PREPARATION OF RIBOSYL DERIVATIVES OF 1,2,4-TRIAZOL-3(2*H*)-ONE AND 5-METHYL-1,2,4-TRIAZOL-3(2*H*)-ONE*

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Reaction of the silylated triazolone *I* with 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide afforded a mixture of the 4-ribosyltriazolone *IXa* and 2,3-diribosyltriazolone *Xa*. Under the same conditions the silylated 5-methyltriazolone *II* gives the 4-ribosyl derivative *XIa* and 2-ribosyl derivative *XIIa*. The 4-phenyl and 4-ribosyltriazoles *VII*, *VIII*, *IXa* and *XIa* were prepared by an alternative synthesis: cyclisation of 1-ethoxymethylene-, 1-(1-ethoxyethylidene)-4-phenyl- and 4-ribosylsemicarbazides *XIII*, *XIV*, *XVa,b* and *XVIa,b* in boiling hexamethyldisilazane in the presence of ammonium sulfate. The semicarbazides *XIII*, *XIV*, *XVa,b* and *XVIa,b* were obtained by reaction of 4-phenyl- or 4-ribosylsemicarbazide with triethyl orthoformate or diethyl orthoacetate. Compounds *XIII* and *XIV* were obtained as the (*E*)-isomers whereas compounds *XV* and *XVI* as mixtures of (*Z*)- and (*E*)-isomers *XVa,b* and *XVIa,b*, respectively. The benzylation of the triazolones *I* and *II* was also studied.

In our recent study[1] we investigated a series of nucleoside analogs as potential cytidine aminohydrolase inhibitors. Of the studied compounds only 4-ribosyl-1,2,4-triazol-3(2*H*)-one (*IXb*) has shown some inhibitory activity. The aim of our present communication was the synthesis of the compound *IXb* and other triazolone derivatives which might possess similar activity.

As a model reaction we first investigated benzylation of sodium salt of the triazolone *I* and the 5-methyltriazolone *II*. Reaction of the former salt (ref.[2]) with 1·5 equivalent of benzyl chloride in dimethylformamide at room temperature gave after 4·5 h a mixture from which we isolated the 4-benzyl derivative *III* (33%), the dibenzyl derivative *IV* (16%) and the unreacted triazolone *I* (30%). Similarly, sodium salt of 5-methyltriazolone *II* (ref.[3]) reacted with benzyl chloride under the same conditions to give the 4-benzyl derivative *V* (25%), the dibenzyl derivative *VI* (21%) and the starting *II* (30%). Daunis and Roumestant reported[4] that reaction of *II* with methyl iodide in boiling methanol gave 2,5-dimethyl-1,2,4-triazol-3(2*H*)-one and 4,5-dimethyl-1,2,4-triazol-3(2*H*)-one in the ratio 35 : 65.

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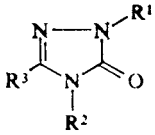
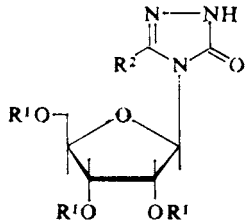
Ribosidation of the triazolones *I* and *II* was performed *via* the silylated triazolones which were reacted with 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide in acetonitrile in the presence of mercuric bromide. The triazolone *I* afforded the protected 4-ribosyl derivative *IXa* in 39% yield and the diribosyl derivative *Xa* in 42·5% yield. Ribosidation of the 5-methyltriazolone *II* had a somewhat different course. Whereas the 4-ribosyl derivative *XIa* was obtained in 60% yield, no diribosyl derivative was observed. Instead, the 2-ribosyl derivative *XIIa* was isolated in 15% yield. The free nucleosides *IXb*, *Xb*, *XIb* and *XIIb* were obtained by methanolysis of the protected derivatives. The diriboside *Xa* was methanolyzed with methanolic solution of barium methoxide, other protected nucleosides with methanolic sodium methoxide.





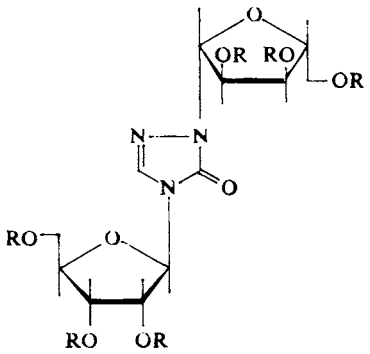
I, $R^1 = R^2 = R^3 = H$
II, $R^1 = R^2 = H$, $R^3 = CH_3$
III, $R^1 = R^3 = H$, $R^2 = C_6H_5CH_2$
IV, $R^1 = R^2 = C_6H_5CH_2$, $R^3 = H$
V, $R^1 = H$, $R^2 = C_6H_5CH_2$, $R^3 = CH_3$
VI, $R^1 = R^2 = C_6H_5CH_2$, $R^3 = CH_3$
VII, $R^1 = R^3 = H$, $R^2 = C_6H_5$
VIII, $R^1 = H$, $R^2 = C_6H_5$, $R^3 = CH_3$

