SYNTHESIS OF 3,5-DISUBSTITUTED 1,2,4-TRIAZOLE DERIVATIVES — AN ALTERNATIVE PREPARATION OF THE C-ANALOGUE OF RIBAVIRIN

Tomáš VANĚK, Jiří FARKAŠ a Jiří GUT

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

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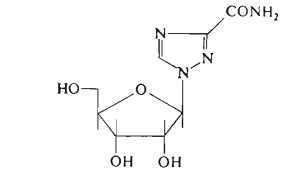
Condensation of ethyl acetothioimidate hydrochloride (*III*) with amidrazones *IV* afforded 3-methyl-5-phenyl-1,2,4-triazole (*Va*) and ethyl 3-methyl-1,2,4-triazole-5-carboxylate (*Vb*). Analogously, the thioimidate hydrochloride *VI* was transformed into ethyl 5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxylate (*VIIa*) which, after removal of benzoyl groups, was ammonolysed to the amide *II*.

The significant virostatic activity of the synthetic nucleoside ribavirin[1,2] (*I*) gave the impetus for synthesis of its analogues. Thus, compounds modified in the carboxamide group[3], in the sugar moiety[4–8] and substituted in the position 5 of the heterocyclic[9] part have been prepared. Another type of analogues are N-glycosyl derivatives with modified number and position of nitrogen atoms in the five-membered heterocyclic nucleus, such as 1,2,3-triazole[10–12], pyrazole[13–15], imidazole[16] and tetrazole[17] derivatives. A wider variety of possible analogues is offered by C-glycosyl derivatives which, in addition to the variability in number and position of the nitrogen atoms, can be modified by introduction of a divalent hetero atom such as oxygen or sulfur, and by corresponding combinations. These types are structurally close to the C-nucleosidic antibiotic pyrazomycin[18].

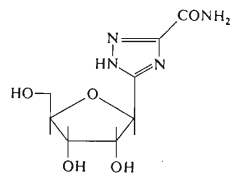
In the course of our investigations concerning preparation of such analogues, two independent syntheses have been published[19,20] of 5-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (*II*) which can be regarded as a C-analogue of ribavirin. In the present paper we describe an alternative synthesis of the compound *II*, which at the same time represents an example of a general synthesis of 3,5-disubstituted 1,2,4-triazole derivatives.

The best starting sugar component for the synthesis of the C-nucleoside *II* is 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl cyanide[21] which can be transformed into reactive intermediates such as imino ethers or alkyl thioimidates. We chose the latter since they are more stable. The second component, required for the formation of the triazole ring, can be an ester of oxalic acid monohydrazide, an ester of oxamic

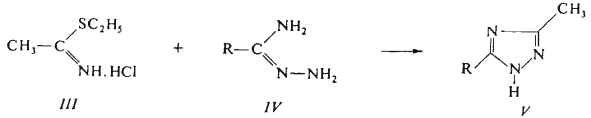
acid or an ester of oxalic acid amidrazone. Since the ester-hydrazide affords low yields of triazoles[22] and the ester-amide is relatively sparingly soluble, the amidrazone *IVb* seemed to be the derivative of choice.



I



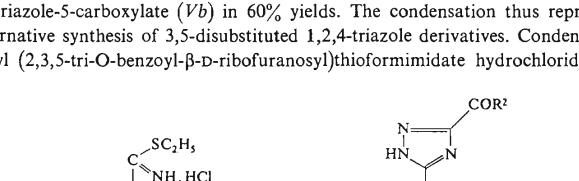
II



III *IV* *V*

In formulae *IV*, *Va*: R = C_6H_5; *b*: R = $COOC_2H_5$

In order to check the attempted condensation of alkyl thioimidates with amidrazones to disubstituted triazoles and to find suitable reaction conditions we treated ethyl acetothioimidate hydrochloride (*III*) with benzamidrazone (*IVa*) or oxalamidrazone ethyl ester (*IVb*). On heating, compounds *III* and *IVa* afforded 3-methyl-5-phenyl-1,2,4-triazole (*Va*), and condensation of *III* with *IVb* gave ethyl 3-methyl-1,2,4-triazole-5-carboxylate (*Vb*) in 60% yields. The condensation thus represents an alternative synthesis of 3,5-disubstituted 1,2,4-triazole derivatives. Condensation of ethyl (2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)thioformimidate hydrochloride (*VI*)



VI, R = COC_6H_5

VIIa, $R^1 = COC_6H_5$; $R^2 = OC_2H_5$
VIIb, R^1 = H; $R^2 = OC_2H_5$

with oxalamidrazone ethyl ester (*IVb*) under analogous conditions afforded the triazole *VIIa* in 67% yield. Removal of the benzoyl groups, followed by ammonolysis, led to the C-analogue of ribavirin *II*. Its physical constants were identical with the compound prepared by the already mentioned procedures[19,20] and we can therefore assume that the product is the β-isomer.

The nucleoside *II* was inactive against herpes 2 and influenza A-NWS viruses[23].

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus. Samples for analysis were dried at room temperature and 13 Pa for 8 h. Mass spectra were measured on an MS 902 (AEI) instrument.

