PREPARATION OF 5-(β-D-RIBOFURANOSYL)PYRAZOLE-3-CARBOXAMIDE

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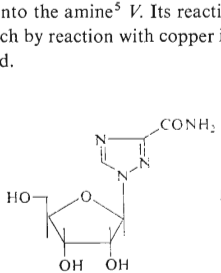
Received November 26th, 1981

Synthesis of the pyrazole analogue of ribavirin (*I*), 5-(β-D-ribofuranosyl)pyrazole-3-carboxamide (*II*), is described. The compound *II* exhibits low virostatic activity.

In our previous paper we described the preparation of ribavirin[1] (*I*) analogues containing thiazole[2] and triazole[3] heterocyclic rings. Other syntheses in this field are summarized in ref.[4]. One of further possible analogues is the compound *II* in which the triazole ring is replaced by pyrazole moiety.

The synthesis of this compound started from the monoester *III*, already described in the synthesis of formycin[5]. The compound *III* was decarboxylated by heating in quinoline in the presence of copper, the yield of the desired compound being only 23%. The remaining material was the totally decarboxylated product *VII* and decomposition products. Because of the low yield, caused probably by the high decarboxylation temperature, we transformed the starting monoester *via* the urethane *IV* into the amine[5] *V*. Its reaction with nitrous acid afforded the diazo compound *VI* which by reaction with copper in acetic acid gave the desired ethyl ester *VIII* in 92% yield.



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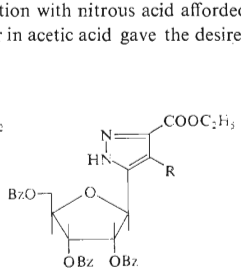
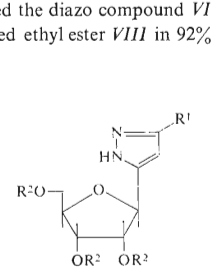


III, R = COOH
IV, R = $NHCOCH_2CHCl_3$
V, R = NH_2
VI, R = N_2



VII, R^1 = H, R^2 = Bz
VIII, R^1 = $COOC_2H_5$, R^2 = Bz
IX, R^1 = $COOC_2H_5$, R^2 = H
II, R^1 = $CONH_2$, R^2 = H

In spite of repeated experiments it was not possible to replace the diazo group by hydroxyl[6] which would constitute a simple path for the preparation of pyrazomycin[7].

The ethyl ester *VIII* was ammonolyzed to give the amide *II via* the unisolated de-blocked ethyl ester *IX*. The virostatic activity of the thus-obtained compound *II* was low in comparison with ribavirin[8].

EXPERIMENTAL

Column chromatography was carried out on silica gel (according to Pitra and Štěrba;30–60 μm; deactivated with 11% water), thin-layer chromatography was performed on silica gel according to Stahl (Merck). Mass spectra were measured on an AEI 902 spectrometer, optical rotation on a Perkin–Elmer 141 polarimeter.

Ethyl 5-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-4-diazopyrazole-3-carboxylate (*VI*)

Acetic acid (5 ml), followed by 1M aqueous solution of sodium nitrite (1·2 ml) and (in portions) 1M-HCl (2 ml), was added at 0°C to a solution of the amine *V* (ref.[5]; 0·599 g; 1 mmol) in ethanol (10 ml). After stirring for 15 min at room temperature, chloroform (20 ml) and water (20 ml) were added. The organic layer was separated, washed with a saturated aqueous solution of sodium hydrogen carbonate (20 ml), water (2 × 20 ml), dried over anhydrous sodium sulfate and taken down *in vacuo*, yielding 0·580 g (98%) of an amorphous product; $[\alpha]_D$ −114·4° (*c* 0·5, $CHCl_3$). For $C_{32}H_{26}N_4O_9$ (610·6) calculated: 62·95% C, 4·29% H, 9·18% N; found: 63·01% C, 4·75% H, 9·42% N.