IXa, $R^1 = C_6H_5CO$, $R^2 = H$
IXb, $R^1 = R^2 = H$
XIa, $R^1 = C_6H_5CO$, $R^2 = CH_3$
XIb, $R^1 = H$, $R^2 = CH_3$

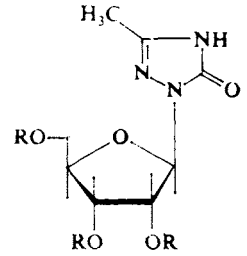
The structure of the 4-benzyl compounds *III*, *V* and the 4-ribosyl derivatives *IXa* and *XIa* was confirmed by their alternative synthesis. Compounds *III* and *V* were obtained by cyclisation of 1-acylsemicarbazides[3,4] in boiling 10% aqueous potassium hydroxide solution. 4-Benzyl-1-formylsemicarbazide and 4-benzyl-1-acetylsemicarbazide were prepared by reaction of 4-benzylsemicarbazide with ethyl formate and acetic anhydride, respectively. Their cyclization afforded 4-benzyltriazolones with melting points, IR and ^1H NMR spectra identical with those of compounds *III* and *V* prepared by benzylation of the triazolones *I* and *II*. The starting 4-benzylsemicarbazide was synthetized according to the described method[5] by a modified procedure.

The 4-ribosyltriazolones *IXa* and *XIa* were obtained by cyclisation of 1-ethoxymethylene- and 1-(1-ethoxyethylidene)-4-ribosylsemicarbazides *XIV* and *XVIa,b*, respectively. The cyclisation reaction was studied with 4-phenylsemicarbazides *XIII* and *XVa,b* the best results being obtained in boiling hexamethyldisilazane in the

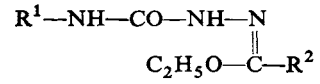
presence of a a small amount of ammonium sulfate. This method was used also in cyclisation of the ribosylsemicarbazides *XIV* and *XVIa,b*. The semicarbazides *XIII*, *XIV*, *XVa,b* and *XVIa,b* were prepared by reaction of triethyl orthoformate or triethyl orthoacetate with 4-phenyl- or 4-ribosylsemicarbazide[6] in dichloromethane. The attempted preparation of the analogous 4-benzyl derivative under the same conditions was unsuccessful, since 4-benzylsemicarbazide afforded N,N'-bis-(N'-benzylureido)formamidine. 1-(1-Ethoxyethylidene)semicarbazides are formed as a mixture of two geometric isomers which were separated by column chromatography on silica gel. In the case of 1-ethoxymethylenesemicarbazides only the (*E*)-isomers were obtained. Infrared spectra of the (*Z*)-isomers *XVa* and *XVIa* in tetra-



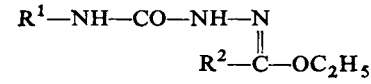
Xa, R = C_6H_5CO
Xb, R = H



XIIa, R = C_6H_5CO
XIIb, R = H



XVa, $R^1 = C_6H_5$, $R^2 = CH_3$
XVIa, R^1 = 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl, $R^2 = CH_3$



XIII, $R^1 = C_6H_5$, $R^2 = H$
XIV, R^1 = 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl
XVb, $R^1 = C_6H_5$, $R^2 = CH_3$
XVIb, R^1 = 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl, $R^2 = CH_3$

chloromethane exhibit bands of the free (3 394·5 and 3 400 cm^{-1}, respectively) and bonded (3 205 and 3 208 cm^{-1}, respectively) NH groups. The ratio of band intensities is the same both in saturated solution and in concentration 0·003 mol l^{-1}, indicating thus the presence of an intramolecular hydrogen bond N^2—H...OC_2H_5. Its existence was also proved by the ^1H NMR spectrum of the phenylsemicarbazide *XVa* in which the signal of the N^4—H proton is at 7·95 ppm whereas the N^2—H

proton signal is shifted up to 10·09 ppm. In the spectra of the tri-O-benzoyl derivatives the NH proton signals cannot be located because they overlap with the multiplet of benzoyl protons. Infrared spectra of the (*E*)-isomers *XIII*, *XIV*, *XVb* and *XVIb* do not exhibit any bonded NH group bands. The ^{1}H NMR signals of the NH protons in the phenylsemicarbazide *XIII* are at 8·67 and 8·98 ppm and in the compound *XVb* at 7·91 and 8·00 ppm.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). The IR spectra were recorded on a UR-20 apparatus (Carl Zeiss, Jena). The ^{1}H NMR spectra were measured on Tesla BS 467 (60 MHz) and Tesla BS 497 (100 MHz) instruments, using tetramethylsilane as internal standard; chemical shifts (δ values) are expressed in ppm and coupling constants in Hz. Column chromatography was performed on Pitra silica gel (particle size 30—60 μm; produced by Service Laboratories of this Institute).

4-Benzylsemicarbazide

Hydrazine hydrate (1 ml) was added to a stirred solution of 3-benzylthiazolidine-2,4-dione[5] (2·1 g; 10 mmol) in acetonitrile (10 ml). After 30 min, the mixture was poured into ethyl acetate (200 ml), washed with water (2 × 30 ml) and saturated sodium chloride solution (30 ml), dried over magnesium sulfate and the solvent was evaporated *in vacuo*. Crystallization of the residue from toluene afforded 1·25 g (76%) of 4-benzylsemicarbazide, m.p. 110·5—111·5°C (reported[5] m.p. 111°C).

