Synthesis of *C*-Nucleosides. Part 14.[1] 5(3)-Glycosyl-1,2,4-triazole-3(5)-carboxamides as Analogues of Ribavirin

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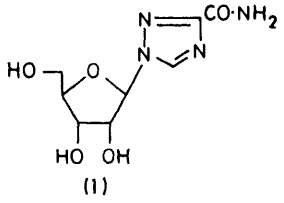
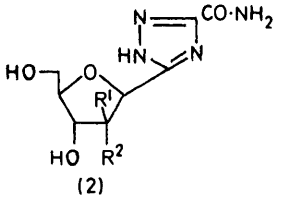
Alkyl thioimidates react with hydrazides of methyl hydrogen oxalate and oxamic acid to yield methyl 1,2,4-triazole-3(5)-carboxylates and -carboxamides. Ribo-, deoxyribo- and arabino-*C*-nucleoside analogues of ribavirin have been prepared and their structures established by n.m.r. and mass spectrometry.

THE synthetic nucleoside analogue 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (ribavirin) (1) possesses broad-spectrum activity against both RNA and DNA viruses *in vitro* and *in vivo*.[2] Various modifications which have been made in the carboxamide group,[3] the site of glycosylation,[4] and the glycosyl moiety [5] did not result in a more active nucleoside. Our interest in *C*-nucleosides led us to consider the synthesis of compounds (2), structurally related to ribavirin.



(1)



(2)

	R^1	R^2
a;	H	OH
b;	H	H
c;	OH	H

Although many routes to 3,5-disubstituted 1,2,4-triazoles are theoretically possible, those permitting access to their carboxylic derivatives are fewer, and of limited use in carbohydrate chemistry. For instance, the carboxylic acids can be prepared by selective oxidation of alkyl [6] or bicyclic [7,8] triazoles, and the corresponding esters have been obtained in two steps from ethyl (ethoxycarbonyl)thioformimidate.[9] As the condensation of hydrazides with imino-ethers seemed a

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[2] R. W. Sidwell, J. H. Huffman, G. P. Khare, L. B. Allen, J. T. Witkowski, and R. K. Robins, *Science*, 1972, **177**, 705; J. T. Witkowski, R. K. Robins, R. W. Sidwell, and L. N. Simon, *J. Medicin. Chem.*, 1972, **15**, 1150; T. H. Maugh, jun., *Science*, 1976, **192**, 128.
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[4] S. R. Naik, J. T. Witkowski, and R. K. Robins, *J. Heterocyclic Chem.*, 1974, **11**, 57.
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[6] T. N. Vereshchagina and V. A. Lopyreu, *Khim. geterotsikl. Soedinenii*, 1970, 1695 (*Chem. Abs.*, 1971, **74**, 99,951y).
[7] K. T. Potts, H. R. Burton, and S. K. Roy, *J. Org. Chem.*, 1966, **31**, 265.
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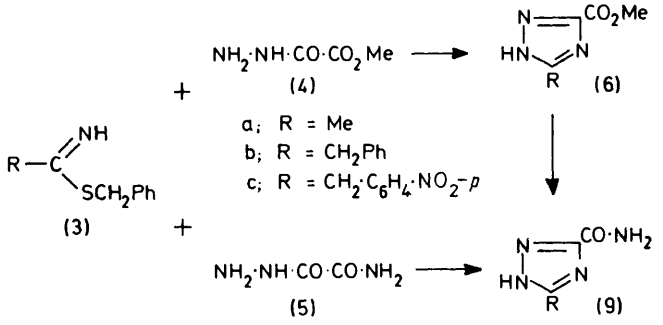
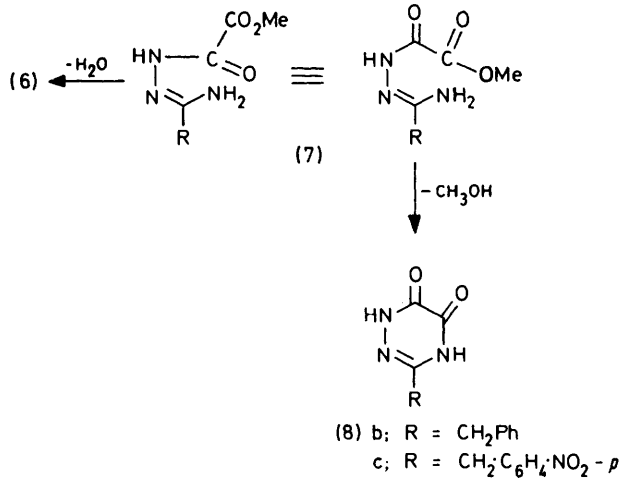
convenient route to 3,5-disubstituted 1,2,4-triazoles,[10,11] we decided to study, as model reactions, the cyclizations of alkyl thioimidates (3) with hydrazides of methoxalic (4) and oxamic (5) acids (Scheme 1).



