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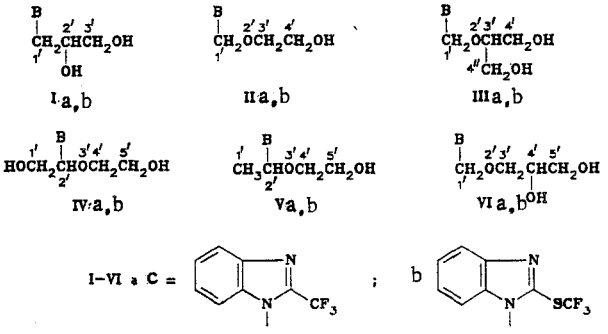
ACYCLIC ANALOGS OF NUCLEOSIDES. SYNTHESIS OF HYDROXYALKYL DERIVATIVES OF 2-TRIFLUOROMETHYL- AND 2-TRIFLUOROMETHYLTHIOBENZIMIDAZOLE

A. É. Yavorskii, A. V. Stetsenko, I. V. Gogoman, V. N. Boiko, S. G. Zavgorodnii, A. I. Sobko, V. N. Tatskaya, V. G. Kvachev, and V. L. Florent'ev

UDC 547.424'785.5'963.32.04

1-(2,3-Dihydroxypropyl)-, 1-(4-hydroxy-2-oxabutyl)-, 1-(3-hydroxymethyl-4-hydroxy-2-oxabutyl)-, 1-(1,5-dihydroxy-3-oxa-2-pentyl)-, 1-(5-hydroxy-3-oxa-2-pentyl)-, and 1-(4,5-dihydroxy-2-oxapentyl)-2-trifluoromethyl- and -2-trifluoromethylthiobenzimidazoles were obtained by condensation of trimethylsilyl derivatives of 2-substituted benzimidazoles with alkylating agents in the presence of $SnCl_4$ or by direct alkylation of the sodium salts of the heterocycles.

A great deal of attention is currently being directed to the study of acyclic analogs of nucleosides [1]. Continuing our previously commenced investigation [2] of the relationship between the structure and biological activity of analogs of nucleosides modified with respect to the sugar and heterocyclic base we studied the effect of the conjunction of the hydrophilic groupings of hydroxyalkyl substituents and hydrophobic substituents in the heterocyclic base on the biological activity of acyclic analogs of nucleosides. In this connection we synthesized a number of derivatives of 2-trifluoromethyl- and 2-trifluoromethylthiobenzimidazole:



2-Trifluoromethylbenzimidazole (VIIa) was obtained by the method in [3], while 2-trifluoromethylthiobenzimidazole (VIIb) was synthesized from 2-mercaptobenzimidazole:

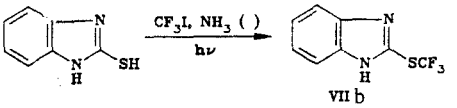
Institute of Molecular Biology, Academy of Sciences of the USSR, Moscow 117984. T. G. Shevchenko Kiev State University, Kiev 252601. Ukrainian Scientific-Research Veterinary Institute, Kiev. All-Union Scientific-Research Institute of Biotechnology, Ministry of the Medical and Microbiological Industry of the USSR, Moscow 125047. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 632-636, May, 1988. Original article submitted November 14, 1986; revision submitted October 8, 1987.

 0009-3122/88/2405-0514$12.50

TABLE 1. Synthesis of Acyclic Analogs of Nucleosides

Heterocycle	Alkylating agent	Protected analogs		Unprotected analogs		
		compound*	yield, %	compound	mp, °C (ether–ethanol)	yield, %
VIIa	VIII	IXa	55	Ia	96—97	90
VIIb	VIII	IXb	50	Ib	Oil	85
VIIa	X	XIa	49	IIa	Oil	90
VIIb	X	XIb	40	IIb	89—90	95
VIIa	XII	XVIa	60	IIIa	93—94	87
VIIb	XII	XVIb	45	IIIb	108—109	80
VIIa	XIII	XVIIa	50	IVa	117—118	90
VIIb	XIII	XVIIb	35	IVb	116—117	95
VIIa	XIV	XVIIIa	48	Va	55—56	95
VIIb	XIV	XVIIIb	70	Vb	70—71	92
VIIa	XV	XIXa	45	VIa	Oil	90
VIIb	XV	XIXb	40	VIb	101—102	87

*Compound XVIIa had mp 69-70°C; the remaining compounds were obtained in the form of oils.