3-Methyl-5-phenyl-1,2,4-triazole (*Va*)

A solution of benzamidrazone (270 mg; 2 mmol) and ethyl acetothioimidate hydrochloride (280 mg; 2 mmol) in methyl cellosolve (20 ml) was heated to 60°C for 5 h, cooled and taken down *in vacuo*. The residue was extracted with boiling benzene and the benzene solution taken down. Crystallisation from benzene–light petroleum (3 : 1) afforded 200 mg (60%) of product, m.p. 164—165°C, undepressed on admixture with a sample prepared by another method[24].

Ethyl 3-Methyl-1,2,4-triazole-5-carboxylate (*Vb*)

A solution of oxalamidrazone ethyl ester (396 mg; 3 mmol) and ethyl acetothioimidate hydrochloride (420 mg; 3 mmol) in methyl cellosolve (30 ml) was heated to 60°C for 5 h. The isolation procedure, described in the preceding experiment, afforded 240 mg (60%) of the product, m.p. 186—188°C; no depression in m.p. with a sample prepared by another route[24].

Ethyl (2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)thioformidate Hydrochloride (*VI*)

Ethanethiol (0·28 ml; 4 mmol) was added to a solution of 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl cyanide (942 mg; 2 mmol) in ether (100 ml). After cooling to 0°C, hydrogen chloride was introduced for 2 h into the mixture which was then set aside for 12 h at 0°C. The separated product was filtered and washed with ether, yielding 950 mg (83%), m.p. 98—100°C. For $C_{29}H_{27}NO_7S.HCl$ (569·8) calculated: 61·13% C, 4·91% H, 2·46% N, 5·63% S, 6·22% Cl; found: 61·17% C, 5·15% H, 2·63% N, 5·96% S, 6·12% Cl. Mass spectrum: 533 (M—HCl), $[\alpha]_D$ +18·2° (*c* 0·5, chloroform).

Ethyl 5-(2,3,4-Tri-O-benzoyl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxylate (*VIIa*)

A solution of the thiomidate hydrochloride *VI* (2·280 g; 4 mmol) and ethyl oxalamidrazone (0·528 g; 4 mmol) in methyl cellosolve (20 ml) was heated to 60°C for 4 h and then taken down *in vacuo*. The residue was chromatographed on a silica gel column (100 g) in toluene–ethyl acetate (4 : 1), affording 1·540 g (67%) of an amorphous product. For $C_{31}H_{27}N_3O_9$ (585·6) calculated: 63·59% C, 4·65% H, 7·18% N; found: 63·48% C, 4·34% H, 6·92% N. Mass spectrum: 585 (M^+), $[\alpha]_D$ −18·7° (*c* 0·5, chloroform).

Ethyl 5-β-D-Ribofuranosyl-1,2,4-triazole-3-carboxylate (*VIIb*)

A solution of the ester *VIIa* (1·170 mg; 2 mmol) and sodium methoxide (0·6 m of 1M methanolic solution) in methanol (20 ml) was set aside for 1 h at room temperature, acidified with acetic acid and taken down *in vacuo*. The residue was dissolved in water (150 ml), the solution washed with ether (2× 100 ml) and the aqueous layer taken down *in vacuo* and codistilled twice with water. The residue was dissolved in water, the solution made alkaline with ammonia and applied to a column (1·5 × 5 cm) of Dowex 1X8. After washing with water (100 ml) the desired compound was eluted with 10% acetic acid, the elution being monitored by UV light. The eluate was taken down and the residue codistilled with water (2× 20 ml) and toluene (2× 20 ml) to give 0·436 g (80%) of the product, melting at 163—165°C (ethanol). For $C_{10}H_{15}N_3O_6$ (273·2) calculated: 43·96% C, 5·23% H, 14·53% N; found: 43·22% C, 5·45% H, 14·72% N. Mass spectrum: 273 (M^+), $[\alpha]^D$ −12·9° (*c* 0·24, methanol).

5-β-D-Ribofuranosyl-1,2,4-triazole-3-carboxamide (*II*)

A. *From the tri-O-benzoyl derivative* VIIa: A solution of the compound *VIIa* (1·170 g; 2 mmol) and ammonia (5 ml of 4·92M methanolic solution) in methanol (20 ml) was set aside for 1 h at room temperature and taken down *in vacuo*. The residue was dissolved in water (50 ml), the solution extracted with ether (3× 30 ml) and the aqueous layer evaporated *in vacuo*. The residue was dissolved in methanol (20 ml) and after addition of methanolic ammonia (10 ml of 4·92M solution) the solution was set aside at room temperature for 100 h. The solvent was distilled off, the residue was dissolved in water, the solution made alkaline with ammonia and subjected to chromatography on Dowex as described for preparation of the compound *VIIb*. The product melted at 194—196°C (water–ethanol 1 : 1), yield 0·355 g (36%). The reported[19,20] melting points are 193—195°C and 195°C. For $C_8H_{12}N_4O_5$ (244·2) calculated: 39·35% C, 4·95% H, 22·94% N; found: 39·32% C, 5·26% H, 23·03% N. Mass spectrum: 244 (M^+), $[\alpha]_{20}^D$ −5·1° (*c* 1·7, water).

B. *From the ribofuranosyl derivative* VIIb: The compound *VIIb* (273 mg; 1 mmol) was ammonolysed for 100 h as described under *A*) and the product was obtained by chromatography on an ion exchange resin according to the procedure described for preparation of *VIIb*. Yield 105 mg (43%) of product, identical with the compound prepared according to *A*).

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