DIOXOLANE ANALOGS OF C-NUCLEOSIDES OF INDOLE AND A SUBSTITUTED 9-DEAZAPURINE

I. D. Shingarova, O. S. Sizova,
and M. N. Preobrazhenskaya

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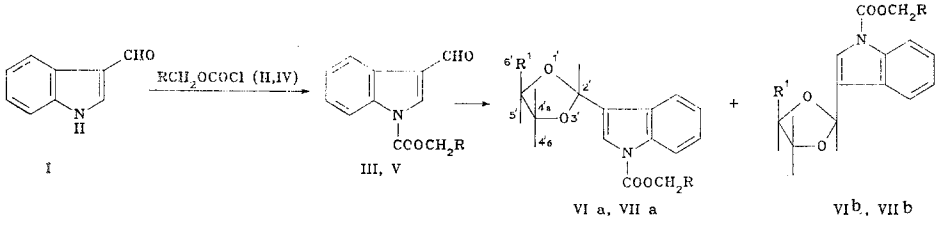
Cyclic acetals of N-acyl derivatives of 3-formylindole and 3-formyl-5-phenyl-7-ethylthiopyrrolo[3,2-d]pyrimidine, which may be viewed as analogs of the α and β anomers of C-nucleosides modified in the carbohydrate part of the molecule, have been obtained.

Among the analogs of nucleosides, nucleosides modified in the carbohydrate part of the molecule, especially those in which the sugar residue is replaced by a noncarbohydrate fragment, have been studied least thoroughly. Nucleosides in which an oxygen atom in the carbohydrate ring has been replaced by a methylene group or a sulfur atom display antimetabolite properties [1, 2]. For this reason it would be interesting to study the possibility of the synthesis of previously unknown C-nucleoside analogs containing a dioxolane fragment instead of a carbohydrate residue.

In the present work we investigated the formation of cyclic acetals of 3-formylindole (I) and 3-formyl-5-phenyl-7-ethylthiopyrrolo[3,2-d]pyrimidine (VIII), which may be viewed as the first dioxolane analogs of C-nucleosides of indole and a substituted 9-deazapurine, respectively. We were not able to obtain cyclic acetals by reacting 3-formylindole (I) with 1,2-propanediol. It is known that in the case of 2- and 3-formylpyrroles, the formation of acetals proceeds with an insignificant yield; a satisfactory result was obtained only in the case of the N-alkyl derivatives of formylpyrroles [3]. However, we were unable to obtain cyclic acetals of 1-methyl-3-formylindole, although it was found that the formation of acetals is facilitated for the N-acyl derivatives of aldehydes. The acylation of indole I by isobutyl chlorocarbonate (II) in dry THF in the presence of triethylamine produces 1-isobutoxycarbonyl-3-formylindole (III) with a 91% yield, and the acylation of indole I by benzyl chlorocarbonate (IV) produces 1-benzyloxycarbonyl-3-formylindole (V) with a 95% yield.



II, III, VI R = $(CH_3)_2CH$; IV, V, VII R = C_6H_5; VI R' = CH_3; VII R' = $CH_2OCH_2C_6H_5$

The reaction of aldehyde III with 1,2-propanediol in the presence of p-toluenesulfonic acid in benzene with the removal of water by distillation produced a mixture of isomeric dioxolanes VIa and VIb, which could not be separated with the aid of TLC on silica gel due to the close values of R_f. The reaction of aldehyde V with 1-O-benzylglycerol under the same conditions produced a mixture of acetals (VIIa and VIIb) with a ratio between the isomers in each case approximately equal to 1:1. It was found that dioxolane derivatives VIa, VIb, VIIa, and VIIb are very unstable compounds. The mixture of isomers recovered after chromatography on silica gel contained approximately 30% original aldehyde, according to the data from the PMR spectra. The geometric isomers VIa, VIb, VIIa, and VIIb were characterized by the PMR spectra (see Tables 1 and 2).

All-Union Oncologic Scientific Center, Academy of Medical Sciences of the USSR, Moscow 115478. S. Ordzhonikidze All-Union Pharmaceutical Chemistry Research Institute, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1500-1503, November, 1983. Original article submitted March 4, 1983; revision submitted July 7, 1983.

