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SYNTHESIS OF NUCLEOSIDES OF SUBSTITUTED 3-HYDROXYPYRAZOLES

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N-Glucoside analogs of the antibiotic pyrazofurine were obtained by fusion of 3-hydroxy-4-ethoxycarbonylpyrazole with tetra-O-acetyl-β-D-ribofuranose in the presence of iodine.

In connection with the fact that the antitumorigenic activity of the antibiotic pyrazofurine (the C-nucleoside of 4-hydroxy-5-carbamoylpyrazole) is well known, the preparation of its N-glycoside analogs seems of interest [1].

As the starting compound for their synthesis we used 3-hydroxy-4-ethoxycarbonylpyrazole (I). 1-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-3-hydroxy-4-ethoxycarbonylpyrazole (IIa) was obtained by fusion of pyrazole I with 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose at 160°C for 30 min *in vacuo* in the presence of iodine. Triacetate IIa was converted to 1-β-D-ribofuranosyl-3-hydroxy-4-ethoxycarbonylpyrazole (IIb) by the action of an alcohol solution of sodium ethoxide. 1-β-D-Ribofuranosyl-3-hydroxy-4-carbamoylpyrazole (IIc) is formed by ammonolysis

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TABLE 1. Data from the PMR Spectra of Substituted 3(5)-Hydroxypyrazoles and Their Nucleosides

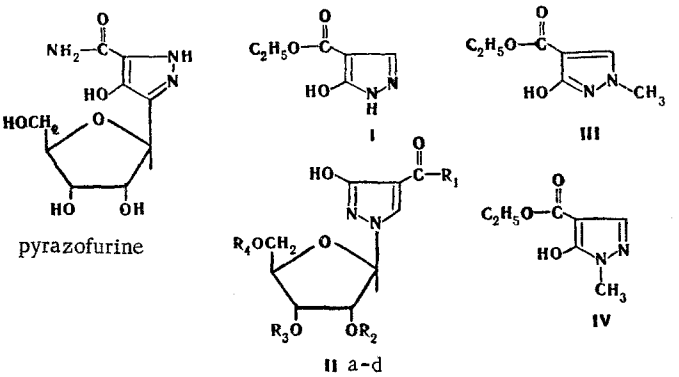
Compound	Chemical shift, δ, ppm (SSCC, Hz)									
	5C—H (3C—H)	1C′—H ($J_{1,2}$)	2C′—H ($J_{2,3}$)	3C′—H ($J_{3,4}$)	4C′—H	5C′—H	O—CH_2	—CH_3	other signals	solvent, 25°C
IIa	7,81	5,50—5,80			4,10—4,60			1,32	2,07; 2,10; 2,10 (CH_3CO)	$CDCl_3$
IIa*	8,46	6,26	5,58					1,24		HMPT
IIb	8,10	5,52			3,44—4,50			1,25		CD_3OD
IIc	8,37	5,62 (4,4)	4,42 (4,8)	4,22 (4,8)	3,95—4,12	3,58—3,82			7,21 (—NH_2)	D_6—DMSO*‡
IId	7,76	5,64 (1,0)	5,04		4,48—4,56	3,60—4,08	4,32	1,34	1,34; 1,56 =$C(CH_3)_2$	$CDCl_3$
III	7,58						4,33	1,32	3,76 (N—CH_3)	$CDCl_3$
III	8,04						4,17	1,24	3,83 (N—CH_3)	HMPT
IV	7,61						4,33	1,34	3,67 (N—CH_3)	$CDCl_3$
IV	7,44						4,17	1,24	3,58 (N—CH_3)	HMPT

*The signals of 3,4,5-C′H and O-CH_2 protons are overlapped by the signals of the protons of HMPT.
†The spectrum was recorded at 70°C.

of IIb with saturated ammonium hydroxide (in an ampul at 100°C for 10 h). Amide IIc can be obtained by ammonolysis of acetylated nucleoside IIa without prior isolation of IIb. 1-(2, 3-O-Isopropylidene-β -D-ribofuranosyl)-3-hydroxy-4-ethoxycarbonylpyrazole (IId) was obtained by the action of 2-methoxypropylene on riboside IIb in the presence of boron trifluoride etherate and red mercuric oxide.

The site of addition of the carbohydrate fragment in nucleosides IIa-d was established on the basis of a comparison of the UV and PMR spectra of nucleoside IIa with the spectra of 1-methyl-3-hydroxy-4-ethoxycarbonylpyrazole (III) and 1-methyl-4-ethoxycarbonyl-5-hydroxypyrazole (IV). Compound III (with mp 161-162°C) and IV (with mp 137-137.5°C) were isolated by fractional crystallization from the mixture formed from the reaction of diethyl ethoxymethylenemalonate with methylhydrazine [2]. The spectra of nucleoside IIa and 3-hydroxypyrazole III coincide and contain two absorption maxima at 220 and 246 nm, whereas one maximum at 219 nm and two shoulders at 237 and 270 nm are observed in the spectrum of 5-hydropyrazole IV. A detailed analysis of the effect of the shift of the signals of the 5-H and 3-H protons in the PMR spectra of 1,3- and 1,5-substituted pyrazoles recorded in chloroform and hexametapol (HMPT) was made in [3]. The $\Delta\delta^{CDCL_3}_{HMPT} = \delta_{CDCl_3} - \delta_{HMPT}$ values for the 5-H proton in 1,3-substituted pyrazoles (that do not contain acceptor substituents) are less than zero, whereas they are greater than zero for the 3-H proton in 1,5-substituted pyrazoles. Thus, for example, $\Delta\delta^{CDCl_3}_{HMPT}$ for the 5-H proton in III is −0.46 ppm, whereas it is +0.17 ppm for the 3-H proton in IV. The shift of the signal of the 5-H proton in nucleoside IIa on passing from $CDCl_3$ to HMPT is −0.65 ppm, which constitutes yet another confirmation of the structure of nucleoside IIa.