SCHEME 1

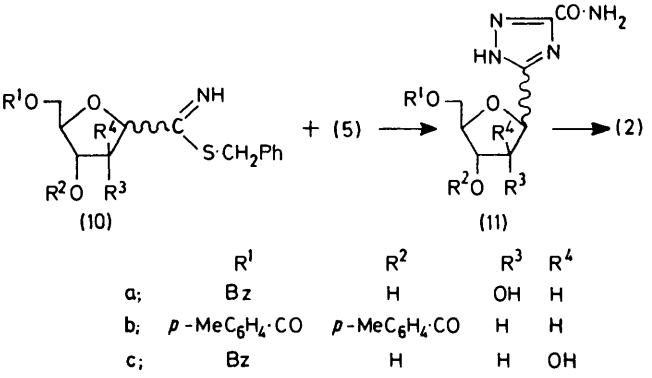
In pyridine at reflux, the reaction between benzyl thioacetimidate (3a) and methyl hydrogen oxalate hydrazide (4) gives a 37% yield of the 1,2,4-triazole (6a).[9] The condensation of methyl acetimidate with ethyl hydrogen oxalate hydrazide has been described as not yielding triazoles;[10a] this discrepancy may be explained by the greater stability of the methyl ester (4) than the ethyl analogue, the greater reactivity of the thioimidate, and the use of boiling pyridine as solvent.



In the same way, benzyl phenyl- and *p*-nitrophenyl-thioacetimidates (3b and c) gave, respectively, 28 and 20% yields of methyl 1,2,4-triazole-3(5)-carboxylates (6b and c). However, in these reactions, an *as*-triazinedione (8) was also isolated (20%). Its formation is not surprising since the cyclization of the intermediate acyl amidrazone (7) may proceed *via* elimination of water as well as of methanol.

Ethanolic ammonia under pressure converts the triazole esters (6a—c) into the corresponding amides (9a—c). The amides (9b and c) have also been obtained directly (50 and 42% yield) from the thioimidates (3b and c) and oxamic acid hydrazide (5). However, under the same conditions, we were unable to isolate compound (9a) from (3a).

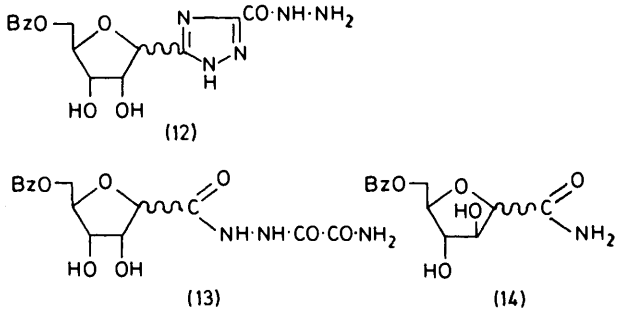
The condensation of the hydrazide (5) (Scheme 2) with benzyl (5-*O*-benzoyl-D-ribofuranosyl)thioformimidate (10a) gave a 21% yield of the triazole (11a) and two by-products assigned structures (12) and (13). Methanolic ammonia at room temperature debenzoylated the amide (11a) quantitatively to afford 5(3)-β-D-ribofuranosyl-1,2,4-triazole-3(5)-carboxamide (2a), the *C*-nucleoside isomer of ribavirin (1). The anomeric configuration was determined by direct measurement of the distance between H-1′ and H-2′ by n.m.r.[12] This distance in a ribonucleoside varies from 2.73 to 3.07 Å, between the two extreme conformers (N and S) for the