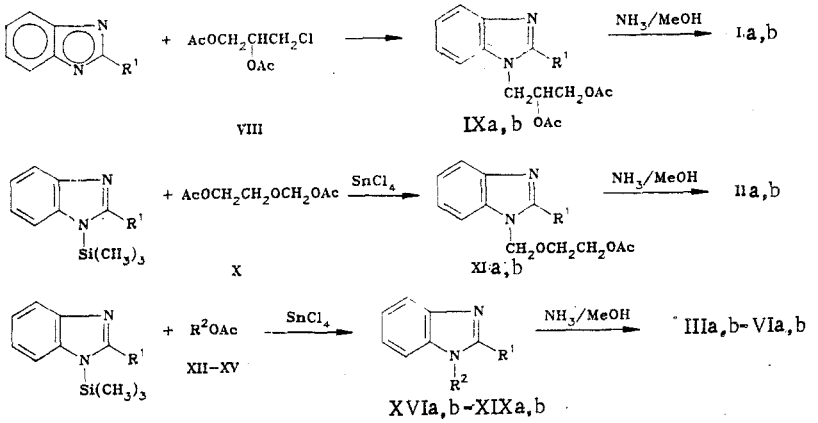


VII b

Protected nucleoside analogs IXa, b were obtained by the reaction of chloride VII with the sodium salt of 2-trifluoromethyl- or 2-trifluoromethylthiobenzimidazole. Condensation of the trimethylsilyl derivatives of heterocyclic bases VIIa, b with the corresponding alkylating agents X and XII-XV in absolute acetonitrile in the presence of $SnCl_4$ led to protected analogs XIa, b and XVIa, b-XIXa, b (Table 1) in 40-50% yields.

Unprotected nucleoside analogs Ia, b-VIa, b (Table 1) were obtained by removing the acyl protective groups by treatment with a semisaturated (at 0°C) methanol solution of ammonia.

Scheme 1



XII, XVIa,b R^2 = $AcOCH_2CH(CH_2OAc)OCH_2$—; XIII, XVIIa,b R^2 = $AcOCH_2CH_2OCHC_2OAc$;

XIV, XVIIIa,b R^2 = $AcOCH_2CH_2OCHCH_3$; XV, XIXa,b R^2 = $AcOCH_2CH(OBz)CH_2OCH_2$—;

a R^1 = CF_3; b R^1 = SCF_3

The structures of the compounds obtained were confirmed by the PMR and UV spectra (Tables 2 and 3). The structures of the hydroxyalkyl substituents of unprotected analogs Ia, b-VIa, b were proved unequivocally by the characteristic signals of OH groups in the PMR spectra of solutions in hexadeuterodimethyl sulfoxide. Thus the doublet and triplet signals in the spectra of Ia, b and VIa, b indicate the presence of secondary and primary hydroxy groups. The two triplet signals with a relative intensity of 1H each in the spectra of IVa, b and the one triplet signal with an intensity of 2H in the spectra of IIIa, b make it possible to speak of the presence of two primary hydroxy groups in the molecules of the nucleoside analogs. Finally, the sole primary OH group of IIa, b and Va, b shows up in the form of a triplet with a relative intensity of 1H.

TABLE 2. PMR Spectra (in d_6-DMSO) of the Acyclic Analogs of Nucleosides of 2-Trifluoromethylbenzimidazole and 2-Trifluoromethylthiobenzimidazole

