SYNTHESIS OF 5-β-D-RIBOFURANOSYL-1,3-THIAZOLE-
-2-CARBOXAMIDE — A THIAZOLE ANALOGUE OF RIBAVIRIN

Tomáš VANĚK, Jiří FARKAŠ and Jiří GUT

Institute of Organic Chemistry and Biochemistry,
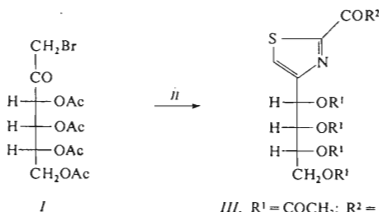*Czechoslovak Academy of Sciences, 166 10 Prague 6*

Condensation of ethyl thioxamate (*II*) with bromomethyl D-*ribo*-1,2,3,4-tetraacetoxybutyl ketone (*I*) or bromomethyl 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl ketone (*IX*) afforded ethyl 5-(D-*ribo*-1,2,3,4-tetraacetoxybutyl)-1,3-thiazole-2-carboxylate (*III*) and ethyl 5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-1,3-thiazole-2-carboxylate (*X*), respectively. Removal of the protecting groups and ammonolysis of the ester gave the respective 5-(D-*ribo*-1,2,3,4-tetrahydroxybutyl)-1,3-thiazole-2-carboxamide (*V*) and 5-(β-D-ribofuranosyl)-1,3-thiazole-2-carboxamide (*XI*).

In our preceding paper[1] we reviewed various syntheses of structural analogues of the virostaticum ribavirin and discussed in general the ways of deriving C-nucleosidic analogues. One of the possible analogue types arises by replacement of the triazole ring with a thiazole nucleus. Four C-ribofuranosylthiazolecarboxamides are thus possible which are structurally analogous to ribavirin. Two of them have been described recently[2], preparation of the third one is the subject of this communication.
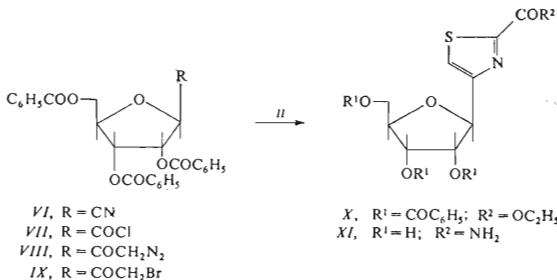
Disubstituted 1,3-thiazole derivatives can be synthesized by condensation of thioamides with α-halo ketones or α-halo aldehydes. If we use this method for the synthesis of a C-nucleoside, the nucleosidic moiety can be bonded to either of the reacting components. 2,5-Anhydro-3,4,6-tri-O-benzoyl-D-allonthioamide[2,3] was used in the mentioned synthesis[2], affording both the possible isomers with the ribose moiety in position 2. Synthesis of a further isomer must start, on the contrary, from a sugar halo ketone and the thioxamate *II*. As model compound for this procedure we used the known[4] 3,4,5,6-tetra-O-acetyl-1-deoxy-1-diazo-D-psicose which was transformed into the bromo ketone *I*. Its condensation with the thioamide *II* afforded ethyl 5-(D-*ribo*-1,2,3,4-tetraacetoxybutyl)-1,3-thiazole-2-carboxylate (*III*) in a 60% yield. The protecting groups were removed by action of ammonia which at the same time transformed the formed ester *IV* into the amide *V*. The ribofuranosyl derivative *XI* was synthesized from 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl cyanide[5] (*VI*) as the starting compound. This was transformed to 2,4,6-tri-O-benzoyl-2,5-anhydro-D-allonoyl chloride (*VII*) and further to the diazo ketone *VIII* and bromo ketone *IX*. Since the latter two compounds are unstable, the reaction sequence *VI*→*IX* was carried out

without isolation and identification of the intermediates. The first isolated compound, obtained in a 62% yield, was ethyl 5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-1,3-triazole-2-carboxylate (X) which was transformed into the amide XI by the above-mentioned procedure.