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TABLE 1. Proton-Magnetic-Resonance Spectra of Compounds VIa, VIb, XIa, and XIb

Compound	Chemical shifts, δ, ppm (spin–spin coupling constant, Hz)									
	2′-H	4′a-H ($J_{4'a4'b}$)	4′b-H ($J_{4'b5'}$)	5′-H ($J_{4'a5'}$)	6′-H ($J_{5'6'}$)	OCH_2–C	C–CH–C	C–CH_3 (J_{CH_3-CH})	2-H	SCH_2CH_3
VIa[a]	6,25	4,30 (6,6)	3,58[b] (6,8)	4,38	1,39 (6,5)	4,22	2,15	1,08 (6,0)	7,70	
VIb[a]	6,08	4,15 (7,5)	3,64[b] (6,0)	4,38 (6,6)	1,44 (6,5)	4,22	2,15	1,05 (6,0)	7,75	
XIa	6,46	4,39 (7,6)	3,64 (6,0)	4,58 (7,1)	1,40[b]	4,24	2,17	1,03 (5,7)	7,94	3,36 1,48[b]
XIb	6,33	4,17 (7,1)	3,75 (7,1)	4,39 (6,0)	1,40[b]	4,26[b]	2,17	1,03 (5,7)	7,98	3,36 1,48[b]

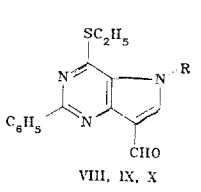
[a]There is an admixture of the original aldehyde III with a chemical shift of the proton in the CHO group at 10.09 ppm in an amount equal to about 30%. [b]The signals overlap.

TABLE 2. Proton-Magnetic-Resonance Spectra of Compounds VIIa, VIIb, XIIa, and XIIb

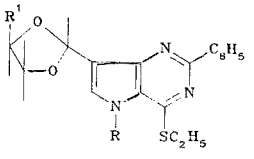
Compound	Chemical shifts, δ, ppm (spin–spin coupling constant, Hz)								
	2′-H	4′a-H ($J_{4'a4'b}$)	4′b-H ($J_{4'b5'}$)	5′-H ($J_{4'a5'}$)	6′-H	$OCOCH_2$	C–OCH_2	2-H	SCH_2CH_3
VIIa	6,22	4,21 (8,2)	3,87 (6,2)	4,43 (5,7)	3,70–3,55[a]	5,40	4,54	7,68	
VIIb	6,06	4,10 (7,8)	3,97 (5,7)	4,43 (5,7)	3,70–3,55[a]	5,40	4,57	7,72	
XIIa	6,43	4,33	3,60–3,80[a]	4,42	3,60–3,80[a]	5,47	4,54	7,99	3,37 1,43
XIIb	6,31	4,15	3,60, 3,88[a]	4,42	3,60–3,88[a]	5,47	4,64	8,02	3,37 1,43

[a]The signals overlap.

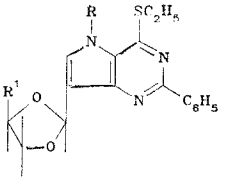
1-Isobutoxycarbonyl (IX) and 1-benzyloxycarbonyl-3-formyl-5-phenyl-7-ethylthiopyrrolo-[3,2-d]pyrimidine (X) were synthesized in an analogous manner on the basis of 3-formyl-5-phenyl-7-ethylthiopyrrolo[3,2-d]pyrimidine (VIII). Mixtures of the isomeric dioxolanes XIa and XIb and the isomeric dioxolanes XIIIa and XIIIb, also with 1:1 ratios, were obtained by reacting aldehyde IX with 1,2-propanediol of aldehyde X with 1-O-benzylglycerol. Unlike the dioxolanes of the indole series, compounds XIa, XIb, XIIa, and XIIb are stable during chromatographic separation and storage. An attempt to remove the isobutoxycarbonyl protection in compounds XIa and XIb under the conditions of alkaline hydrolysis, however, produced the original aldehyde. Hydrogenolysis of a mixture of dioxolanes XIIa and XIIb over 10% Pd/C in methanol also resulted in the formation of the aldehyde. The comparatively high hydrolytic stability of the dioxolane derivatives of pyrrolo[3,2-d]pyrimidines in comparison to the dioxolane derivatives of indole is apparently attributable to the stronger electron-acceptor properties of the pyrrolopyrimidine nucleus.