Compound	Chemical shift, δ, ppm*						
	1′-CH_2 (or 1′-CH_3)	2′-CH	3′-CH_2 or 3′-CH)	4′-CH_2 and 4″-CH_2 or 4′-CH)	5′-CH_2	—OH	CH_3CO
IXa	4,35 m	5,50 m	3,85 d	—	—	—	1,96 d
Ia	3,95 d	3,84—4,61 m		—	—	5,14 d 4,94 t	—
XIa	5,75 s	—	3,67 m	4,20 m	—	—	1,96 s
IIa	5,86 s	—	3,48—3,55 m		—	4,76 t	—
XVIa	5,82 s	—	3,90—4,12 m			—	1,86 s
IIIa	5,92 s	—	3,40—3,55 m			4,70 t 4,36 t	—
XVIIa	4,77 dd**						
	4,46 dd	5,95 m	—	4,21 t | 3,71 m		—	1,94 s
IVa	3,91 t	5,78 t	—	3,49 m		5,25t 4,71t	—
XVIIIa	1,76 d	5,84 q	—	3,55 m | 4,17 m		—	1,92 s
Va	1,76 d	6,03 q	—	3,54 m		4,72 t	—
XIXa	5,75 s	—	3,75 d	5,41 m | 4,29 d		—	1,91 s
VIa	5,83 s	—	3,40—3,65 m			4,81d 4,52 t	—
IXb	4,29 m	5,21 m	3,66 d	—	—	—	2,01 d
Ib	4,08 dd **						
	4,36 dd **	5,48 m	3,77 m	—	—	5,29 t	—
XIb	5,80 s	—	3,65 m	4,17 m	—	—	1,98s
IIb	5,28 s	—	3,49—3,61 m		—	4,48t	—
XVIb	5,87 s	—	4,00—4,37 m			—	1,88 s
IIIb	5,90 s	—	3,15—3,63m			3,85s	—
XVIIb	4,70 dd **	6,19 dd	—	3,68 m | 4,21 m		—	1,96s
	4,37 dd **						1,98 s
IVb	3,85 m	5,95 dd	—	3,49 m		5,28 t 4,74 t	—
XVIIIb	1,80 d	6,16 q	—	3,55 m | 4,18 m		—	1,96 s
Vb	1,72 d	6,16 q	—	3,20—3,46 m		4,71 t	—
XIXb	5,81 s	—	3,77 dd	5,35 m | 4,30 d		—	1,96 s
VIb	5,81 s	—	3,40—3,83 m			4,79 d, 4,51 t	—

*The signals of the hydroxyalkyl residue are presented; the signals of the protons of the benzene ring show up in the form of a complex multiplet at 7-8 ppm.

**The protons of the CH_2 group are chemically nonequivalent (diastereotopic); this leads to geminal coupling (J = 12-14 Hz).

TABLE 3. UV Spectra of the Acyclic Analogs of Nucleosides in Ethanol

Protected analogs		Unprotected analogs	
compound	λ_{max}, nm (ε · 10^{-3})	compound	λ_{max}, nm (ε · 10^{-3})
IXa	254 (8,7), 281 (5,4), 290 (4,4)	Ia	255 (9,8), 281 (5,9), 290 (4,8)
IXb	282 (9,15)	Ib	281 (9,1)
XIa	253 (8,2), 280 (5,3), 290 (4,0)	IIa	253 (8,7), 280 (4,4), 290 (4,4)
XIb	282 (9,2)	IIb	281 (8,9)
XVIa	253 (10,1), 280 (7,1), 290 (5,1)	IIIa	253 (9,8), 280 (7,0), 290 (4,9)
XVIb	281 (8,5)	IIIb	282 (9,0)
XVIIa	253 (9,5), 280 (5,6), 289 (4,6)	IVa	253 (9,3), 280 (5,8), 290 (4,4)
XVIIb	281 (9,2)	IVb	281 (8,9)
XVIIIa	253 (8,2), 280 (5,4), 290 (4,1)	Va	254 (7,8), 280 (5,2), 289 (3,7)
XVIIIb	281 (9,7)	Vb	282 (8,1)
XIXa	254 (11,6), 280 (8,0), 290 (5,5)	VIa	252 (11,6), 280 (7,8), 290 (5,6)
XIXb	281 (8,3)	VIb	281 (9,9)

Biological tests did not reveal substantial antivirus activity of Ia, b-VIa, b with respect to both corona virus – the pathogen of transmissive gastroenteritis – and swine enterovirus. Weakly expressed antivirus activity was detected only for IVb in a concentration close to the toxic level (500 μg/ml). Acyclic analogs of nucleosides of 2-trifluoromethylbenzimidazole Ia-VIa do not have cytotoxic activity in concentrations of 5-500 μg/ml, while 2-trifluoromethylthiobenzimidazole derivatives Ib-VIb display cytotoxicity in a concentration of 500 μg/ml. The latter can be explained by an increase in the lipophilicity of these compounds due to the SCF_3 group. The damage to the membrane structures of cells that we observed in a cytological investigation was a consequence of this.