III, R¹ = COCH₃; R² = OC₂H₅
IV, R¹ = H; R² = OC₂H₅
V, R¹ = H; R² = NH₂

VI, R = CN
VII, R = COCl
VIII, R = COCH₂N₂
IX, R = COCH₂Br

X, R¹ = COC₆H₅; R² = OC₂H₅
XI, R¹ = H; R² = NH₂

In order to assign configuration to the anomeric center, the nucleoside XI was transformed to the isopropylidene derivative XII. Comparison of chemical shifts of the methyl groups ($\Delta\delta$ 0·2) in the ^{1}H-NMR spectrum of compound XII with the shifts obtained by systematic studies of Imbach[6] shows that the thiazole analogue XI has β-configuration.

The compound XI was found to be inactive against the herpes 2 and influenza A-NWS viruses[8] (tissue cultures).

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus. Analytical samples were dried at room temperature at 13 Pa for 8 h. ^{1}H-NMR spectra were measured on a Tesla BS 467 instrument (60 MHz); mass spectra on an MS 902 (AEI) spectrometer.

Ethyl 5-(D-*ribo*-1,2,3,4-Tetraacetoxybutyl)-1,3-thiazole-2-carboxylate (*III*)

A 2M solution of hydrogen bromide in benzene (2 ml) was added at 0°C to a solution of 3,4,5,6--tetra-O-acetyl-1-deoxy-1-diazo-D-psicose (0·358 g; 1 mmol) in ether, the reaction mixture was stirred for 15 min at room temperature, diluted with ether (15 ml) and poured into water (50 ml). The ethereal layer was washed with a sodium hydrogen carbonate solution (20 ml) and water (2 × 20 ml) and taken down *in vacuo*. The crude bromo ketone *I* was dissolved in acetonitrile (20 ml) and mixed with ethyl thioxamate (*II*) (0·133 g; 1 mmol). The mixture was stirred for 5 h at room temperature, taken down *in vacuo* and the residue chromatographed on a silica gel column (20 g) in toluene–ethyl acetate (4 : 1), yielding 0·270 g (60%) of the product *III*, m.p. 107–110°C. For $C_{18}H_{23}N_{10}S$ (445·4) calculated: 48·50% C, 5·20% H, 3·10% N, 7·20% S; found: 48·13% C, 4·92% H, 3·02% N, 7·41% S. Mass spectrum: 445 (M$^+$), $[\alpha]_{20}^{D}$ +53·2° (*c* 0·3, CHCl$_3$).

5-(D-*ribo*-1,2,3,4-Tetrahydroxybutyl)-1,3-thiazole-2-carboxamide (*V*)

A 4·92M ammonia solution in methanol (10 ml) was added to a solution of the ester *III* (0·445 g; 1 mmol) in methanol (20 ml), the mixture was set aside at room temperature for 100 h and taken down *in vacuo*. Chromatography of the residue on a silica gel column (20 g) in toluene–ethyl acetate (4 : 1) afforded 0·107 g (43%) of an amorphous product. For $C_8H_{12}N_2O_5S$ (248·2) calculated: 38·72% C, 4·78% H, 11·29% N; found: 39·21% C, 5·03% N. Mass spectrum: 248 (M$^+$), $[\alpha]_{20}^{D}$ +37·3° (*c* 0·5, CHCl$_3$).

Ethyl 5-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-1,3-thiazole-2-carboxylate (*X*)

A solution of 2,4,6-tri-O-benzoyl-2,5-anhydro-D-allonoyl chloride (*VII*) (prepared by known[7] procedure from 1·884 g — 3 mmol — of ribofuranosyl cyanide *VI*) in benzene (50 ml) was added dropwise at 0°C during 20 min to a stirred ethereal solution of diazomethane (50 ml, prepared from 1·6 g of nitrosomethylurea). The mixture was set aside for 5 h at room temperature and taken down. The crude diazo ketone *VIII* was dissolved in ether (20 ml), the solution cooled to 0°C and after addition of a 2M hydrogen bromide solution in benzene (8 ml) stirred for 15 min at room temperature. After dilution with ether (50 ml) the mixture was poured into water (100 ml), the ethereal layer washed with a saturated solution of sodium hydrogen carbonate (20 ml) and water (2 × 40 ml) and dtaken down *in vacuo*. The crude bromo ketone *IX* was dissolved in acetonitrile (100 ml), mixed with the ester *II* (0·532 g; 4 mmol), stirred for 5 h at room temperature and taken down *in vacuo*. Chromatography of the residue on a silica gel column (80 g) in toluene--ethyl acetate (4 : 1) afforded 1·490 g (62%) of the amorphous product *X*. For $C_{32}H_{27}NO_9S$ (601·6) calculated: 63·79% C, 4·48% H, 2·32% N, 5·32% S; found: 63·92% C, 4·35% H, 2·63% N, 5·31% S. Mass spectrum: 601 (M$^+$). $[\alpha]_{20}^{D}$ −29·9° (*c* 0·2, CHCl$_2$).