Ethyl 5-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)pyrazole-3-carboxylate (*VIII*)

A) Copper powder (5 mg) was added to a solution of the monoester[5] *III* (0·628 g; 1 mmol) in quinoline (3 ml). After heating to 220°C for 25 min the mixture was diluted with benzene (30 ml), poured into water (50 ml) and acidified with 5% hydrochloric acid (30 ml). The organic layer was separated, washed with saturated sodium hydrogen carbonate solution (20 ml) and water (2 × 20 ml), dried over sodium sulfate and taken down *in vacuo*. The residue was chromatographed on a column of silica gel (5 g) in toluene–ethyl acetate (4 : 1), affording 0·120 g (22·6%) of an amorphous product, $[\alpha]_D^{20}$ −35·9° (*c* 0·5, chloroform). Mass spectrum: 462 (M^+ −122). For $C_{32}H_{28}N_2O_9$ (584·6) calculated: 65·75% C, 4·83% H, 4·79% N; found: 65·40% C, 5·07% H, 4·63% N.

B) Copper powder (0·300 g) was added to a solution of the diazo compound *VI* (0·611 g; 1 mmol) in acetic acid (6 ml). The mixture was heated to 100°C for 15 min, diluted with benzene (30 ml), filtered and poured into water (50 ml). The organic layer was separated, washed with 5% hydrochloric acid (20 ml), water (2 × 20 ml), saturated sodium hydrogen carbonate solution (2 × 20 ml), again with water (2 × 20 ml), dried over sodium sulfate and taken down *in vacuo*, affording 0·520 g (92%) of an amorphous product, identical with the compound prepared according to the procedure *A*).

5-(β-D-Ribofuranosyl)pyrazole-3-carboxamide (*II*)

A solution of ethyl ester *VIII* (1·168 g; 2 mmol) in methanolic ammonia (5 ml; 4·92 mol l^{-1}) and methanol (20 ml) was set aside for 1 h at room temperature and taken down. The residue

was dissolved in water (50 ml), the aqueous solution washed with ether (3 × 30 ml) and taken down *in vacuo*. A solution of the residue in methanol (20 ml) was mixed with methanolic solution of ammonia (10 ml; 4·92 mol l^{-1}) and set aside at room temperature for 100 h. After evaporation, the residue was dissolved in water (20 ml), the solution made alkaline with ammonia and applied on a column (1·5 × 5 cm) of Dowex 1X8 (acetate cycle). After washing the column with water (100 ml) the product *II* was eluted with 10% acetic acid (elution was monitored by UV light). Evaporation *in vacuo* and codistillation with toluene (2 × 20 ml) afforded 0·250 g (51·7%) of the amorphous product, α_D^{20} −18·8° (*c* 0·3; chloroform). Mass spectrum: 243 (M^+). For $C_9H_{13}N_3O_5$ (243·2) calculated: 44·45% C, 5·39% H, 17·28% N; found: 44·32% C, 5·18% H, 17·35% N.

Elemental analyses were determined in the Analytical Laboratory of this Institute (Dr J. Horáček, Head), mass spectra were taken and interpreted by Dr L. Dolejš and Dr J. Kohoutová, optical rotation measurements were carried out by Mrs Z. Ledvinová. Our thanks are due to all of them.

REFERENCES

1. Witkowski J. T., Robins R. K., Sidwell R. W., Simon K. N.: J. Med. Chem. *15*, 1150 (1972)
2. Vaněk T., Farkaš J., Gut J.: This Journal *44*, 1338 (1979).
3. Vaněk T., Farkaš J., Gut J.: This Journal *44*, 1339 (1979).
4. Poonian M. S., Nowosviat E. F.: J. Org. Chem. *45*, 203 (1980).
5. Kalvoda L.: This Journal *43*, 1431 (1978).
6. Kalvoda L.: Private communication.
7. Suhadolnik R. J.: *Nucleoside Antibiotics*, p. 390. Wiley-Interscience, New York 1970.
8. Šmejkal F.: Unpublished results.

Translated by M. Tichý.