4-Benzyl-1,2,4-triazol-3(2*H*)-one (*III*)

A) A solution of the triazolone *I* (172 mg; 2 mmol) in 1 mol l^{-1} methanolic sodium methoxide (4 ml) was taken down *in vacuo*. The residue was stirred with dimethylformamide (4 ml) and benzyl chloride (0·5 ml) was added with stirring. After stirring for 4·5 h at room temperature, the mixture was taken down *in vacuo*, the residue was mixed with water (10 ml), shaken with chloroform (3 × 15 ml) and the chloroform solution was dried over magnesium sulfate. The solvent was evaporated *in vacuo* and the residue was chromatographed on a column of silica gel (50 g) in ethyl acetate. The first fraction after evaporation of the solvent and crystallization of the residue from toluene–n-heptane afforded 83 mg (16%) of 2,4-dibenzyl-1,2,4-triazol-3(2*H*)-one (*IV*), m.p. 91—93°C. ^{1}H NMR Spectrum (60 MHz, deuteriochloroform): 4·78 (s, 2 H, CH_2), 4·97 (s, 2 H, CH_2), 7·34(s, 11 H, H_5, C_6H_5). For $C_{16}H_{15}N_3O$ (265·3) calculated: 72·43% C, 5·70% H, 15·84% N; found: 72·63% C, 5·52% H, 16·02% N.

The second chromatographic fraction was crystallized from toluene affording 115 mg (33%) of the monobenzyl derivative *III*, m.p. 117·5—120·5°C. IR Spectrum (chloroform): 3 474 cm^{-1} (NH), 1 714 cm^{-1} (C=O). ^{1}H NMR spectrum (60 MHz, deuteriochloroform): 4·80 (s, 2 H, CH_2), 7·34 (s, 6 H, H_5, C_6H_5), 11·12 (broad s, 1 H, H_2). $C_9H_9N_3O$ (175·2) calculated: 61·70% C, 5·18% H, 23·99% N; found: 61·77% C, 5·01% H, 24·22% N.

The aqueous solution after extraction with chloroform was taken down and the residue was chromatographed on a column of silica gel (15 g) in an ethyl acetate–acetone–ethanol–water mixture (36 : 6 : 5 : 3), affording 52 mg (30%) of the starting triazolone *I*.

B) A solution of 4-benzylsemicarbazide (165 mg; 1 mmol) in boiling ethyl formate (1·75 ml) was refluxed for 15 min. After standing at room temperature for 16 h, the separated compound

(138 mg) was filtered and heated with a 10% aqueous potassium hydroxide solution (0·75 ml) to 115°C (bath temperature) for 2 h. The cold solution was neutralized with concentrated hydrochloric acid, the separated product was collected on a filter, washed with water and dried. Crystallization from toluene gave 66 mg (38%) of the benzyltriazolone *III*, m.p. 117–119°C; its IR and ^{1}H NMR spectra were identical with those of the compound prepared according to procedure *A*), also the mixture melting points showed no depression.

4-Benzyl-5-methyl-1,2,4-triazol-3(2*H*)-one (*V*)

A) Benzylation of 5-methyltriazolone *II* (ref.[3]; 198 mg; 2 mmol) was performed in the same manner as described for *I*. Chromatography on a column of silica gel (50 g) in ethyl acetate afforded 118 mg (21%) of sirupy 2,4-dibenzyl-5-methyl-1,2,4-triazol-3(2*H*)-one (*VI*). ^{1}H NMR spectrum (60 MHz, deuteriochloroform): 2·04 (s, 3 H, CH_3), 4·79 (s, 2 H, CH_2), 4·93 (s, 2 H, CH_2), 7·30 (s, 10 H, C_6H_5). For $C_{17}H_{17}N_3O$ (279·3) calculated: 73·09% C, 6·14% H, 15·04% N; found: 73·29% C, 6·23% H, 15·19% N.

The residue after evaporation of the second fraction was crystallized from toluene, yielding 96 mg (25%) of the monobenzyl derivative *V*, m.p. 142·5–145·5°C. ^{1}H NMR Spectrum (60 MHz, deuteriochloroform): 2·08 (s, 3 H, CH_3), 4·82 (s, 2 H, CH_2), 7·25 (s, 5 H, C_6H_5), 10·80 (broad s, 1 H, H_2). For $C_{10}H_{11}N_3O$ (189·2) calculated: 63·47% C, 5·86% H, 22·21% N; found: 63·32% C, 5·91% H, 22·20% N.

B) Finely ground 4-benzylsemicarbazide (330 mg; 2 mmol) was stirred with acetic anhydride (0·2 ml) for 1 h. The mixture was mixed with ether, the solid was filtered (345 mg) and heated with 10% aqueous potassium hydroxide solution (1·5 ml) to 120°C for 2 h. After cooling, the solution was neutralized with hydrochloric acid, the separated compound was filtered, washed with water and dried. Crystallization from toluene gave 260 mg (69%) of compound *V*, m.p. 143–146°C; no melting point depression on admixture with the compound prepared according to *A*). Also the ^{1}H NMR spectra of both compounds were identical.