SCHEME 2

β-anomer, and from 2.34 to 2.43 Å for the α-anomer. The spin-lattice relaxation time T_1 at 250 MHz gives a mean value of 2.75 Å (±0.15 Å), which indicates definitively a β-configuration.

In the deoxyribose series, the formation of the triazolecarboxamide proceeds in higher yield: condensation of the thioimidate (10b) with the hydrazide (5) gave a



53% yield of a mixture of anomers (11b). Detoluoylation as for the ribonucleoside, gave the 5(3)-(2-deoxy-α- and β-D-*erythro*-pentofuranosyl)-1,2,4-triazole-3(5)-carboxamides (2b). Separation of anomers was achieved by

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chromatography on silica [for the nucleosides (11b)] or on Sephadex gel [for the nucleosides (2b)] (β : α 4 : 1).

The configuration of the deoxynucleosides was assigned by the n.m.r. on the basis of the criteria previously described.[13,14] In the case of the protected nucleoside (11b) β-anomer a difference of 0.06 p.p.m. was observed between the two doublets due to the *ortho*-protons of the toluoyl group; in the case of the α-anomer, this difference is larger (0.30 p.p.m.). This attribution was confirmed with the nucleosides (2b): the H-1′ signal is broader for the β-anomer ($J_{1',2'a} + J_{1',2'b}$ = 15.3 Hz) than for the α-anomer ($J_{1'2'a} + J_{1'2'b}$ = 14 Hz).

With the arabinosylthioimidate (10c), the condensation gives, besides a 9% yield of the amide (14), a 23% yield of the nucleoside (11c), which is debenzoylated to give 5(3)-arabinofuranosyl-1,2,4-triazole-3(5)-carboxamide (2c). The configuration is tentatively assigned as α, based on previous work [15] with the same thioimidate (10c) which always gave the α-anomer predominantly. Moreover, the anomeric proton H-1′ in the nucleoside (11c) has the same chemical shift (δ 4.86) as in the 5′-*O*-benzoyl ribonucleoside (11a), indicative of a *cis*-configuration with the 2′-OH [a *trans*-configuration (β-anomer) would result in a downfield shift]. The optical rotations of the arabinosyl nucleosides (11c) and (2c) are opposite to those of the ribosyl series whose configuration is β.

The mass spectra of the triazoles (2) show the characteristic peaks of *C*-nucleosides: low intensity for the ions BH (*m/e* 112) or B + 2H (113) and a major peak at *M* − 89 [155 for (2a and c) and 139 for (2b)]. In the case of a pair of anomers, such as (2b), the ion at *M* − 31 (197) has a greater intensity in the spectrum of the β-anomer than in that of the α-anomer.[14]

Compounds (2a and b) showed no inhibition of viral replication.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage aparatus. I.r. and u.v. spectra were obtained with a Perkin-Elmer 21 or 237 and a Perkin-Elmer 137 UV or Cary 118 C instrument. Unless stated otherwise, n.m.r. spectra were recorded with a Varian XL 100 spectrometer [solvent $(CD_3)_2SO$; Me_4Si as internal standard]. Mass spectra were recorded with a Varian CH7 or A.E.I. MS9 instrument and optical rotations were measured with a Perkin-Elmer 241 MC spectropolarimeter.

Analytical t.l.c. was carried out on Merck silica gel $HF_{254+366}$ (0.25 mm thickness), and spots were located with a u.v. lamp (λ 254 nm). Column chromatography was carried out with Mallinckrodt Silicar (100 mesh; grade I).

