ACYCLIC ANALOGS OF NUCLEOSIDES. SYNTHESIS OF HYDROXYALKYLBENZIMIDAZOLES AND -BENZOTRIAZOLES

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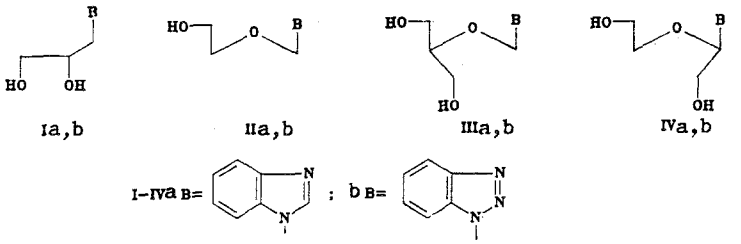
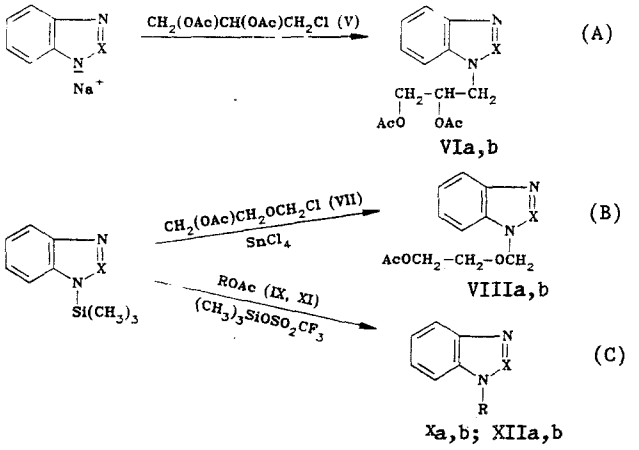
Condensation of trimethylsilyl derivatives of benzimidazole and benzotriazole with alkylating agents in the presence of trimethylsilyl trifluoromethanesulfonate or $SnCl_4$, or direct alkylation of the sodium salts of benzimidazole and benzotriazole, gives 1-(2,3-dihydroxypropyl)-, 1-(3-hydroxy-2-oxabutyl)-, 1-(3-hydroxymethyl-4-hydroxy-2-oxabutyl)-, and 1-(1,5-dihydroxy-3-oxapent-2-yl)benzimidazole and -benzotriazole.

One approach to obtaining biologically active compounds [1] is to synthesize conformationally labile analogs of naturally-occurring compounds, especially acyclic analogs of nucleosides. Compounds such as 9-(4-hydroxy-2-oxabutyl)-guanine (acyclovir), 9-(3-hydroxymethyl-4-hydroxy-2-oxabutyl)guanine (BIOLF-62), and 9-(2,3-dihydroxypropyl)adenine, together with many others, possess high antiviral activity [2].

Another approach to the synthesis of biologically active analogs of nucleosides is by modifying the nucleic base. The present investigation combines both these approaches, and is devoted to the synthesis of acyclic analogs of nucleosides with modified nucleic bases (Ia,b)-(IVa,b):



The nucleoside analogs were obtained by methods A-C:



IX, X R = $(AcOCH_2)_2CHOCH_2$—; XI, XII R = $AcOCH_2CH_2OCHCH_2OAc$; VI, VIII, X, XII a X=CH, b X=N

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TABLE 1. Synthesis of Acyclic Nucleoside Analogs

alkylating agent	method	reaction product	mp, °C	yield, %	reaction product	mp, °C (ethanol–ether)	yield, %
Starting base, benzimidazole							
V	A	VIa	oil	45	Ia	60—61	95
VII	B	VIIIa	oil	40	IIa	85—86	95
IX	C	Xa	73—74	30	IIIa	113—114*	95
XI	C	XIIa	70—71	32	IVa	75—76	95
Starting base, benzotriazole							
V	A	VIb	oil	42	Ib	oil	88
		XIII	oil	9	XIV	108—109	80
VII	B	VIIIb	oil	45	IIb	oil	90
IX	C	Xb	96—97	46	IIIb	104—105	98
XI	C	XIIb	oil	36	IVb	oil	90

*From ethanol.