EXPERIMENTAL

The PMR spectra were recorded with a Bruker-100SV spectrometer. The UV spectra were obtained with a Specord UV-vis spectrophotometer (East Germany). Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates. Silica gel (40-100 μm, Czechoslovakian SSR) was used for column chromatography. The results of elemental analysis of all of the synthesized compounds differed from the calculated values by no more than 0.2%. The synthesis of alkylating agents VIII, X, XII, and XIII was described in [2], while the synthesis of agent XV was described in [4].

2-Methyl-1,3-dioxolane. A 1 g sample of p-toluenesulfonic acid was added with cooling and stirring to a mixture of 112.4 ml [88g (2 moles)] of acetaldehyde and 166.9 ml (186.2 g (3 moles)] of ethylene glycol, after which the mixture was stirred with cooling for 1 h and allowed to stand at 20°C for 20 h. Potassium carbonate (10 g) was added, and the mixture was stirred for 0.5 h. The product was removed by distillation with collection of the fraction with bp 60-85°C, which was dried with potassium carbonate and redistilled to give a product with bp 80-83°C. The yield was 101.15 g (57%).

2,5-Diacetoxy-3-oxapentane (XIV). A mixture of 101.15 g (1.15 moles) of 2-methyl-1,3-dioxolane with 40 ml of AcOH and 360 ml of Ac_2O was cooled to −10°C, and 3 g of $ZnCl_2$ was added with stirring. At the end of the exothermic reaction, cooling was discontinued, and the mixture was maintained for 12 h at 20°C and evaporated in vacuo. The residue was poured into 200 ml of a saturated solution of $NaHCO_3$, and the mixture was stirred until the evolution of CO_2 ceased. It was then extracted with ether, the extracts were dried with Na_2SO_4, and the solvent was removed in vacuo. The residue was distilled to give 96.9 g (44%) of a product with bp 68-70°C (12 mm). PMR spectrum ($CDCl_3$): 5.93 (t, 2-CH), 4.21 (t, 5-CH_2), 3.74 (m, 4-CH_2), 2.08 (s, two CH_3CO), 1.40 ppm (d, 1-CH_3).

2-Trifluoromethylthiobenzimidazole (VIIb). A 69-g (0.35 mole) sample of trifluoromethyl iodide was added to 16 g (0.107 mole) of 2-mercaptobenzimidazole [5] in 150 ml of liquid ammonia, and the mixture was illuminated with a PRK-4 UV lamp with stirring for 4 h. After evaporation of the ammonia, the residue was washed with 100 ml of water and crystallized from aqueous methanol to give 12 g (51%) of a product with mp 205-206°C.

Nucleoside Analogs Ia, b and IXa, b. A 0.6 g sample of sodium hydride in the form of an 80% suspension in mineral oil (20 mmole of pure sodium hydride) was added in small portions to a solution of 2 g (10.74 mmole) of VIIa or 2 g (9.16 mmole) of VIIb in 30 ml of absolute acetonitrile, and the mixture was stirred for 1 h. A 1.9 ml (12 mmole) sample of chloride VIII was added, and the mixture was refluxed for 3 h. It was then cooled and evaporated in vacuo, and the residue was treated with 100 ml of saturated $NaHCO_3$ solution. The resulting mixture was extracted with chloroform (four 30-ml portions), the combined extracts were dried with Na_2SO_4, and the chloroform was evaporated in vacuo. The residue was chromatographed with a column (2 by 40 cm) filled with silica gel; the products were eluted with a 2% solution of methanol in chloroform. The resulting protected analogs IXa, b were dissolved in 100 ml of a semisaturated (at 0°C) methanol solution of ammonia, and the solutions were maintained for 24 h at 20°C and evaporated in vacuo. The residue was chromatographed with a column (2 by 15 cm) packed with Silasorb C-18 silica gel (15 μm) with a mixture of methanol and water (1:1).