Methyl 5(3)-*Methyl*-1,2,4-*triazole*-3(5)-*carboxylate* (6a).—A solution of the hydrazide (4) [16] (5.9 g, 50 mmol) and benzyl thioacetimidate (3a) (10.1 g, 50 mmol) in dry pyridine (100 ml) was stirred at room temperature for 3 h, then heated under reflux for 3 h, and evaporated. The residue was dissolved in boiling dimethylformamide (100 ml), and the solution filtered and cooled to yield the triazole (6a) (2.6 g, 37%), m.p. 228° (from H_2O) (lit.,[10] 231°), $\nu_{max.}$ (KBr) 1 732 cm^{-1}, R_F 0.31 (benzene–ethanol 4 : 1) (Found: C, 42.65; H, 5.05; N, 29.6. Calc. for $C_5H_7N_3O_2$: C, 42.55; H, 5.0; N, 29.8%).

Methyl 5(3)-*Benzyl*-1,2,4-*triazole*-3(5)-*carboxylate* (6b).—The procedure was similar. The solution in pyridine was heated under reflux for 3 h, treated as above with hot water, filtered to remove an oil, and evaporated to dryness. The residual solid was extracted with boiling xylene. The extracts give, on cooling, the *triazole* (6b) (28%), m.p. 175—177°, $\nu_{max.}$ (KBr) 1 740 cm^{-1}, R_F 0.49 (benzene–ethanol 4 : 1) (Found: C, 60.85; H, 4.9; N, 19.45. $C_{11}H_{11}N_3O_2$ requires C, 60.85; H, 5.05; N, 19.35%). The insoluble fraction was recrystallized from ethanol to yield 3-*benzyl*-1,2,4-*triazine*-5,6-*dione* (8b) (20%), m.p. 254°, $\nu_{max.}$ (KBr) 1 720 and 1 677 cm^{-1}, R_F 0.38 (benzene–ethanol 4 : 1) (Found: C, 59.05; H, 4.35; N, 20.85. $C_{10}H_9N_3O_2$ requires C, 59.1; H, 4.45; N, 20.7%).

Methyl 5(3)-p-*Nitrobenzyl*-1,2,4-*triazole*-3(5)-*carboxylate* (6c).—This was prepared as for (6b). The residue solid was extracted with methanol. The extract afforded the *triazole* (6c) (20%), m.p. 260°, $\nu_{max.}$ (KBr) 1 710 cm^{-1}, R_F 0.61 (benzene–ethanol 4 : 1) (Found: C, 50.65; H, 4.0; N, 21.25. $C_{11}H_{10}N_4O_4$ requires C, 50.4; H, 3.85; N, 21.35%). The residue gave the *triazinedione* (8c) (1 g, 20%), m.p. 285—287°, $\nu_{max.}$ (KBr) 1 720 and 1 650 cm^{-1}, R_F 0.30 (benzene–ethanol 4 : 1) (Found: C, 48.0; H, 3.3; N, 22.85. $C_{10}H_8N_4O_4$ requires C, 48.4; H, 3.25; N, 22.6%).

5(3)-*Methyl*-1,2,4-*triazole*-3(5)-*carboxamide* (9a).—A solution of the ester (6a) (3 g) in ethanolic ammonia (150 ml) was heated in a sealed vessel at 100 °C for 3 h. Recrystallization from acetonitrile gave the *amide* (9a) (1 g, 37%), m.p. 221—225°, $\nu_{max.}$ (KBr) 1 685 cm^{-1}, R_F 0.17 (benzene–ethanol 4 : 1) (Found: C, 38.1; H, 4.8; N, 44.45. $C_4H_6N_4O$ requires C, 37.95; H, 4.75; N, 44.65%).