According to the principle in [4], in the PMR spectra of β-D-ribofuranosides the $\Delta\delta = \delta_2 - \delta_1$ difference between the chemical shifts of the two methyl groups in 2,3-O-isopropyli-



IIa $R_1=OC_2H_5$, $R_2=R_3=R_4=Ac$; b $R_1=OC_2H_5$, $R_2=R_3=R_4=H$; c $R_1=NH_2$, $R_2=R_3=R_4=H$; d $R_1=OC_2H_5$, R_2, $R_3=C(CH_3)_2$, $R_4=H$

dene derivatives is greater than 0.15 ppm, whereas $\Delta\delta<0.15$ ppm for α-D-ribofuranoside. The $\Delta\delta$ value for nucleoside IId is 0.22 ppm, which constitutes evidence for a β configuration for nucleosides IIa-d.

EXPERIMENTAL

The PMR spectra were recorded with JNM-MH-100 and Varian A 60A spectrometers with tetramethylsilane as the internal standard. The UV spectra were recorded with a Unicam SP-800 spectrophotometer. The specific rotations were determined by means of a Perkin-Elmer 241 polarimeter. Analytical thin-layer chromatography (TLC) was carried out on Silufol UV-254, while preparative TLC was carried out on plates with a fixed layer of Merck F-254.

1-(2,3,5-Tri-O-acetyl-β-D-ribufuranosyl)-3-hydroxy-4-ethoxycarbonylpyrazole (IIa). A mixture of 0.5 g (3.2 mmole) of 3-hydroxy-4-ethoxycarbonylpyrazole (I) and 1.05 g (3.5 mmole) of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose was heated at 170°C for 30 min *in vacuo* in the presence of 0.05 g of iodine, after which it was cooled and dissolved in chloroform. The solution was filtered through a 1-cm thick layer of silica gel, the silica gel was washed with chloroform, and the filtrates were combined and evaporated. Workup of the residue from preparative TLC in chloroform–acetone (4:1) gave 0.7 g (55%) of riboside IIa in the form of an oil (R_f 0.7). UV spectrum, λ_{max} (log ε), in alcohol: 220 (3.90) and 246 nm (3.90).

1-β-D-Ribofuranosyl-3-hydroxy-4-ethoxycarbonylpyrazole (IIb). Compound IIa without prior purification was dissolved in 50 ml of absolute alcohol, 1 ml of a 1 N solution of sodium ethoxide in alcohol was added, and the mixture was maintained in a hermetically sealed flask for 3 h. It was then neutralized with Dowex-50 resin (H^+), after which the resin was removed by filtration and washed with 10 ml of alcohol. The filtrates were combined and evaporated, and the residue was crystallized from methanol-ether to give 0.56 g (55% based on 3-ethoxycarbonyl-4-hydroxypyrazole) with mp 115-116°C. UV spectrum, λ_{max} (log ε), in alcohol: 220 (3.93) and 246 nm (4.02). The product had $[\alpha]_D^{20}$ -57.0° (methanol, c 1.06). Found: C 46.0; H 5.6; N 10.0%. $C_{11}H_{16}N_2O_7$. Calculated: C 45.8; H 5.6; N 9.7%.

1-β-D-Ribofuranosyl-3-hydroxy-4-carbamoylpyrazole (IIc). Compound IIa was heated in 50 ml of concentrated ammonium hydroxide in a sealed ampul at 100°C for 18 h, after which the reaction mixture was evaporated, and the residue was purified by refluxing with activated charcoal in aqueous alcohol. The charcoal was removed by filtration, the filtrate was evaporated, and the residue was dissolved in the minimum volume of ethyl acetate–methanol–acetone-water (6:1:1:1) and passed through a 2-cm layer of silica gel and eluted with the same system. The filtrate was evaporated, and the residue was crystallized from methanol to give 0.74 g (50%) of a product with mp 177-178°C. UV spectrum, λ_{max} (log ε), in water: pH 1, 244 (3.90); pH 7, 215 (3.70), 244 (3.84); pH 11, 203 (3.96), 275 nm (3.60). Found: C 41.4; H 5.1; N 16.4%. $C_9H_{13}N_3O_6$. Calculated: C 41.7; H 5.1; N 16.2%.

1-(2,3-O-Isopropylidene-β-D-ribofuranosyl)-3-hydroxy-4-ethoxycarbonylpyrazole (IId). A mixture of 0.1 g (0.3 mmole) of riboside IIb, 0.1 g (3.0 mmole) of 2-methoxypropylene, 0.2 ml of boron trifluoride etherate, and a few crystals of red mercuric oxide in 3 ml of absolute acetone was stirred at 20°C for 3 h, after which it was neutralized with a saturated solution of sodium bicarbonate and evaporated. The residue was extracted with acetone, and the extract was evaporated. Preparative TLC on silica gel in a chloroform–methanol system (20:1) gave isopropylidene derivative IId in virtually quantitative yield in the form of an oil (R_f 0.6). Found: C 51.4; H 6.4%. $C_{14}H_{20}N_2O_7$. Calculated: C 51.2; H 6.2%.

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