SYNTHESIS AND ANTIVIRAL ACTIVITY OF HYDROXYALKYL-2-BENZYL- AND 2-[α-HYDROXY-BENZYL]BENZIMIDAZOLES

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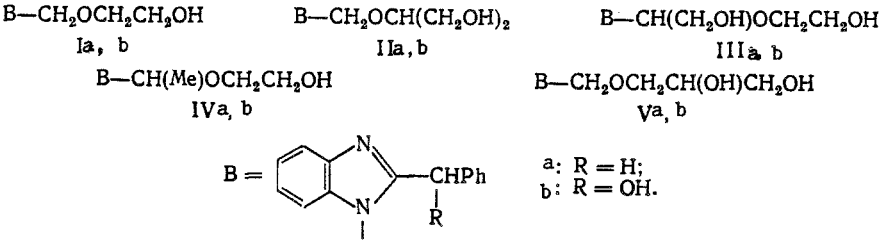
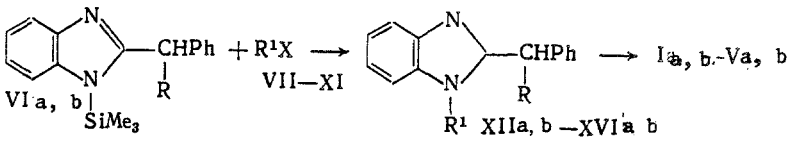
The search for antiviral drugs among acyclic analogs of nucleosides is currently receiving much attention [4-5]. Continuing earlier studies [2-3] of the relationship between structure and biological activity in acyclonucleosides of 2-substituted benzimidazoles, we have synthesized some hydroxyalkyl derivatives of 2-benzyl and 2-[α-hydroxybenzyl]benzimidazole (Ia, b-Va, b):



Alkylation of the trimethylsilyl derivatives of 2-benzyl-(VIa) and 2-(α-hydroxybenzyl) benzimidazole (VIb) with the chloride (VII) or acetates (VIII-XI) in the presence of trifluoromethanesulfonic acid (method A) or $SnCl_4$ (method B) gave 50-70% yields of the protected nucleotide analogs (XIIa, b-XVIa, b):



R = H (a), OH (b); R^1 = $CH_2O(CH_2)_2OAc$ (VII, XIIa,b), $CH_2OCH(CH_2OAc)_2$ (VIII, XIIIa,b), $CH(CH_2OAc)O(CH_2)_2OAc$ (IX, XIVa,b), $CH(Me)O(CH_2)_2OAc$ (X, XVa,b), $CH_2OCH_2CH(OBz)CH_2OAc$ (XI, XVIa,b); X = Cl (VII), OAc (VIII—XI).

The acyl protecting groups were removed by treatment with semisaturated (at 0°C) methanolic ammonia. The yields and melting points of the unprotected nucleoside analogs (Ia, b-Va, b) are given in Table 1.

The structures of the products were confirmed by their PMR and UV spectra (Tables 2 and 3). Proof of the structure of the unprotected analogs (Ia, b-Va, b) was provided by the characteristic signals for the OH group in the PMR spectra obtained in hexadeuterodimethyl sulfoxide. For example, the primary hydroxyl groups in (Ia, b) and (IVa, b) are seen as a single triplet. The presence of two triplet signals of relative intensity 1H each in the spectra of (IIIa, b) and a single triplet (2H) in the spectra of (IIa, b) indicate the presence of two primary hydroxyl groups. In the spectra of (Va, b) one triplet and one doublet signal of the same intensity are present, showing the presence in the nucleoside analogs of primary secondary hydroxyl groups.

The mixture of diasteroisomers of (IVb), which contains two asymmetric carbon atoms, was separated by HPLC. The RR/SS and RS/SR isomers had different melting points (Table 1). In the PMR spectra of these compounds, there were differences in the chemical shifts of the methine and methyl protons of the hydroxyalkyl substituent. In one pair of enantiomers, the chemical shifts of these protons were 5.77 and 1.58 ppm, and for the other, 6.07 and 1.88 ppm respec-

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TABLE 1. Synthesis of Acyclic Nucleoside Analogs*

Method of prep-aration	Protected analogs		Unprotected analogs		
	compound	yield, %	compound	yield, %	mp, °C
A	XIIa	77	I a	91	109—10
B	XIIb	60	I b	92	oil
A	XIIIa	54	II a	90	128—9
A	XIIIb**	49	II b	95	130—1
A	XIVa	42	III a	93	139—40
B	XIVb	53	III b	91	94—5
A	XVb	41	IV b	92	***
B	XVIa	45	V a	90	88—9
	XVIb	50	V b	86	69—70

*The UV spectra of the products correspond to those of 1-substituted 2-benzyl- and 2-(α-hydroxybenzyl)benzimidazoles.
**The melting point of (XIIIb) was 91-92°C. The remaining compounds were oils.
***Compound (XVb) was obtained as the RR/SS abd RS/SR isomers. mp 65-66 and 74-75°C respectively.

tively. The shift to higher field of the signal for the methyl group in the second case may be rationalized as being due to the effect of the ring current in the phenyl group of the hydroxybenzyl substituent as a result of the close spatial arrangement. Examination of sphere-and-rod models and Newman projection of the two pairs of enantiomers shows that the latter situation holds in the case of isomers with the RS/SR configuration of the chiral centers.