4-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-1,2,4-triazol-3(2*H*)-one (*IXa*)

A) A mixture of triazolone *I* (800 mg; 12 mmol), hexamethyldisilazane (30 ml) and ammonium sulfate (30 mg) was heated for 4 h to 140°C (bath temperature). The solution was taken down *in vacuo*, the crystalline residue was codistilled with toluene (30 ml) and dissolved in a solution of 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide (prepared from 5·06 g, 10 mmol of 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose) in acetonitrile (20 ml). Mercuric bromide (1 g) and molecular sieves (Linde Molekularsieb 4 A; 2 g) were added and the mixture was stirred at room temperature for 4 h. The mixture was filtered, the solids were washed with acetonitrile (10 ml) and the solvent was evaporated *in vacuo*. The residue was dissolved in chloroform (100 ml), the solution was washed with 10% potassium iodide solution (3 × 40 ml), and water (2 × 40 ml), dried over magnesium sulfate and taken down *in vacuo*. The residue was crystallized from ethanol (500 ml) to give 2·07 g (42·5% based on 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose) of the diribosyltriazolone *Xa*, m.p. 231–236°C. IR Spectrum (chloroform): 1 732 cm^{-1} (C=O of benzoate), 1 692 cm^{-1} (C=O of triazolone). For $C_{54}H_{43}N_3O_{15}$ (973·9) calculated: 66·59% C, 4·45% H, 4·31% N; found: 66·48% C, 4·41% H, 4·23% N.

The mother liquors were stripped of the solvent and the residue was crystallized from ethanol (100 ml) affording 1·50 g (28% based on 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose) of the ribosyltriazolone *IXa*, m.p. 203–204°C. A further amount of *IXa* (0·6 g, 11%), m.p. 201–204°C, was obtained from the mother liquors by crystallization from ethanol. IR Spectrum (chloroform):

3 469 cm^{-1} (NH), 1 733 cm^{-1} (C=O benzoate, triazolone). For $C_{28}H_{23}N_3O_8$ (529·5) calculated: 63·51% C, 4·38% H, 7·94% N; found: 63·55% C, 4·42% H, 7·97% N.

B) A mixture of semicarbazide *XIV* (576 mg; 1 mmol), xylene (6 ml), hexamethyldisilazane (1·6 ml) and ammonium sulfate (7 mg) was refluxed for 10 h, cooled and taken down *in vacuo*. The residue was dissolved in methanol (3 ml) and 3 drops of water were added. The solution deposited 280 mg (53%) of *IXa*, m.p. 200–203°C. Infrared spectrum of this product was identical with that of the compound prepared by procedure *A*).

4-β-D-Ribofuranosyl-1,2,4-triazol-3(2*H*)-one (*IXb*)

A solution of the benzoyl derivative *IXa* (529 mg; 1 mmol) in 0·1 mol l^{-1} methanolic sodium methoxide (25 ml) was allowed to stand for 2 h at room temperature and neutralized with Dowex 50 (H^+; pre-washed with methanol). The ion exchange resin was filtered and washed with methanol (180 ml), the combined filtrates were taken down *in vacuo* and the residue was crystallized from methanol, affording 120 mg (56%) of compound *IXb*, m.p. 175–176°C. Chromatography of the mother liquors on a silica gel column (25 g) in ethyl acetate–acetone–ethanol–water (15 : : 3 : 4 : 3), followed by crystallization from methanol furnished further amount (48 mg; 22%) of *IXb*. IR Spectrum (KBr): 3 513 and 3 435 cm^{-1} (OH, NH), 1 702 and 1 669 cm^{-1} (C=O), 1 574 and sh 1 568 cm^{-1} (C=N). ^{1}H NMR Spectrum (60 MHz, hexadeuteriodimethyl sulfoxide): 3·38–3·60 (m, 2 H, $H_{5'}$), 3·69–4·40 (m, 3 H, $H_{2'}$, $H_{3'}$, $H_{4'}$), 4·81–5·43 (m, 4 H, $H_{1'}$, OH), 8·05 (s, 1 H, H_5), 11·75 (broad s, 1 H, H_2); after exchange with deuterium oxide: 3·48 (m, 2 H, $H_{5'}$), 3·69–4·40 (m, 3 H, $H_{2'}$, $H_{3'}$, $H_{4'}$), 5·28 (d, 1 H, $H_{1'}$, $J_{1',2'} = 6·0$), 8·05 (s, 1 H, H_5). For $C_7H_{11}N_3O_5$ (217·2) calculated: 38·71% C, 5·11% H, 19·35% N; found: 38·88% C, 5·13% H, 19·45% N.

