. This was filtered off, washed with water, and dried over phosphorus pentoxide to give 80-85% of product.

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1,2,3,9a-TETRAHYDRO-1-AZAFLUORENES

N. S. Prostakov, A. T. Soldatenkov,
V. O. Fedorov, A. I. Semikopnyi,
I. A. Sytinskii, M. I. Borisov,
and T. P. Mufazalova

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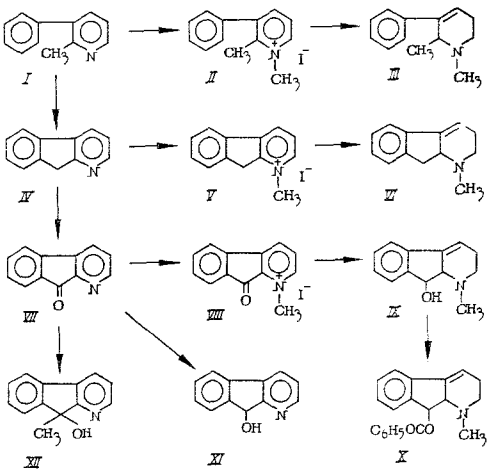
Some partially hydrogenated indenopyridines possess quite high physiological activity [1-4]. One compound of this type, used as an antiallergic drug, is teforine (2-methyl-9-phenyl-1,2,3,4-tetrahydroindano[2,3-c]pyridine tartrate [5]). Of the partially hydrogenated indenopyridines isomeric with respect to the position of the nitrogen atom, 1,2,3-9a-tetrahydro-1-azafluorenes have received virtually no attention (although they may be regarded as cyclic analogs of drugs of the amphetamine series). This is due to the lack of practicable methods for the preparation of starting materials for their synthesis, in particular 1-azafluorene. We have developed a method for the preparation of 1-azafluorene [6] by the catalytic dehydrocyclization of 2-methyl-3-phenylpyridine (I), which has enabled a study to be undertaken of its conversion, by the sodium borohydride reduction of quaternary salts of 1-azafluorene and the corresponding ketone, into partially hydrogenated 1-azafluorenes.

The methiodide of the pyridine base I (II) was first reduced. 1,2-Dimethyl-3-phenyl-1,2,5,6-tetrahydropyridine was isolated both as the free base and the hydrochloride. The PMR spectrum of (III) displayed a doublet signal for the methyl group at C_2 (δ = 0.85 ppm), and a multiplet of integral intensity one proton unit at δ = 5.70 ppm, assigned to the vinyl proton. Such multiplet signals are evidence of the location of the doublet bond between C_3 and C_4.



Sodium borohydride reduction of 1-azafluorene methiodide (V) [obtained from 1-azafluorene (IV)] gave 1-methyl-1,2,3,9a-tetrahydro-1-azafluorene (VI). The position of the double bond in its nitrogen-containing ring is apparently the same as in (III). Only signals due to the protons of the $=NCH_3$ group, and one vinyl proton at δ = 5.90 ppm, are seen in its PMR spectrum. Sodium borohydride reduction of 1-azafluorenol methiodide (VIII) [obtained from 1-azafluorenone (VII)] gives both pyridine ring and carbonyl group reduction products. 1-Methyl-9-hydroxy-

Patrice Lumumba People's Friendship University, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal Vol. 15, No. 8, pp. 67-71, August, 1981. Original article submitted December 29, 1980.