5(3)-*Benzyl*-1,2,4-*triazole*-3(5)-*carboxamide* (9b). The *amide* (9b), prepared from (6b) as above (47%), had m.p. 225—228° (from ethanol–benzene), $\nu_{max.}$ (KBr) 1 648 cm^{-1}, R_F 0.26 (benzene–ethanol 4 : 1) (Found: C, 59.15; H, 4.85; N, 27.9. $C_{10}H_{10}N_4O$ requires C, 59.4; H, 5.0; N, 27.7%). Identical material was obtained from the hydrazide (5) (21 g, 20 mmol) and (3b) (5.6 g, 20 mmol) in pyridine (100 ml) under reflux for 16 h, by extraction of the residue with hot water (yield 2 g, 50%).

5(3)-p-*Nitrobenzyl*-1,2,4-*triazole*-3(5)-*carboxamide* (9c).—The *amide* (9c) was similarly obtained from (6c) (45%); m.p. 245° (from methanol), $\nu_{max.}$ (KBr) 1 670 cm^{-1}, R_F 0.26 (benzene–ethanol 4 : 1) (Found: C, 48.7; H, 3.75; N, 28.3. $C_{10}H_9N_5O_3$ requires C, 48.6; H, 3.65; N, 28.35%), and also from (3c) (6.5 g, 20 mmol) (yield 2 g, 42%).

5(3)-(5-O-*Benzoyl*-β-D-*ribofuranosyl*)-1,2,4-*triazole*-3(5)-*carboxamide* (11a).—A solution of the hydrazide (5) (3.3 g, 32 mmol) and the thioimidate (10a) (13.5 g, 31.8 mmol) in dry pyridine (50 ml) was heated under reflux for 15 h, then evaporated to dryness. The solid was dissolved in aqueous ethanol and neutralized to pH 7 with N-sodium hydroxide. Concentration gave a residue which was chromatographed over silica (300 g) with chloroform–ethanol (9 : 1) then chloroform–ethanol–acetic acid (89 : 10 : 1) as eluant to

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[14] T. Huynh-Dinh, A. Kolb, C. Gouyette, J. Igolen, and S. Tran Dinh, *J. Org. Chem.*, 1975, **40**, 2825.

[15] G. Barnathan, T. Huynh-Dinh, A. Kolb, and J. Igolen, *European J. Medicin. Chem.*, 1976, **11** (1), 67; G. Barnathan, Thèse Doctorat 3ème Cycle, June 1974, Paris.

[16] J. S. Zmuszkovicez and M. E. Greig, *J. Medicin. Chem.*, 1961, **4**, 259.

yield: (*a*) the *riboside* (11a) (2.28 g, 21%), m.p. 117°, $[\alpha]_D$ −10° (*c* 0.29 in Me_2N·CHO), δ 7.92—7.60 (5 H aromatic), 4.86 (H-1′, d, $J_{1',2'}$ 4 Hz), and 4.20 (m, other glycosyl protons), *m/e* 348 (M^+), R_F 0.39 (chloroform–ethanol 4 : 1) (Found: C, 51.45; H, 5.05; N, 16.45. $C_{15}H_{16}N_4O_6$ requires C, 51.7; H, 4.65; N, 16.1%); (*b*) the corresponding *hydrazide* (12) (0.14 g), m.p. 200°, $\nu_{max.}$ (KBr) 1 720, 1 690, and 1 670 cm^{-1}, *m/e* 363 (M^+), R_F 0.34 (chloroform–ethanol 4 : 1) (Found: C, 49.35; H, 4.8; N, 19.1. $C_{15}H_{17}N_5O_6$ requires C, 49.5; H, 4.7; N, 19.3%); and (*c*) the *oxamoylhydrazino-derivative* (13) (0.07 g), m.p. 219°, $\nu_{max.}$ (KBr) 1 710, 1 690, and 1 670 cm^{-1}, *m/e* 367 (M^+), R_F 0.13 (chloroform–ethanol 4 : 1) (Found: C, 48.95; H, 4.75; N, 11.45. $C_{15}H_{17}N_3O_8$ requires C, 49.05; H, 4.65; N, 11.45%).