2,4-Bis-(β-D-ribofuranosyl)-1,2,4-triazol-3(2*H*)-one (*Xb*)

The benzoyl derivative *Xa* (325 mg; 0·33 mmol) was shaken with 0·1 mol l^{-1} methanolic solution of barium methoxide (20 ml) at room temperature for 6 h. The mixture was saturated with carbon dioxide, water (1 ml) was added, followed by aqueous ammonia to slightly alkaline reaction. The precipitate was filtered through a layer of silica gel which was then washed with methanol until the eluate no more absorbed in the UV region. The combined filtrates were taken down *in vacuo* and the residue was crystallized from methanol to give 90 mg (76%) of the hemihydrate of *Xb*, m.p. 178·5–180·5°C. IR Spectrum (KBr): 1 642 cm^{-1} (C=O), 1 563 cm^{-1} (C=N); (dimethyl sulfoxide): 1 677 cm^{-1} (C=O), 1 568 cm^{-1} (C=N). For $C_{12}H_{19}N_3O_9 . 0·5\ H_2O$ (358·3) calculated: 40·22% C, 5·63% H, 11·73% N; found: 40·13% C, 5·83% H, 11·66% N.

4-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-5-methyl-1,2,4-triazol-3(2*H*)-one (*XIa*)

A) A mixture of the triazolone *II* (1·19 g; 12 mmol), hexamethyldisilazane (30 ml) and ammonium sulfate (30 mg) was heated to 140°C (bath temperature) for 4·5 h. After evaporation *in vacuo*, the residue was codistilled with toluene (30 ml). The thus-obtained silyl derivative was ribosylated in the same manner as described for the triazolone *I*. Chromatography of the crude product on a silica gel column (600 g) in toluene–ethyl acetate (3 : 2) afforded 3·23 g (59%) of the 4-ribosyl derivative *XIa* as a foam. ^{1}H NMR Spectrum (60 MHz, deuteriochloroform): 2·28 (s, 3 H, CH_3), 4·71 (m, 3 H, $H_{4'}$, $H_{5'}$), 5·73 (d, 1 H, $H_{3'}$, $J_{3',2'} = 3$), 6·20 (m, 2 H, $H_{1'}$, $H_{2'}$), 7·13–8·22 (m, 15 H, benzoate H), 10·10 (s, 1 H, H_2). For $C_{29}H_{25}N_3O_8$ (543·5) calculated: 64·08% C, 4·64% H, 7·73% N; found: 63·87% C, 4·75% H, 7·52% N.

The second UV-absorbing fraction afforded 0·75 g (14%) of the 2-ribosyl derivative *XIIa*, m.p. 170–172°C (toluene). ^{1}H NMR Spectrum (60 MHz, deuteriochloroform): 2·11 (s, 3 H, CH_3), 4·67 (s, 3 H, $H_{5'}$, $H_{4'}$), 6·13 (s, 3 H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 7·13–8·22 (m, 15 H, benzoate H), 11·60 (broad s, 1 H, H_4). For $C_{29}H_{25}N_3O_8$ (543·5) calculated: 64·08% C, 4·64% H, 7·73% N; found: 64·00% C, 4·70% H, 7·73% N.

B) A mixture of the semicarbazides *XVIa,b* (590 mg; 1 mmol), xylene (6 ml), hexamethyldisilazane (1·6 ml) and ammonium sulfate (7 mg) was refluxed for 12 h and taken down *in vacuo*. The residue was codistilled with toluene (6 ml) and methanol (6 ml) and chromatographed on a column of silica gel (50 g) in toluene–ethyl acetate (1 : 1), affording 271 mg (50%) of the triazolone *XIa* (foam). Its ^{1}H NMR spectrum was identical with that of the compound prepared by ribosylation of *II*. Also the ^{1}H NMR and IR spectra of the free ribosyltriazolone *XIb* prepared by methanolysis were identical with those of the compound obtained by ribosylation of *II* and subsequent methanolysis.

4-β-D-Ribofuranosyl-5-methyl-1,2,4-triazol-3(2*H*)-one (*XIb*)

A solution of the benzoyl derivative *XIa* (543 mg; 1 mmol) in 0·1 mol l^{-1} methanolic solution of sodium methoxide (15 ml) was set aside for 2 h at room temperature and neutralized with Dowex 50 (H^+; pre-washed with methanol). The Dowex was filtered, washed with methanol (20 ml) and the combined filtrates were taken down *in vacuo*. The residue was chromatographed on a column of silica gel (35 g) in ethyl acetate–acetone–ethanol–water (15 : 3 : 4 : 3) to give 145 mg (58%) of *XIb* as a solid foam. ^{1}H NMR Spectrum (60 MHz, hexadeuteriodimethyl sulfoxide): 2·18 (s, 3 H, CH_3), 3·37–3·60 (m, 2 H, $H_{5'}$), 3·67–5·15 (m, 3 H, $H_{2'}$, $H_{3'}$, $H_{4'}$), 4·15–5·17 (m, 3 H, OH), 5·25 (d, 1 H, $H_{1'}$, $J_{1',2'} = 6·5$), 11·43 (broad s, 1 H, H_2). For $C_8H_{13}N_3O_5.H_2O$ (249·2) calculated: 38·55% C, 6·07% H, 16·86% N; found: 38·64% C, 6·00% H, 16·73% N.