TABLE 2. PMR Spectra of Acyclic Nucleosides

Compound	Chemical shift*, δ, ppm (coupling constant, Hz)							
	1′-CH_2	2′-H	3′-CH_2 or 3′-H	4′-CH_2 and 4″-CH_2	5′-CH_2 (m)	OH	CH_3CO (s)	2-H † (s)
VIa	4,05 d.d (5,4; 12,3) 4,26 d.d (4,8; 12,3)	5,30 m	4,35 d (6)	—	—	—	1,95 2,00	7,78
Ia		3,60—4,45	—	—	—	5,05d ; 4,80t	—	8,05
VIb	4,05 d.d (5,4; 12) 4,35 d.d (4,8; 12)	5,43 m	4,80 d.d (2,8; 8,2) 4,91 d.d (1,5; 8,2)	—	—	—	1,92 2,05	—
Ib	4,56 d.d (7; 14) 4,81 d.d (5; 14)	4,95 m	3,43 d (6)	—	—	5,10d ; 4,00t	—	—
VIIIa	5,56 s	—	3,61 t (5,2)	4,15 t (5,2)	—	—	1,96	8,02
IIa	5,62 s	—	3,54 t (4,8)	3,73 t (4,8)	—	4,70 t	—	7,98
VIIIb	6,06 s	—	3,71 t (4,7)	4,15 t (4,7)	—	—	1,92	—
IIb	6,15 s	—	3,45 m		—	4,72 t	—	—
Xa	5,67 s	—	3,87 m	4,08 m	—	—	1,85	8,00
IIIa	5,70 s	—	3,59 m	3,49 m	—	4,57 t	—	8,24
Xb	6,11 s	—	4,06 m		—	—	1,76	—
IIIb	6,16 s	—	3,72 m	3,64 m	—	4,60 t	—	—
XIIa	5,40 d.d (7; 13) 5,60 d.d (6; 13)	5,77 d.d (6; 7)	—	3,66 m	4,20	—	1,97 1,99	8,03
IVa	3,95 d.d (6; 9) 4,09 d.d (5; 9)	5,73 t (6)	—	3,51 m	3,70	4,60t; 5,12t	—	8,22
XIIb	4,55 d.d (5; 12) 4,79 d.d (6; 12)	6,37 d.d (5, 6)	—	3,68 m	4,18	—	1,94 1,97	—
IVb	4,01 d.d (6; 10) 4,23 d.d (5; 10)	6,22 t (6)	—	3,47 m	—	4,60t, 5,15t	—	—
XIV	4,56d.d (7,6; 13,4) 4,83 d.d (4,6; 13,4)	4,14 m	3,49 d (6)	—	—	4,20d; 5,00t	—	—

*The spectra of (Ia, b), (IIa, b), (IIIa, b), (IVa, b), and (XIV) were obtained in hexadeuterodimethyl sulfoxide, and the remainder in deuterochloroform.

†The signals for the benzene ring protons were seen as a complex multiplet at 7-8 ppm (Fig. 1).

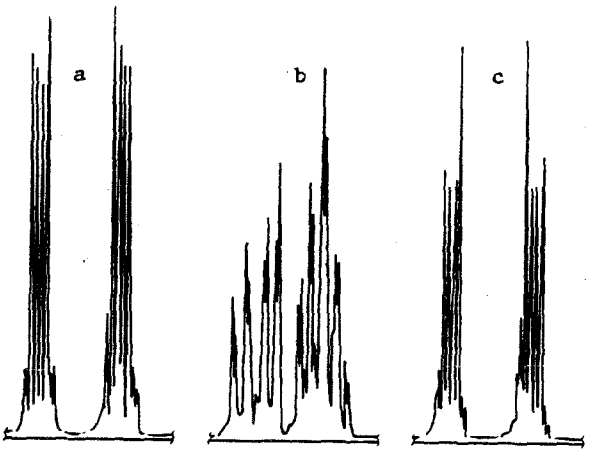
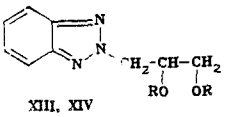


Fig. 1. Aromatic proton region in the PMR spectra (in DMSO-D_6) of benzotriazole (a) and its derivatives (Ib) (b) and (XIV) (c).