The acyclonucleosides (Ia, b-Va, b) were tested for antiviral activity against swine entero- and coronaviruses. The test results (Table 3) showed that hydroxyalkyl derivatives of 2-(α-hydroxybenzyl)benzimidazole possess moderate activity against both types of virus. With the 2-benzyl-benzimidazole nucleosides, antiviral activity against enteroviruses was shown only in the case of (Ia) and (Va). It is noteworthy that the diastereoisomers of (IVb) had different antiviral activity.

EXPERIMENTAL (CHEMISTRY)

PMR spectra were recorded on a Bruker WP-100 SY spectrometer (West Germany). UV spectra were obtained on a Specord UV-VIS (East Germany). TLC was carried out on Silufol UV-254 plates (Czech SSR) in the system chloroform—methanol (9:1). The sorbent used in column chromatography was silica gel 40-100 μm (Czech SSR). HPLC was carried out on a 9.6 × 250 mm column with Zorbax C-8 as sorbent, in an LC-233 liquid chromatograph. The elemental analyses of all the products were within 0.2% of the calculated values. The synthesis of reactants (VII-IX) has been described in [3], of (X) in [2], and of (XI) in [1].

Method A. Nucleoside Analogs (Ia-IIIa), (Va), (IIb), and (IIIb). To a suspension of 200 mg (0.97 mmole) of (VIa) or 200 mg (0.89 mmole) of (VIc) in 20 ml of dry acetonitrile was added 1.1 mmole of the appropriate alkylating agent (Table 1), 0.23 ml (1.1 mmole) of hexamethyldisilazane, 0.15 ml (1.2 mmole) of $ClSiMe_3$, and 0.105 ml (1.2 mmole) of trifluoromethanesulfonic acid. The residue following evaporation of the acetonitrile was treated with 50 ml of saturated $NaHCO_3$ solution, and extracted with chloroform (4 × 40 ml). The combined extracts were dried over Na_2SO_4, and the chloroform removed under reduced pressure. The residue was chromatographed on a 2.5 × 20 cm column of silica gel, 40-100 μm. The products were eluted, initially with 300 ml of a 25% solution of heptane in chloroform, then with pure chloroform. The protected analogs (XIIa), (XIIa, b), (XIVa, b) and (XVIa) thus obtained were dissolved in 40 ml of methanolic ammonia, semi-saturated at 0°C. The mixture was kept for 24 h at 20°C, and evaporated under reduced pressure. The residue was treated with dry ether, and recrystallized from ether—ethyl acetate. The yields and melting points of the products are given in Table 1.

Method B. Nucleoside Analogs (Ib), (IVb), and (Vb). To a suspension of 200 mg (0.89 mmole) of (IVb) in 20 ml of dry acetonitrile was added with stirring 1.2 mmole of the appropriate alkylating agent (Table 1), 0.46 ml (2.2 mmole) of hexamethyldisilazane, 0.3 ml (2.4 mmole) of $ClSiMe_3$, and 0.23 ml (2 mmole) of $SnCl_4$. The mixture was boiled for 2 h, cooled, and the acetonitrile removed under reduced pressure. The subsequent isolation and removal of the acyl protecting groups were carried out as in method A. The yields and melting points of the products are given in Table 1.

TABLE 2. PMR Spectra of Acyclic Nucleoside Analogs*

Compound	Chemical shifts (ppm) and multiplicity of signals				
	1'-CH_2 or 1'-CH_3	2'-CH	3'-CH_2 or 3'-CH	CH_3CO_2 or OH	2-CH_2 or 2-CH
XIIa	5,23 s	—	3,24 m	1,84 s	4,22 s
Ia	5,64 s	—	3,64 m	4,70 t	4,33 s
XIIb	5,35 s	—	3,27 m	1,96 s	6,17 s
Ib	5,64 d 5,77 d	—	3,28 m	4,65 t	6,15 d
XIIIa	5,30 s	—	3,85 m	1,76 s	4,24 s
IIa	5,70 s	—	3,50 m	4,71 t	4,34 s
XIIIb	5,42 d 5,58 d	—	3,86 m	1,77 s	6,31 s
IIb	5,80 s	—	3,36 m	4,63 t	6,15 d
XIVa	4,48 d.d	5,72 d.d	—	1,94 s	4,16 d
	4,25 d	5,72 d.d	—	1,96 s	4,52 d
IIIa	3,77 m	5,61 t	—	5,14 t 4,56 t	4,32 s
XIVb	4,24 m	5,90 m	—	1,92 s	6,21 s
IIIb	3,64 m	5,87 t	—	4,56 t 4,99 t	6,14 d
XVb**	1,11 d	5,92 q	—	2,08 s	6,31 s
XVb***	1,57 d	5,77 q	—	2,06 s	6,31 s
IVb**	1,08 d	6,07 q	—	4,57 t	6,18 d
IVb***	1,58 d	5,77 q	—	4,47 t	6,15 d
XVIa	5,42 s	—	3,40 d	1,92 s	4,35 s
Va	5,62 s	—	3,35 m	4,75 d 4,49 t	4,33 s
XVIb	5,42 s	—	3,31 m	1,90 s 1,92 s	6,18 s
Vb	5,62 d 5,79 d	—	3,40 m	4,70 d 5,37 t	6,15 d