2-β-D-Ribofuranosyl-5-methyl-1,2,4-triazol-3(2*H*)-one (*XIIb*)

The title compound was obtained as a solid foam in 61% yield (141 mg) from the benzoyl derivative *XIIa* (543 mg; 1 mmol) as described for the methanolysis of *XIa*. ^{1}H NMR Spectrum (100 MHz, hexadeuteriodimethyl sulfoxide): 2·07 (s, 3 H, CH_3), 3·40 (m, 4 H, $H_{5'}$, OH), 3·74 (q, 1 H, $H_{4'}$, $J_{4',3'} = J_{4',5'} = 5$), 3·98 (t, 1 H, $H_{3'}$, $J_{3',2'} = J_{3',4'} = 5$), 4·25 (t, 1 H, $H_{2'}$, $J_{2',1'} = J_{2',3'} = 5$), 4·40–5·30 (broad d, 2 H, OH, H_4), 5·36 (d, 1 H, $H_{1'}$, $J_{1',2'} = 5$). For $C_8H_{13}N_3O_5$ (231·2) calculated: 41·56% C, 5·67% H, 18·17% N; found: 41·36% C, 5·80% H, 18·33% N.

(*E*)-1-Ethoxymethylene-4-phenylsemicarbazide (*XIII*)

Formic acid (10 µl) was added to a solution of 4-phenylsemicarbazide[7] (302 mg; 2 mmol) in a mixture of dichloromethane (25 ml) and triethyl orthoformate (5 ml). After standing at 20°C for 3 h, the mixture was concentrated *in vacuo* to about 5 ml and the separated crystals were collected; yield 337 mg (81%) of *XIII*, m.p. 142–144°C. IR Spectrum (chloroform, 0·003 mol l^{-1}): 3 392 cm^{-1} (NH): *c* 2%: 1 694 cm^{-1} (amide I), 1 658 cm^{-1} (C=N), sh 1 603, 1 595, 1 503 and 1 449 cm^{-1} (ring), 1 538 cm^{-1} (amide II), 1 391 cm^{-1} (CH_3, OC_2H_5), sh 1 122 cm^{-1} (amide III), 1 100 cm^{-1} (CH_3, OC_2H_5), 861 cm^{-1} (N=CH); CCl_4, 0·003 mol l^{-1}: 3 402·5 cm^{-1}; saturated solution: 1 709 cm^{-1} (amide I), 1 652 cm^{-1} (C=N), 1 600 and 1 448 cm^{-1} (ring), 1 540 cm^{-1} (amide II). ^{1}H NMR Spectrum (60 MHz, hexadeuteriodimethyl sulfoxide): 1·12 (t, 3 H, CH_3, $J_{CH_3,CH_2} = 7$), 3·20 (s, 1 H, CH), 4·02 (q, 2 H, CH_2, $J_{CH_2,CH_3} = 7$), 6·68–7·60 (m, 5 H, C_6H_5), 6·67 (s, 1 H, NH), 8·98 (s, 1 H, NH). For $C_{10}H_{13}N_3O_2$ (207·2) calculated: 57·96% C, 6·32% H, 20·28% N; found: 57·89% C, 6·25% H, 20·53% N.

(*Z*)- and (*E*)-1-(1-Ethoxyethylidene)-4-phenylsemicarbazide (*XVa* and *XVb*)

Formic acid (40 μl) was added to a cold (+3°C) solution of 4-phenylsemicarbazide (605 mg; 4 mmol) in a mixture of dichloromethane (50 ml) and triethyl orthoacetate (10 ml). After standing for 1 h at 3°C, the solution was concentrated *in vacuo* to about 10 ml and light petroleum (50 ml) was added. The precipitate was filtered and chromatographed on a column of silica gel (140 g) in toluene–ethyl acetate (1 : 1). The first fraction was stripped of the solvents and the residue on crystallization from 2-propanol gave 385 mg (43·5%) of *XVa*, m.p. 157–159°C. The mother liquors furnished another portion (29 mg; 3%) of the product. IR Spectrum (chloroform, 0·003 mol l^{-1}): 3 392 cm^{-1} (free NH); 2%: 3 391 cm^{-1} (free NH), 3 214 cm^{-1} (bonded NH), 1 690 cm^{-1} (amide I), 1 666 cm^{-1} (C=N), sh 1 602, 1 595, sh 1 504 and 1 449 cm^{-1} (ring), 1 538 cm^{-1} (amide II), 1 379 cm^{-1} (CH_3), 1 308 cm^{-1} (C_6H_5—N); tetrachloromethane, 0·003 mol . . l^{-1}: 3 394·5 cm^{-1} (free NH), 3 205 and 3 100 cm^{-1} (bonded NH), 1 694·5 cm^{-1} (amide I); saturated solution: 3 392 cm^{-1} (free NH), 3 205 and 3 098 cm^{-1} (bonded NH), 1 693 cm^{-1} (amide I), 1 667 cm^{-1} (C=N), sh 1 603, 1 595, sh 1 504 and 1 449 cm^{-1} (ring), 1 539 cm^{-1} (amide II); ^{1}H NMR spectrum (60 MHz, deuteriochloroform): 1·36 (t, 3 H, CH_3, J_{CH_3,CH_2} = 7), 2·11 (s, 3 H, CH_3), 4·15 (q, 2 H, CH_2, J_{CH_2,CH_3} = 7), 6·96–7·60 (m, 5 H, C_6H_5), 7·95 (broad s, 1 H, N^4—H), 10·09 (broad s, 1 H, N^2—H). For $C_{11}H_{15}N_3O_2$ (221·25) calculated: 59·71% C, 6·83% H, 18·99% N; found: 59·93% C, 6·86% H, 19·06% N.