5(3)-β-D-*Ribofuranosyl*-1,2,4-*triazole*-3(5)-*carboxamide* (2a).—The ester (11a) was quantitatively debenzoylated with methanolic ammonia at room temperature for 48 h. The *product* (2a) had m.p. 195°, $[\alpha]_D$ −10° (*c* 0.23 in H_2O), $\nu_{max.}$ (KBr) 1 675 cm^{-1}: δ (250 MHz; D_2O) 5.03 (d, H-1′, $J_{1',2'}$ 6.1 Hz), 4.38 (H-2′, $J_{2,'3'}$ 5.3 Hz), 4.24 (H-3′, $J_{3',4'}$ 4.9 Hz), 4.12 (H-4′, $J_{4',5'a}$ 3.4 Hz), 3.86 (H-5′a, $J_{4',5'a}$ 4.9 Hz), and 3.74 (H-5′b, $J_{5'a,5'b}$ 12.5 Hz), *m/e* 224 (M^+, 1%), 213 (M − 30, 14), 155 (M − 89, 100), 141 (B + 30, 80), and 112 (BH, 32), R_F 0.32 (ethyl acetate–ethanol 4 : 1) (Found: C, 39.4; H, 5.3; N, 22.45. $C_8H_{12}N_4O_5$ requires C, 39.35; H, 4.95; N, 22.95%).

5(3)-(2-*Deoxy*-3,5-*di*-O-p-*toluoyl*-α- *and* -β-D-erythro-*pentofuranosyl*)-1,2,4-*triazole*-3(5)-*carboxamides* (11b).—The same procedure as for (11a) with the thioimidate (10b) (22.4 g, 41.5 mmol) and (5) (4.28 g, 41.5 mmol) gave a residue which was chromatographed over silica (300 g) with ethyl acetate. A second chromatography with the same eluant gave (*a*) the β-*anomer* of (11b) (8.1 g, 42%), m.p. 214°, $[\alpha]_D$ −10° (*c* 0.29 in Me_2N·CHO) δ 5.53 (H-1′), 2.70 (2 H-2′), 5.60 (H-3′), 4.47 (H-4′ and 2 H-5′), 7.95 and 7.87 (aromatic H_o), and 7.39 and 7.34 (aromatic H_m), *m/e* 464 (M^+), R_F 0.75 (chloroform–ethanol 10 : 1) (Found: C, 61.8; H, 5.35; N, 12.15. $C_{24}H_{24}N_4O_6$ requires C, 62.05; H, 5.2; N, 12.05%); and (*b*) the α-*anomer* (2.1 g, 11%), m.p. 120°, $[\alpha]_D$ +32° (*c* 0.29 in Me_2N·CHO), δ 5.53 (H-1′ and -3′), 2.89 and 2.60 (2 H-2′), 4.59 (H-4′), 4.49 (2 H-5′), 7.93 and 7.62 (aromatic H_o), and 7.36 and 7.76 (aromatic H_m), *m/e* 464 (M^+), R_F 0.65 (chloroform–ethanol 10 : 1) (Found: C, 62.45; H, 5.5; N, 11.7. $C_{24}H_{24}N_4O_6$ requires C, 62.05; H, 5.2; N, 12.0%).