VIII, IX, X



XI a, XII a



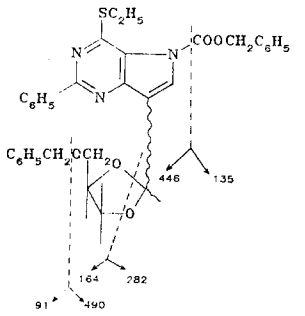
XIb, XIIb

VIII R=H; IX, XI R=$(CH_3)_2CHCH_2OCO$; X, XII R=$C_6H_5CH_2OCO$; XI R^1=CH_3; XII R^1=$C_6H_5CH_2OCH_2$

The assignment of the a and b isomers of VI, VII, XI, and XII to the trans and cis series was made in analogy to the 4-substituted 1,3-dioxolanes in [4, 5]. In all cases, the signal of the 2′-H proton in the PMR spectra of the cis isomers (b) undergoes an upfield shift in comparison to the corresponding trans isomers (a), in analogy to the shifts usually

observed in the PMR spectra for the anomeric protons in β- and α-nucleosides (Tables 1 and 2) [6].

In the mass spectra of isomeric compounds XIIa and XIIb there is a peak of the molecular ion with m/z 581, as well as peaks of fragments, which attest to fragmentation according to the following scheme:



EXPERIMENTAL

The PMR spectra of compounds V, VIa, VIb, VIIa, VIIb, IX, X, XIa, and XIb were recorded on a Bruker instrument (360 MHz), and the spectra of compounds III, XIIa, and XIIb were recorded on a Joel instrument (100 MHz) in deuterochloroform with TMS as an internal reference. The mass spectrum of the mixture of XIIa and XIIb was recorded on a Varian MAT-311A instrument. The compounds synthesized were isolated with the aid of thin-layer chromatography on plates measuring 20 × 20 cm with an unimmobilized layer of Silica Gel LSL 5/40 (Czechosolvakia). The thickness of the layer was 1 mm. Chloroform was used for the TLC, and the isolation of compounds VIa and VIb was conducted in a 3:1 benzene–acetone solvent system. The analytical TLC was carried out on Silufol UV-254, the R_f values of the compounds obtained being given in chloroform. The development of the substances was carried out in UV light.

3-Formyl-1-isobutoxycarbonylindole (III). 3-Formylindole (I) in an amount equal to 0.43 g (3 mmole) is placed in 8 ml of dry THF containing 1 ml of dry triethylamine. The solution is cooled to 3-5°C, and 1.63 g (12 mmole) of isobutyl chlorocarbonate (II) is slowly added dropwise. The reaction mass is stirred for 0.5 h with cooling by ice and for 2 h at room temperature, and then it is poured into finely crushed ice (60 g). The organic layer is separated and dried over $CaCl_2$, and the solvent is driven off in a vacuum at 40°C. Indole III is obtained after purification with the aid of TLC with a 0.66-g (91%) yield and R_f 0.69. PMR spectrum: 1.06 (CH_3); 2.19 (CH), 4.27 (CH_2, J_{HH} = 7 Hz), 8.21 (2-H), 10.09 ppm (CHO). Found: C, 68.3; H, 6.4; N, 5.8%. Calculated for $C_{14}H_{15}NO_3$: C, 68.6; H, 6.1; N, 5.7%.

1-Benzyloxycarbonyl-3-formylindole (V). A 0.43-g portion (3 mmole) of 3-formylindole I in 1 ml of dry triethylamine is placed in 8 ml of dry THF. The solution is cooled to 3-5°C and given a dropwise addition of 1.02 g (6 mmole) of benzyl chlorocarbonate (IV). The mixture is treated in a manner similar to that described for indole III. The yield of V is 0.8 g (96%), and the R_f value is 0.93. PMR spectrum: 5.46 (CH_2), 7.79-8.25 (aromatic protons), 8.17 (2-H), 10.01 ppm (CHO). Found: C, 72.8; H, 4.9; N, 5.1%. Calculated for $C_{17}H_{13}NO_3$: C, 73.1; H, 4.7; N, 5.0%.

cis and trans-2-(1-Isobutoxycarbonylindol-3-yl)-4-methyl-1,3-dioxolane (VIa and VIb). A 0.25-g portion (1 mmole) of indole III and a 20-mg portion of p-toluenesulfonic acid are placed in 10 ml of dry benzene. The mixture is given an addition of 1 ml of 1,2-propanediol and boiled for 18 h with the removal of water by distillation. The reaction mass is applied to six plates, and a mixture of dioxolanes VIa and VIb is isolated after chromatography with a 0.27-g (80%) yield and R_f 0.4 and 0.5.

