SYNTHESIS AND BIOLOGICAL ACTIVITY OF 5-FLUOROALKYLTHIO-6-AZAURIDINES

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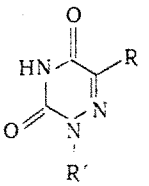
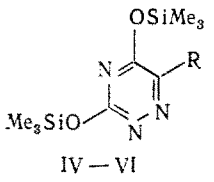
Derivatives of 6-azapyrimidine are of practical interest as compounds with multi-faceted biological activity [7].

One method for synthesizing N-glycosides is the condensation of silylated nitrous heterocycles with peracylcarbohydrates in the presence of a Lewis acid type catalyst [12], fluoroalkylsulfonic acids [11], or trimethyliodosilane [9, 10]. There has been little study of the latter catalyst, although it does have a number of advantages over the other ones mentioned. It is obtained by reacting trimethylchlorosilane with sodium iodide in acetonitrile and is brought into condensation *in situ*. We previously also obtained 6-azauridine and a number of its 5-substituted derivatives by using trimethyliodosilane [5]. In consideration of the chemical and biological features of the fluorinated nucleosides [4], we thought it would be of interest to synthesize the 5-fluoroalkylthio-6-azauridine.



I — III, VIII — XIII



IV — VI

I, IV, VIII, XI: R = $SCHF_2$; II, V, IX, XII: R = SCF_3; III, VI, X, XIII: R = SC_3F_7; I — III: R′ = H; VIII — X: R′ = 2, 3, 5-tri-O-benzoyl-D-ribofuranosyl-1; XI — XIII R′ = D-ribofuranosyl-1

The three-step synthesis of 5-fluoroalkylthio-6-azauridines (XI-XIII) consists of the silylation of 5-difluoromethylthio-(I), 5-trifluoromethylthio-(II), and 5-perfluoropropylthio-(III) of 6-azauracyls by hexamethyldisilazane (HMDS) and trimethylchlorosilane (TMCS) and subsequent condensation of the silyl derivatives (IV-VI) with 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose (VII) in the presence of a quantity of trimethyliodosilane that is triple that of the peracyl sugar. The final step is the deacylation of the tribenzoates VIII-X followed by the separation and purification of the target compounds XI-XIII.

In the glycosilation process the IV-VI derivatives are introduced without separation. At the same time it is generally recognized that heterocyclic silylation reactions always proceed to the 90% level. Therefore the starting compounds I-III were introduced into the silylation reaction at a 25% excess in order to obtain a complete condensation of IV-VI and peracylribose. This considerably simplified the separation and chromatographic purification of the acylribosides VIII-X and facilitated the regeneration of any unreacted I-III material.

The physical and chemical characteristics of the separated compounds are given in the Table. The β-anomer structure of ribofuranosides XI-XIII was confirmed by PMR spectral data based on the chemical shifts of the anomer proton H_1' of ribofuranose and the values for the spin-spin coupling constant with an $H_{2''}$-atom: $\beta_{H_1'}$, ppm, ($J_{H_1'-H_2''}$, Hz) for XI — 6.04; (4.0); XII — 6.06 (3.5); XIII — 6.09 (4.0).

EXPERIMENTAL CHEMICAL PART

Uv spectra were recorded on a Specord UV-VIS spectrometer (GDR), and the PMR spectra were recorded on a Tesla BS487C instrument (80 MHz) (Czechoslovakia) in deuterated water with DSS as the internal standard.

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TLC was performed on Silufol UV-254 plates in the systems: Chloroform-methanol (14:1) and (9:2). Column chromatography was performed on silica gel L 40/100 (Czechoslovakia). The eluant was chloroform-methanol (14:1).

1-O-Acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose (VII) was obtained by the method described in [6]. The starting substances I-III were obtained by the method described in [2, 3].

The acetonitrile was twice distilled over P_2O_5, and then over CaH_2.

Silylated 5-substituted 6-azauracyls (IV-VI) were obtained by heating 6.4 mmoles of I-III in a mixture of 20 ml of HMDS and 2 ml of TMCS at 150-160°C for 2-4 h. After the excess of the reagents was vacuum evaporated, the residues IV-VI were dissolved in 60 ml of acetonitrile and used in the subsequent condensation reactions.

Trimethyliodosilane. A 1 g portion of 0.4 nm molecular sieves was added to 1.2 g (14.2 mmoles) of dry sodium iodide in 40 ml of acetonitrile, followed by the addition of 1.55 ml (14.2 mmoles) of TMCS. The mixture was then agitated for 30 min.

Glycosylation of Compounds (IV-VI). A 4.8 mmole portion of VII was added to a solution of trimethyliodosilane and the mixture was stirred for 30 min. A 60 ml portion of 6.4 mmoles of the silyl derivatives in acetonitrile was then added to the mixture which was stirred for an additional 4-6 h. The reaction was controlled by TLC of reaction mixture samples. The reaction mixture was filtered, the filtrate was concentrated in a vacuum, and the residue was dissolved in 200 ml of chloroform, and the solution was subsequently washed (2 × 100 ml) with saturated $NaHCO_3$, 10% $Na_2S_2O_3$, and water and then dried over Na_2SO_4. The solvent was evaporated, and the products were chromatographed on silica gel. After the solvent was distilled off the residues were crystallized: VIII from ethanol; IX from 60% ethanol; X from a 1:2 ethylacetate-hexane mixture.