The second fraction after evaporation and crystallization from 2-propanol gave 58 mg (6·5%) of the (*E*)-isomer *XVb*, m.p. 123–126°C. IR Spectrum (chloroform, 0·003 mol l^{-1}): 3 393 cm^{-1} (free NH); 2%: 3 393 cm^{-1} (NH), 1 686 cm^{-1} (amide I), sh 1 666 cm^{-1} (C=N), sh 1 602, 1 595, sh 1 504 and 1 450 cm^{-1} (ring), 1 540 cm^{-1} (amide II), 1 383 cm^{-1} (CH_3), 1 306 cm^{-1} (C_6H_5—N); tetrachloromethane, 0·003 mol l^{-1}: 3 401·5 cm^{-1} (NH), 1 711 cm^{-1} (amide I), 1 667 cm^{-1} (C=N); saturated solution: 1 701 cm^{-1} (amide I), sh 1 667 cm^{-1} (C=N), 1 604, 1 595, 1 501 and 1 448 cm^{-1} (ring), 1 537 cm^{-1} (amide II). ^{1}H NMR Spectrum (60 MHz, deuteriochloroform): 1·32 (t, 3 H, CH_3, J_{CH_3,CH_2} = 7), 2·05 (s, 3 H, CH_3), 4·07 (q, 2 H, CH_2, J_{CH_2,CH_3} = 7), 6·80–7·70 (m, 5 H, C_6H_5), 7·91 (broad s, 1 H, NH), 8·00 (broad s, 1 H, NH). For $C_{11}H_{15}N_3O_2$ (221·25) calculated: 59·71% C, 6·83% H, 18·99% N; found: 59·48% C, 6·92%H, 19·24% N.

(*E*)-4-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-1-ethoxymethylenesemicarbazide (*XIV*)

Formic acid (20 μl) was added to a solution of 4-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)semicarbazide[6] (1·04 g; 2 mmol) in dichloromethane (30 ml) and triethyl orthoformate (6 ml). After standing for 4 h at room temperature, the solution was concentrated to 2 ml and mixed with light petroleum. The precipitate was filtered and washed with light petroleum, affording 1·13 g (98%) of compound *XIV*, m.p. 143–146°C. An analytical sample was crystallized from ethanol; m.p. 145–147°C. IR Spectrum (chloroform, 2%): 3 400 cm^{-1} (NH), 1 694 cm^{-1} (amide I), 1 531 cm^{-1} (amide II), 1 436, 1 391 and 1 046 cm^{-1} (O C_2H_5); tetrachloromethane, saturated solution: 3 403 cm^{-1} (NH), 1 731 cm^{-1} (C=O benzoate), sh 1 706 cm^{-1} (amide I), sh 1 653 cm^{-1} (C=N), 1 603, 1 589, sh 1 501 cm^{-1} (ring), 1 521 cm^{-1} (amide II). ^{1}H NMR Spectrum (60 MHz, deuteriochloroform): 1·28 (t, 3 H, CH_3, J_{CH_3,CH_2} = 7), 4·04 (q, 2 H, CH_2, J_{CH_2,CH_3} = = 7), 4·61 (broad s, 3 H, $H_{4'}$, $H_{5'}$), 5·48–6·23 (m, 3 H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 6·27 (s, 1 H, CH), 6·80 (d, 1 H, NH, $J_{NH,1'}$ = 9), 7·10–8·22 (m, 16 H, NH, C_6H_5CO). For $C_{30}H_{29}N_3O_9$ (575·55) calculated: 62·60% C, 5·08% H, 7·30% N; found: 62·55% C, 5·03% H, 7·29% N.

(*Z*)- and (*E*)-4-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-1-(1-ethoxyethylidene)semicarbazide (*XVIa* and *XVIb*)

A solution of 4-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)semicarbazide[6] (519 mg; 1 mmol) in dichloromethane (15 ml) and triethyl orthoacetate (3 ml) was cooled to +3°C and formic acid (30 μl) was added. After standing at +3°C for 2 h, the solution was concentrated *in vacuo* to about 3 ml and mixed with light petroleum (20 ml). The oil was separated and chromatographed on a column of silica gel (200 g) in toluene–ethyl acetate (1 : 1). The (*Z*)-isomer *XVa* was eluted first and was obtained as a solid foam (342 mg, 58%). IR Spectrum (tetrachloromethane, 0·003 mol. $.l^{-1}$): 3 400 cm^{-1} (N^4H), 3 208 cm^{-1} (N^2H); saturated solution: 3 400 cm^{-1} (N^4—H), 3 208 cm^{-1} (N^2H), 1 733 cm^{-1} (C=O benzoate), 1 692 cm^{-1} (amide I), sh 1 672 (C=N), 1 604, 1 585 and sh 1 496 cm^{-1} (ring), 1 528 cm^{-1} (amide II), 1 379 cm^{-1} (CH_3). ^1H NMR Spectrum (60 MHz, deuteriochloroform): 1·17 (t, 3 H, CH_3, $J_{CH_3,CH_2} = 7$), 1·92 (s, 3 H, CH_3), 3·90 (q, 2 H, CH_2, $J_{CH_2,CH_3} = 7$), 4·60 (broad s, 3 H, $H_{4'}$, $H_{5'}$), 5·48—6·15 (m, 3 H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 6·70 (d, 1 H, NH, $J_{NH,1'} = 9$), 7·17—8·23 (m, 16 H, NH, C_6H_5CO). For $C_{31}H_{31}N_3O_9$ (589·6) calculated: 63·15% C, 5·30% H, 7·13% N; found 63·41% C, 5·18% H, 6·95% N.