Analogs (VIa, b) were obtained by heating the chloride (V) with the sodium salt of the heterocycle in dimethylformamide (method A). With the reactive chloride (VII), satisfactory results were obtained by reacting (VII) with the trimethylsilyl derivatives of the heterocycles in the presence of $SnCl_4$ in acetonitrile at ~20°C (method B). Finally, the reaction of the trimethylsilyl derivatives of the heterocycles with acetates (IX) and (XI) was carried out in the presence of trimethylsilyl triflate by boiling in acetonitrile (method C). The yields of the substituted compounds (VIa, b), (VIIIa, b), and (Xa, b), and their melting points, are given in Table 1.

When benzotriazole was reacted with the chloride (V), 9% of a byproduct was obtained, which according to its PMR and UV spectra was 2-(2,3-diacetoxypropyl)benzotriazole (XIII).



XIII, XIV

XIII R=CH_3CO; XIV R=H

With other alkylating agents, no products of $N_{(2)}$-alkylation of benzotriazole were obtained. Deacetylation was accomplished by treatment with methanolic ammonia, the nucleoside analogs (Ia,b)–(IVa,b) being obtained in near-quantitative yields (Table 1).

The structures of the products were confirmed by PMR and UV spectroscopy (Tables 2 and 3). The structure of the hydroxyalkyl substituent follows from the multiplicity of the OH signal in the PMR spectra obtained in DMSO-D_6 for compounds. These signals are readily identified in the PMR spectra, since they disappear on adding D_2O to the sample. The doublet and triplet signals in the spectra of (Ia, b) show the presence of secondary and primary hydroxy-groups respectively. The single primary hydroxy-group in (IIa, b) appears as a triplet. Proof of the presence of two symmetrically located primary hydroxy-groups in (IIIa, b) is provided by the triplet signal of relative intensity 2H. Finally, the two triplet signals, each of relative intensity 1H, lead to the conclusion that (IVa, b) contain two unsummetrically located primary hydroxy-groups.

The alkylation of benzimidazole is an unambiguous reaction, but that of benzotriazole alkylation could take place at either $N_{(1)}$ or $N_{(2)}$. The PMR spectra enable the site of substitution to be established with certainty. The aromatic protons of unsubstituted benzotriazole are present as a AA'XX' system, seen as two multiplets which are symmetrical relative to the center, each of which consists of ten peaks (Fig. 1a). Unsymmetrical substitution at the 1-position changes the chemical shifts of the adjacent protons, and the spectrum becomes a complex multiplet for the strongly-coupled four-spin system (Fig. 1b). Substitution at the 2-position does not affect the symmetry, and therefore, does not, of course, result in changes in the atomic proton region (Fig. 1c). Further confirmation of the site of substitution in benzotriazoles is provided by the UV spectra (Table 3). The spectrum of (Ib) has three absorption maxima (at 261, 266, and 278 nm), corresponding to substitution at $N_{(2)}$ of the benzotriazole molecule [4]. In the case of (XIV), however, the UV spectrum is differ-

TABLE 3. UV Spectra of Acyclic Nucleoside Analog in Ethanol

Compound	UV spectrum, λ_{max}, nm (ε)	Compound	UV spectrum, λ_{max}, nm (ε)
VIa	254 (5270), 251 (5270), 272 (3370), 280 (3070)	Ia	245 (5400), 252 (5400), 273 (3740), 281 (3390)
VIb	260 (5700), 265 (5650), 275 (4640)	Ib	261 (5370), 266 (5590), 278 (4530)
VIIIa	245 (5280), 273 (3050), 280 (3310)	IIa	245 (6080), 274 (3860), 280 (4050)
VIIIb	254 (6520), 281 (4330)	IIb	255 (5710), 281 (3670)
Xa	249 (6150), 273 (3070), 280 (3530)	IIIa	245 (6910), 274 (4080), 280 (4330)
Xb	254 (6370), 281 (3670)	IIIb	254 (5700), 282 (3470)
XIIa	245 (5340), 273 (2950), 280 (3060)	IVa	246 (6130), 274 (3660), 281 (3800)
XIIb	253 (5700), 279 (3690)	IVb	255 (5650), 282 (3380)
XIII	277 (7100)	XIV	277 (7500)

ent, possessing a single absorption maximum at 277 nm, characteristic of $N_{(1)}$-alkylated derivatives.