5-(β-D-Ribofuranosyl)-1,3-thiazole-2-carboxamide (*XI*)

A solution of the ester *X* (0·602 g; 1 mmol) in methanol (20 ml) was mixed with methanolic ammonia (10 ml of 4·92M solution) and after standing for 1 h at room temperature taken down

in vacuo. The residue was dissolved in water (50 ml), taken up in ether (3 × 30 ml) and the aqueous solution was taken down. The residue was dissolved in methanol (20 ml), mixed with methanolic ammonia (10 ml of 4·92M solution), set aside for 100 h at room temperature and taken down *in vacuo.* Chromatography of the residue on a silica gel column (30 g) in ethyl acetate–ethanol (9 : 1) afforded 0·115 g (46%) of the product *XI*, m.p. 131—133°C. For $C_9H_{12}N_2O_5S$ (260·2) calculated: 41·54% C, 4·65% H, 10·76% N, 12·32% S; found: 41·76% C, 4·75% H, 10·88% N, 12·36% S. Mass spectrum: 260 (M$^+$). $[\alpha]^D$ −6·9° (*c* 0·5, CHCl$_3$). ^{1}H-NMR spectrum (hexadeuteriodimethyl sulfoxide +1% CD$_3$COOD): δ 7·94 (s, 1 H, H$_5$); 4·81 (d, 1 H, H$_1$, $J_{1',2'}$ = 4·1 Hz). CD spectrum (methanol). $[\Theta]_{275·5}$ + 1 705°, $[\Theta]_{275·5}$ −200°, $[\Theta]_{235}$ +5717°, $[\Theta]_{215}$ −8 626°.

Isopropylidene derivative XII was obtained as a syrup by reaction of the compound *XI* with 2,2-dimethoxypropane, acetone and a trace of *p*-toluenesulfonic acid. Mass spectrum: 300 (M$^+$), 285 (M−CH$_3$), 270 (M−CH$_2$O), 242 (M−CH$_3$COCH$_3$), 225, 211, 157 (B + 30); ^{1}H-NMR spectrum (hexadeuteriodimethyl sulfoxide +1% CD$_3$COOD): δ 7·92 (s, 1 H, H$_5$), 5·01 (s, 1 H, H$_1$), 1·49 (s, 3 H, CH$_3$), 1·29 (s, 3 H, CH$_3$).

REFERENCES

1. Vaněk T., Farkaš J., Gut J.: This Journal *44*, 1338 (1979).
2. Srivastava P. C., Pickering M. V., Allen L. B., Streeter D. G., Campbell M. T., Witkowski J. T., Sidwell E. W., Robins R. K.: J. Med. Chem. *20*, 256 (1977).
3. Fuertes M., García-Lopez M. T., García-Munoz G., Madronero R.: J. Carbohyd. Nucleosides, Nucleotides *2*, 277 (1975).
4. Wolfrom M. L., Thompson A., Evans E. F.: J. Amer. Chem. Soc. *67*, 1793 (1945).
5. Bobek M., Farkaš J.: This Journal *34*, 247 (1969).
6. Imbach J.-L., Barascut J.-L., Kam B. L., Tapiero C.: Tetrahedron Lett. *1974*, 129.
7. Kalvoda L.: This Journal *43*, 1431 (1978).
8. Šmejkal F.: Acta Virol., in press.

Translated by M. Tichý.