5-Difluoromethylthio (XI), 5-Trifluoromethylthio-(XII), and 5-Perfluoropropylthio (XIII) 6-Azauridines. A 2.5 mmole portion of VIII-X was treated with a mixture of 5 ml of 1 N sodium methylate and 50 ml of methanol at 20°C for 3 h. The solvent was evaporated and the residue was dissolved in 100 ml of water and extracted by a 2:1 ethylacetate-ether mixture (3 × 20 ml). Resin KU-2 was then added to the aqueous layer until the pH reached 3. The cation exchanger was then filtered off, the filtrate was evaporated, and the following residues were crystallized: XI from a 1:2 ethylacetate-ether mixture: XII from absolute ethanol; XIII from water.

Data on element analysis, yields, and physical and chemical characteristics of VIII-XIII are given in the Table.

EXPERIMENTAL BIOLOGICAL PART

The biological activity of the ribosides XI-XIII was tested on one of the protozoa species *Tetrahymena pyriformis* as compared to a standard Osarsol preparation (3-acetoamido-4-oxyphenyl arsenic acid) which is used to treat protozoan infections.

The tests were conducted by titrating the compounds under study by means of a twofold series dilution on a peptone medium. The peptone medium was prepared in the following manner: The following ingredients (in g) were added to 100 ml of distilled water: Medical grade glucose — 0.5, enzymatic peptone — 2.0, sea salt — 0.1, and yeast extract — 0.1. A 0.1 ml portion of a three-day culture of *Tetrahymena pyriformis* was inserted into each test tube with the titered substance. The test tubes with the cultures were allowed to stand exposed to light at room temperature (20-25°C) for 24 h. Osarsol was used as the standard reference, and the control was a modification of the standard with a three-day culture in a peptone medium (0.1 ml). The experiment was repeated four times. The compounds' activity was determined 24 h after the cultures were placed in contact with the dissolved test substances in accordance with the method described in [8]. In the follow-up we counted the number of infusoria and appraised their mobility as well as morphology. Infusoria deaths or a reliable reduction in their growth served as indicators of the test compounds' biological activity. The toxic concentration of the tested substances was considered to be that which provided a 100% death rate of the *Tetrahymena pyriformis*.

Our experiment demonstrated that a 500 μg/ml concentration of compounds XI and XIII completely suppressed culture reproduction, whereas that suppression was accomplished by compound XII and the standard at a concentration of 1 mg/ml.

TABLE 1. 5-Fluoroalkylthio-6-azauridines

Compound	Yield, %	mp, °C	R_f	UV spectra, nm (ε 10^{-3})		Found, %		Empirical formula	Calculated, %	
				ethanol	0.1 N KOH	N	F		N	F
VIII	80	144—145	0,38	—	—	5,74	6,56	$C_{30}H_{23}F_2N_3O_9S$	5,94	6,57
IX	79	150—151	0,47	—	—	8,72	6,70	$C_{30}H_{22}F_3N_3O_9S$	8,67	6,39
X	73	143—144	0,53	—	—	17,62	5,40	$C_{32}H_{22}F_7N_3O_9S$	17,55	5,55
XI	74	137—138	0,28	298 (6,09)	288 (5,02)	11,35	12,35	$C_9H_{11}F_2N_3O_6S$	11,61	12,83
XII	67	136—137	0,23	289 (6,22)	284 (5,53)	16,47	12,16	$C_9H_{10}F_3N_3O_6S$	16,51	12,17
XIII	73	163—164	0,39	282 (6,65)	282 (6,05)	9,45	30,08	$C_{11}H_{10}F_7N_3O_6S$	9,46	29,93

Note. Yield of VIII-X calculated for the initial peracylribofuranose: R_f for VIII-X in a 14:1 chloroform-methanol system, R_f for XI-XIII in a 9:2 chloroform-methanol system.

Acute toxicity of compounds XI-XIII was assayed by the standard method [1] on white mice (males and females) weighing from 18 to 22 g, by means of an im injection of an emulsion of the preparations at various concentrations. Animal deaths were counted 24 h after the injections.

The toxicity of XI-XIII was greater than 1000 mg/ml.

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SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF THE ALKALOID KOMAROVININE AND ITS TETRAHYDRO DERIVATIVE

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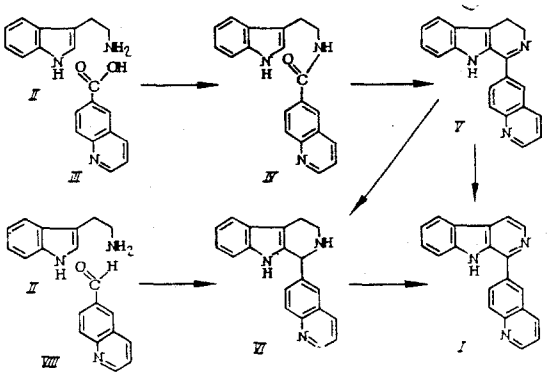
It was shown earlier [2, 4] that alkaloids of *Nitraria* L. plants and certain of their synthetic analogs possess spasmolytic, hypotensive, and hypertensive activity. The goal of the present work was the synthesis and pharmacological study of komarovinine (I) and 1,2,3,4-tetrahydrokomarovinine (VI). The isolation and establishment of the structure of I have been described earlier [3].



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