EXPERIMENTAL

PMR spectra were obtained on a Bruker WP-100SV spectrometer. Chemical shifts are given relative to TMS. The sorbent used for column chromatography was silica gel L 40-100 μm (Czech SSR). The elemental analyses of the products did not differ from the theoretical values by more than 0.2%. The chloride (VII) was obtained as described in [5].

1,2-Diacetoxy-3-chloropropane (V). To a mixture of 18 g (0.2 mole) of epichlorohydrin in 25 g (0.25 mole) of acetic anhydride was added in small portions with cooling 0.5 g (3 mmole) of fused sodium acetate. The mixture was kept for 24 h at 20°C, $FeCl_3$ added (2.46 g, 0.031 mole), stirred for 1 h, and evaporated under reduced pressure. The residue was dissolved in 100 ml of ether, the ether solution washed with 10% $NaHCO_3$ until carbon dioxide was no longer evolved, followed by 10 ml of water, and dried over sodium sulfate. The ether was evaporated, and the residue distilled in vacuo to give 35 g (90%) of product, bp 70-71°C (2 mm); lit. value [6], bp 114-125°C (11 mm). PMR spectrum (CCl_4): 5.11 (m, CH), 4.23 (m, CH_2O), 3.65 (m, CH_2Cl), 2.05 and 1.99 ppm (both s, $CH_3CO \times 2$).

1,4-Dichloro-3-chloromethyl-2-oxabutane. A stream of gaseous hydrogen chloride, dried by bubbling through conc. sulfuric acid, was passed with stirring into a mixture of 64.5 g (0.5 mole) of glycerol α,γ-dichlorohydrin and 32.4 g (1.08 mole) of paraformaldehyde in 1.3 liter of redistilled chloroform at 0°C until the solid dissolved (4.5–5 h). The solution was stirred for 16 h at 0°C, dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The product was distilled in vacuo. Yield 80 g (90%), bp 55-60°C (1 mm). PMR spectrum ($CDCl_3$): 5.54 (s, OCH_2Cl), 3.73 (d, J = 6 Hz, CH_2Cl), 4.08 ppm (m, CH).

1,4-Diacetoxy-3-acetoxymethyl-2-oxabutane (IX). To 1 liter of dry DMF was added 264 g (3 mole) of fused sodium acetate and 1,4-dichloro-3-chloromethyl-2-oxabutane obtained from 0.5 mole of glycerol α,γ-dichlorohydrin. The mixture was stirred at 140°C for 6 h, and kept for 18 h at 20°C. It was then poured into 6 liters of water, and extracted in portions of 1.5 liter with chloroform (3 × 250 ml). The combined extracts were washed with saturated sodium bicarbonate solution and water, dried over sodium sulfate, filtered, and the chloroform evaporated under reduced pressure. The residue was distilled in vacuo to give 80 g (63%) of product, bp 132-135°C (1 mm). PMR spectrum ($CDCl_3$): 5.13 (s, OCH_2O), 4.13 [br.s, $(OCH_2)_2CH$], 2.11 (s, $CH_3CO \times 2$), 2.01 ppm (s, CH_3CO).

2,5-Diacetoxy-1-chloro-3-oxapentane. A mixture of 36.8 g (0.3 mole) of 2-chloromethyl-1,3-dioxolane, 10 ml of acetic acid, 90 ml of acetic anhydride, and 3 g (0.022 mole) of zinc chloride was stirred at 20°C for 2 h, then kept overnight. It was then evaporated, and the residue poured into 200 ml of saturated sodium bicarbonate solution and cautiously stirred until evolution of CO_2 ceased. It was the extracted with ether (3 × 50 ml), the extracts dried over sodium sulfate, and the solvent removed. The residue was distilled in vacuo to give 58.7 g (87%) of product, bp 117-118°C (4 mm).