The second fraction gave 165 mg (28%) of the (*E*)-isomer *XVIb* as a solid foam. IR Spectrum (tetrachloromethane): 3 403 cm^{-1} (NH), 1 731 cm^{-1} (CO benzoate), sh 1 706 cm^{-1} (amide I), sh 1 653 cm^{-1} (C=N), 1 603, 1 589 and sh 1 501 cm^{-1} (ring), 1 521 cm^{-1} (amide II). ^1H NMR Spectrum (60 MHz, deuteriochloroform): 1·28 (t, 3 H, CH_3, $J_{CH_3,CH_2} = 7$), 1·93 (s, 3 H, CH_3), 4·05 (q, 2 H, CH_2, $J_{CH_2,CH_3} = 7$), 4·63 (broad s, 3 H, $H_{4'}$, $H_{5'}$), 5·50—6·30 (m, 3 H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 6·82 (d, 1 H, NH, $J_{NH,1'} = 9$), 7·17—8·30 (m, 16 H, NH, C_6H_5CO). For $C_{31}H_{31}N_3O_9$ (589·6) calculated: 63·15% C, 5·30% H, 7·13% N; found: 63·43% C, 5·20% H, 6·91% N.

4-Phenyl-1,2,4-triazol-3(2*H*)-one (*VII*)

A mixture of the semicarbazone *XIII* (207 mg; 1 mmol), hexamethyldisilazane (6 ml) and ammonium sulfate (3 mg) was refluxed for 8 h at 140°C (bath). The residue after evaporation *in vacuo* was codistilled with toluene (2 × 5 ml) and crystallized from methanol, affording 93 mg (58%) of the triazolone *VII*, m.p. 186—187·5°C (reported[8] m.p. 189°C). The mother liquors gave another 34 mg (21%) of the product. ^1H NMR Spectrum (60 MHz, hexadeuteriodimethyl sulfoxide): 7·20—7·85 (m, 5 H, C_6H_5), 8·40 (s, 1 H, H_5), 11·97 (broad s, 1 H, H_2).

5-Methyl-4-phenyl-1,2,4-triazol-3(2*H*)-one (*VIII*)

A mixture of (*Z*)- and (*E*)-semicarbazones *XVa,b* (111 mg; 0·5 mmol), hexamethyldisilazane (6 ml) and ammonium sulfate (3 mg) was refluxed for 5 h and taken down *in vacuo*. The residue was codistilled with toluene (2 × 5 ml) and dissolved in aqueous methanol. After 15 min, the solvent was evaporated and the residue was crystallized from 2-propanol to give 47 mg (51%) of compound *VIII* as a hemihydrate, m.p. 154—156°C (reported[8] m.p. 155°C and 154°C (ref.[9]); the cited references[8,9] do not describe *VIII* as a hemihydrate). ^1H NMR Spectrum (60 MHz, deuteriochloroform): 2·12 (s, 3 H, CH_3), 7·17—7·61 (m, 5 H, C_6H_5), 10·83 (broad s, 1 H, H_2).

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REFERENCES

1. Kára J., Bártová M., Ryba M., Hřebabecký H., Brokeš J., Novotný L., Beránek J.: This Journal *47*, 2824 (1982).
2. Runti C., D'Osualdo V., Ulian F.: Ann. Chim. (Rome) *49*, 1668 (1959); Chem. Abstr. *54*, 22 602 h (1960).
3. Kröger C.-F., Hummel L., Mutscher M., Beyer H.: Chem. Ber. *98*, 3025 (1965).
4. Daunis J., Roumestant M.-L.: Bull. Soc. Chim. Fr. *1975*, 1191.
5. Turkevich N. M., Vvedenskii V. M., Petlichnaya L. M.: Ukr. Khim. Zh. *27*, 680 (1961); Chem. Abstr. *56*, 14 254 e (1962).
6. Hřebabecký H., Točík Z., Beránek J.: This Journal *44*, 1475 (1979).
7. Wheeler A. S.: Org. Syn., Coll. Vol. *I*, 450 (1946).
8. Gehlen H., Schade W.: Justus Liebigs Ann. Chem. *675*, 180 (1964).
9. Gehlen H., Dosk J., Cermak J.: Justus Liebigs Ann. Chem. *639*, 100 (1961).

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