cis- and trans-2-(1-Benzyloxycarbonylindol-3-yl)-4-benzyloxymethyl-1,3-dioxolane (VIIa and VIIb). A 0.8-g portion (2.8 mmole) of indole V and 45 mg of p-toluenesulfonic acid are placed in 25 ml of dry benzene, and the mixture is given an addition of 1.1 ml of 1-O-benzylglycerol and boiled for 18 h with the removal of water by distillation. The resultant mixture is treated in analogy to the synthesis of dioxolane VIa and VIb. The yield of the mixture of dioxolanes VIIa and VIIb is 1.18 g (93%), and the R_f values are 0.8 and 0.7. Found: N, 3.1%. Calculated for $C_{27}H_{25}NO_5$: N, 3.2%.

1-Isobutoxycarbonyl-3-formyl-5-phenyl-7-ethylthiopyrrolo[3,2-d]pyrimidine (IX). A 0.42-g g portion (1.5 mmole) of aldehyde VIII is placed in 8 ml of dry THF, 0.5 ml of dry triethylamine is added, and the reaction mixture is cooled to 3-5°C and given a dropwise addition of 0.82 g (6 mmole) of isobutyl chlorocarbonate (II). The further treatment is carried out in analogy to the synthesis of indole III. The yield of pyrrolopyrimidine IX is 0.42 g (74%), and the R_f value is 0.91. PMR spectrum: 1.07 (CH_3, J_{CH_3-H} = 6.7 Hz), 1.48 (CH_3), 2.2 (CH), 3.40 (CH_2), 4.31 (CH_2, J_{CH-CH_2} = 6.8 Hz), 8.44 (2-H), 10.50 ppm (CHO).

1-Benzyloxycarbonyl-3-formyl-5-phenyl-7-ethylthiopyrrolo[3,2-d]pyrimidine (X). A suspension of 0.2 g (0.7 mmole) of aldehyde VIII in 8 ml of dry THF is given an addition of 0.25 ml of dry triethylamine. The mixture is cooled to 3-5°C and given a dropwise addition of 0.47 g (2.8 mmole) of benzyl chlorocarbonate with stirring. The further treatment is carried out in analogy to that described for indole III. Compound X is isolated with a 0.15-g (51%) yield and R_f 0.58. PMR spectrum: 1.45 (CH_3), 3.36 (CH_2), 5.49 (CH_2), 8.40 (2-H), 10.01 ppm (CHO). Found: N, 10.2%. Calculated for $C_{23}H_{19}N_3O_3$: N, 10.1%.

cis- and trans-2-(1-Isobutoxycarbonyl-5-phenyl-7-ethylthiopyrrolo[3,2-d]pyrimidin-3-yl)-4-methyl-1,3-dioxolane (XIa and XIb). A 0.16-g portion (4 mmole) of aldehyde IX and a 10-mg portion of p-toluenesulfonic acid are placed in 8 ml of dry benzene containing 0.5 ml of 1,2-propanediol, and the mixture is boiled for 18 h with the removal of water by distillation. The further treatment is carried out in analogy to that described for dioxolanes VIa and VIb. The yield of the mixture of dioxolanes XIa and XIb is 0.17 g (92%), and the R_f value is 0.68.

cis- and trans-2-(1-Benzyloxycarbomyl-5-phenyl-7-ethylthiopyrrolo[3,2-d]pyrimidin-3-yl)-4-benzyloxymethyl-1,3-dioxolane (XIIa and XIIb). A 0.16-g portion (3.8 mmole) of aldehyde X and a 10-mg portion of p-toluenesulfonic acid are mixed in 8 ml of dry benzene containing 0.4 ml of 1-O-benzylglycerol. The further treatment is carried out in analogy to that described for dioxolanes VIa and VIb. The yield of the mixture of dioxolanes XIIa and XIIb is 0.2 g (89%), and the R_f values are 0.4 and 0.3. Found: C, 67.9; H, 5.5; N, 4.2%. Calculated for $C_{33}H_{31}N_3O_5$: C, 68.1; H, 5.4; N, 7.2%.

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