Nucleoside Analogs IIa, b-VIa, b, XIa, b, and XVIa, b-XIXa, b. A 1 ml sample of trimethylchlorosilane was added to a suspension of 1 g (5.37 mmole) of VIIa or 1 g (4.58 mmole) of VIIb in 10 ml of hexamethyldisilazane, and the mixture was refluxed for 2 h, cooled, and evaporated to dryness in vacuo. The residue was dissolved in 20 ml of absolute acetonitrile, 6 mmole of the corresponding alkylating agent X or XII-XV and 1 ml (8.64 mmole) of $SnCl_4$ were added, and the mixture was maintained for 5 h at 20°C. It was then poured into 50 ml of saturated $NaHCO_3$ solution. The subsequent isolation and purification of the protected analogs XIa, b and XVIa, b-XIXa, b, the removal of the protective groups, and the purification of unprotected compounds IIa, b-VIa, b were carried out as in the preceding experiment.

The antivirus activity of the synthesized preparations was tested in a system of an implanted (for 2-3 days) culture of cells of the embryonal kidney of a swine with HKP induced by the Purdue reference strain of the swine transmissive gastroenteritis virus of the 115th transfer (titer 6 log $TCID_{50/1.0}$)* and the vaccine strain of swine enterovirus of serotype 6 with respect to Derbyshire (1982) of the 70th transfer (titer 8 log $TCID_{50/1.0}$)*. The antivirus activity was evaluated from inhibition of the cytopathogenic effect of viruses taken

*Tissue culture infective dose.

in a dose of 1000 $TCID_{50}$ in a volume of 1 ml. The investigated preparations were titrated by dilution of the culture medium (with 5% hemhydrolyzate) to concentrations of 500, 50, and 5 μg/ml. Corresponding controls of the cytopathogenic activity of the virus, controls of the medium without the addition of the preparation, and controls of the toxicities of the investigated substances without the introduction of the virus were set up. The cytopathogenic activity of the virus in the controls and in the presence of the investigated preparations was evaluated 24, 48, 96, and 120 h after inoculation of the cell culture.

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MASS SPECTRA OF LIQUID CRYSTALS.

2.* ESTERS OF ALKOXY-SUBSTITUTED NICOTINIC AND PICOLINIC ACIDS

T. Yu. Samgina, P. A. Sharbatyan, L. S. Shishkanova, N. A. Andronova, A. I. Pavlyuchenko, and V. V. Titov

UDC 543.51:547.826

Esters of alkoxypicolinic and alkoxynicotinic acids are reliably identified by means of their mass spectra and PMR spectra. While the alkoxypyridoyl cation in the case of the β esters undergoes fragmentation only with the successive splitting out of an olefin via the McLafferty mechanism and then a CO molecule, these processes also take place in the reverse order in the case of the α esters. The principal characteristic fragment ions by means of which such compounds in liquid-crystal mixtures can be identified and quantitatively determined were established.

In a previous study [1] we established the basic principles of the fragmentation of arylalkylpyridines under electron impact and determined the characteristic fragment ions, the signals of which can be used for the identification and qualitative and quantitative analysis of similar compounds in liquid-crystal compositions. The present communication is devoted to the mass-spectral investigation of aryl esters of alkoxy-substituted picolinic and nicotinic acids (I-IX), which are also liquid-crystal mesogens.

It is apparent from the PMR spectral data (Table 1) that the signals of the α, β, and γ protons of the pyridine ring are highly characteristic. The magnetic anisotropy of the carbonyl group in the case of the esters of nicotinic acid is responsible for deshielding of the γ protons, and their signal is shifted to weak field (~8.15 ppm). The signal of the β protons is shifted to weak field (~8.1 ppm) in the case of the esters of picolinic acid. These data make it possible to reliably distinguish the isomeric compounds.

The relative intensities of the peaks of the molecular and characteristic fragment ions are presented in Table 2. In some cases the M^+ peaks have insignificant intensities; this is due to facile cleavage of the ester bond, in which a substituted phenoxy radical is eliminated in the form of a neutral fragment, and the charge is always retained on the pyridoyl

*See [1] for Communication 1.

Scientific-Research Institute of Organic Intermediates and Dyes, Moscow 103787.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 637-641, May, 1988. Original article submitted August 19, 1986.

0009-3122/88/2405-0518$12.50