1,2,5-Triacetoxy-3-oxapentane (XI). A mixture of 42 g (0.2 mole) of 2,5-diacetoxy-1-chloro-3-oxapentane and 32.8 g (0.4 mole) of fused sodium acetate in 250 ml of dry DMF was boiled for 5 h. After cooling, the mixture was poured into 1 liter of water and extracted with chloroform (3 × 200 ml), the extracts dried over sodium sulfate, and the solvent evaporated. The residue was distilled in vacuo to give 20.4 g (41%) of product, bp 140-141°C (2.5 mm). PMR spectrum ($CDCl_3$): 6.00 (m, OCH), 4.20 (m, OCH_2CH_2O), 3.95 (m, OCH_2), 2.10 (s, $CH_3CO \times 2$), 2.01 ppm (s, CH_3CO).

Alkylation of Benzimidazole and Benzotriazole. A. 1 To a solution of 2 g (16.9 mmole) of benzimidazole or 2 g (16.8 mmole) of benzotriazole in 20 ml of dry DMF was added 0.6 g of sodium hydride as an 80% suspension in vaseline oil (20 mmole of pure sodium hydride), the mixture stirred for 1 h, and 3.2 ml (20 mmole) of chloride (V) added. The mixture was kept at 80°C for 3 h, the solvent removed under reduced pressure, and the residue treated with 100 ml of water. If necessary, the pH of the aqueous layer was adjusted to 7. Extraction was carried out with chloroform (4 × 50 ml), and the extracts dried over sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on a column (2 × 40 cm) of silica gel, the products being eluted with a 2-10% solution of methanol in chloroform. The protected analogs (VIa, b) were dissolved in 100 ml of semisaturated methanolic ammonia at 0°C, and the solution kept for 24 h at 20°C, then evaporated under reduced pressure. The residue was treated with 50 ml of dry ether, and the resulting unprotected analogs (Ia, b) recrystallized from alcohol–ether. The mp's and yields of (Ia, b) are given in Table 1.

B. To a suspension of 2 g (16.9 mmole) of benzimidazole or 2 g (16.8 mmole) of benzotriazole in 10 ml of hexamethyldisilazane was added 1.5 ml of trimethylchlorosilane, and the mixture boiled for 2 h and evaporated to dryness under reduced pressure. The residue was dissolved in 30 ml of dry acetonitrile, and 2.5 ml of the chloride (VII) added followed by dropwise addition of 1.5 ml (11.5 mmole) of $SnCl_4$. The mixture was kept for 4 h at 20°C, and poured into 150 ml of saturated sodium bicarbonate. The isolation of (VIa, b) and deacetylation were carried out as described in method A.

C. To a solution of the silylated base (see method B) in 30 ml of dry acetonitrile was added 15 mmole of the acetate (IX) of (XI) and 2.2 ml (13.8 mmole) of trimethylsilyl trifluoromethanesulfonate. The mixture was boiled for 1.5 h. The protected derivatives (Xa, b) and (XIIa, b) were isolated and deacetylated as in method B.

LITERATURE CITED

1. A. M. Kritsyn, S. N. Mikhailov, and V. L. Florent'ev, Mol. Biol., 9, 121 (1975).
2. C. K. Chu and S. J. Culter, J. Heterocycl. Chem., 23, 289 (1986).
3. M. N. Preobrazhenskaya and S. Ya. Mel'nik, Itogi Nauki i Tekhniki (Science and Technology Summaries), VINITI, Bioorg. Khim., 1, 1 (1983).
4. R. K. Roberts, J. Chem. Soc., No. 11, 5556 (1963).
5. L. Yu. Tychinskaya and V. L. Florent'ev,1 Bioorg. Khim., 4, 1461 (1978).
6. E. Knoevenagel, Ann. Chem., 402, 135 (1913).