5(3)-(2-*Deoxy*-α- *and* -β-D-erythro-*pentofuranosyl*)-1,2,4-*triazole*-3(5)-*carboxamides* (2b).—The mixture of anomers (11b) was quantitatively detoluoylated with methanolic ammonia at room temperature (3 weeks). The anomers were separated on Sephadex G-10 gel (60 g) to yield (*a*) the β-*anomer* of (2b), m.p. 204—206°, $[\alpha]_D$ +50° (*c* 0.28 in H_2O), $\nu_{max.}$ (KBr) 1 675 cm^{-1}, δ 5.13 (H-1′, $J_{1',2'a}$ 6.6 Hz), 2.23 (H-2′a, $J_{1',2'a}$ 8.7 Hz), 2.13 (H-2′b, $J_{2'a,2'b}$ 12.7 Hz), 4.22 (H-3′, $J_{2'a,3'}$ 2.8, $J_{2'b,3'}$ 5.3 Hz), 3.80 (H-4′, $J_{3',4'}$ 2.5 Hz), and 3.42 (H-5′a and -5′b, $J_{4',5'a}$ 5.2, $J_{5'a,5'b}$ 0 Hz), *m/e* 229 (M + 1, 1%), 197 (M − 31, 15), 181 (M − 47, 17), 139 (B + 28, 100), and 113 (B + 2, 10), R_F 0.33 (chloroform–ethanol 4 : 1) (Found: C, 42.0; H, 5.45; N, 24.1. $C_8H_{12}N_4O_4$ requires C, 42.1; H, 5.3; N, 24.55%); and (*b*) the α-*anomer*, m.p. 70—75°, $[\alpha]_D$ −11° (*c* 0.07 in H_2O), $\nu_{max.}$ (KBr) 1 675 cm^{-1}, δ 5.14 (H-1′, $J_{1',2'a} = J_{1',2'b}$ = 7.0 Hz), 2.48 (H-2′a), 2.21 (H-2′b), 4.52 (H-3′), 3.90 (H-4′), 3.49 (H-5′a), and 3.45 (H-5′b), *m/e* 197 (M − 31, 11%), 181 (M − 47, 39), 139 (B + 28, 100), and 113 (B + 2, 11); R_F 0.26 (chloroform–ethanol 4 : 1) (Found: C, 39.75; H, 5.7; N, 22.7. $C_8H_{12}N_4O_4.H_2O$ requires C, 39.0; H, 5.75; N, 22.75%).

5(3)-(5-O-*Benzoyl*-α-D-*arabinofuranosyl*)-1,2,4-*triazole*-3(5)-*carboxamide* (11c).—By the same procedure as for (11a), the thioimidate (10c) (5.33 g, 12.6 mmol) gave (*a*) 5-O-*benzoylarabinofuranosylformamide* (14) (0.3 g, 9%), m.p. 135—137°, *m/e* 281 (M^+), R_F 0.38 (chloroform–ethanol 5 : 1) (Found: C, 55.6; H, 5.65; N, 5.6. $C_{13}H_{15}NO_6$ requires C, 55.5; H, 5.35; N, 5.0%); and (*b*) the *arabinoside* (11c) (1 g, 23%), m.p. 172°, $[\alpha]_D$ +18° (*c* 0.08 in Me_2N·CHO), $\nu_{max.}$ (KBr) 1 675 cm^{-1}, δ 8.0—7.60 (5 H, aromatic), 4.85 (H-1′, $J_{1',2'}$ 5 Hz), and 4.20 (m, other glycosyl protons), *m/e* 348 (M^+), R_F 0.24 (chloroform–ethanol 5 : 1) (Found: C, 51.4; H, 4.9; N, 15.55. $C_{15}H_{16}N_4O_6$ requires C, 51.7; H, 4.65; N, 16.1%).

5(3)-α-D-*Arabinofuranosyl*-1,2,4-*triazole*-3(5)-*carboxamide* (2c).—Debenzoylation of (11c) for 24 h gave the *product* (2c), m.p. 100°, $[\alpha]_D$ +25° (*c* 0.09 in H_2O), $\nu_{max.}$ (KBr) 1 675 cm^{-1}, δ 4.76 (H-1′, $J_{1',2'}$ 6 Hz), 4.28 (H-2′), 3.90 (H-3′ and -4′), and 3.50 (2 H-5′), *m/e* 244 (M^+, 4%), 213 (M − 30, 16), 155 (M − 89, 100), 141 (B + 30, 60), and 112 (BH, 10), R_F 0.17 (chloroform–ethanol 4 : 1) (Found: C, 39.0; H, 5.4; N, 22.85. $C_8H_{12}N_4O_5$ requires C, 39.35; H, 4.95; N, 22.95%).

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