*Only the more characteristic signals are given. The signals for the aromatic protons were seen as a complex multiplet at 7-8 ppm.
**RS/SR isomer.
***RR/SS isomer.

TABLE 3. Effects of Acyclic Analogs 2-Benzyl- and 2-[α-Hydroxybenzyl)benzimidazole Nucleosides on the Reproduction of Swine Corona- and Enteroviruses in SEKV Culture

Compound	Concentration, μg/ml	Reduction in virus infective titer, log TCD_{50}/ml	
		enterovirus	coronavirus
Ia	62,5	0,83	0,5
Ib	125	0,0	0,5
IIa	125	0,0	0,0
IIb	125	0,34	1,0
IIIa	62,5	0,0	0,0
IIIb	125	1,33	0,5
IVb*	125	1,84	0,0
IVb**	125	0,5	0,0
Va	125	0,5	0,0
Vb	125	0,5	0,5

*RS/SR isomer.
**RR/SS isomer.

Separation of the isomers of (IVb) was carried out on a 9.4 × 250 mm column with sorbent Zorbax C-8 with 60% aqueous methanol, flow rate 4 ml/min. The retention time of the RR/SS isomer was 6 min, and of the RS/SR isomer, 8.7 min.

EXPERIMENTAL (BIOLOGY)

Exmination for antiviral activity was carried out using swine enterovirus B386/79 with an infective titer of 7.0-7.33 log TCD_{50}/ml and swine coronavirus Purdue-115, infective

titer 5.5 log TCD_{50}/ml. The viruses were titrated in a tube culture of swine enbryo kidney virus (SEKV) by the cytopathic effect. The compounds were taken in the maximum tolerated concentrations (MTC).

After contact for 1 h of a tenfold dilution of the virus and the culture, the former was decanted off and 1 ml of the supporting nutrient medium (50% medium 199 + 50% of 0.5% lactalbumin) containing the compound in solution. The test results were determined 120 h following infection. The antiviral activity was assessed by the inhibition of the cytopathic effects of the viruses.

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF DERIVATIVES OF DIBENZO-18-CROWN-6

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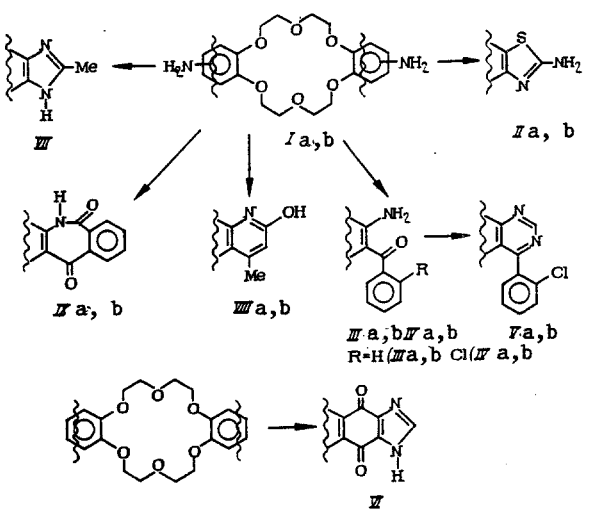
The continued interest of research workers in macroheterocycles is due partly to their uniqueness as complexones, and partly to their wide spectrum of biological activity.



Since some crown ethers are known to display antiviral activity [1], it was decided to synthesize some derivatives of dibenzo-18-crown-6 (DBC) and examine their antiviral activity.

The starting materials used for the syntheses were syn-2,14-diamino- and anti-2,13-diaminodibenzo-18-crown-6 (Ia, b) [4], together with unsubstituted DBC. The benzothiazole derivatives (IIa, b) were obtained by reacting (Ia) and (Ib) with dithiocyanogen in acetic acid [3]. Reaction of the diamines (I) with benzoyl chlorides under Friedel–Crafts conditions afforded the crown o-aminoketones (III) and (IV) [5], which on boiling in formamide

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