5-Amino-4-carbamoyl-1-β-D-ribofuranosyl-ν-triazole (14). KOH (0.28 g) was dissolved in H_2O (3 ml), and cyanoacetamide (0.42 g) in DMF (30 ml) was added. The mixture was cooled to 0°, and tri-*O*-Bz-β-D-ribofuranosyl azide[16] (**13**, 2.44 g) was added. The mixt was stirred for 3 hr, and the solvent was evapd *in vacuo*. Na (50 mg), previously dissolved in MeOH (30 ml), was added, and the reaction mixt was kept at 0° for 60 hr. After neutralization with Dowex 50 (H^+) and filtration, the solvent was evapd and the residue was triturated with Et_2O (3 × 50 ml). The residual semisolid was crystd from MeOH (5 ml) to yield 0.59 g of product (46%). Recrystn from MeOH gave the analytical sample: mp 159°; $[\alpha]^{25}D$ −100.2° (*c* 1, DMF); uv $\lambda_{max}^{pH\ 7}$ 234 (ε 8900), 261 nm (8600); nmr (DMSO-d_6) δ 7.1 and 6.5 [s, broad, 4, 4-NH_2 and 5-$CONH_2$ (exchange with D_2O)], 5.8 (d, 1, $J_{1',2'}$ = 5 Hz, H_1). *Anal.* ($C_8H_{13}O_5N_5$) C, H, N.

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Azapurine Nucleosides. 2. Synthesis and Antiviral Activity of 7-Amino-3-α-D-arabinofuranosyl-ν-triazolo[4,5-*d*]pyrimidine and Related Nucleosides†

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Fusion of 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride with 7-methylthio-ν-triazolo[4,5-*d*]pyrimidine and aminolysis in methanolic NH_3 gave a mixture of several benzylated 7-amino-ν-triazolo[4,5-*d*]pyrimidine nucleosides [**1**, **3**, and **5** (anomeric mixture)], whose structures could not be unambiguously assigned on the basis of spectral properties. Treatment of the same glycosyl halide with sodium azide in refluxing acetonitrile gave the corresponding benzylated α- and β-arabinofuranosyl azides (**6** and **7**). Subsequent resolution of anomers and ring closure with cyanoacetamide and KOH in aqueous DMF gave the anomeric 5-amino-1-D-arabinofuranosyl-4-carbamoyl-ν-triazoles (**10** and **13**) which could be converted to 3-α- or -β-D-arabinofuranosyl-ν-triazolo[4,5-*d*]pyrimid-7-one. Dehydration of **10** or **13** with *p*-toluenesulfonyl chloride in pyridine gave 5-amino-1-α- or -β-D-arabinofuranosyl-4-cyano-ν-triazole (**17** and **20**), which was subsequently converted to 7-amino-3-α- or -β-D-arabinofuranosyl-ν-triazolo[4,5-*d*]pyrimidine by a multistep procedure. Rigorous spectral comparison of the unequivocally synthesized α and β nucleosides with the products of the fusion reaction showed them to be identical with **3** and **1**, respectively. Debenzylation of the nucleosides could be accomplished at either the ν-triazole or the ν-triazolo[4,5-*d*]pyrimidine stage. The structure assignments are confirmed by uv comparisons and nmr spectral data. 8-Aza-α-ara-A (**4**, 7-amino-3-α-D-arabinofuranosyl-ν-triazolo[4,5-*d*]pyrimidine) showed significant antiherpes virus activity in cell culture experiments.

The biological activity of 9-β-D-arabinofuranosyladenine (ara-A) is well documented,[2,3] and, in particular, its antiviral action has recently received considerable study.[4] It was the goal of this investigation to discover the effect of alteration of the heterocyclic moiety of ara-A upon its antiviral activity, specifically replacement of the 8-CH by N (8-aza-ara-A, 7-amino-3-β-D-arabinofuranosyl-ν-triazolo[4,5-*d*]pyrimidine). Previously described syntheses of ν-triazolo[4,5-*d*]pyrimidine nucleosides have employed a variety of methods (chloromercury derivative[5,6] and fusion[7,8]), but in each case the nature of the sugar (ribose or xylose derivative) was such that the β configuration of the nucleoside was assured by the trans rule.[9] When a β-arabinosyl linkage is desired, an arabinose derivative with nonparticipating groups must be utilized to avoid selective formation of the α-anomer. Fusion of the trimethylsilyl derivative of 7-methylthio-ν-triazolo[4,5-*d*]pyrimidine[10] with 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride[11] gave a syrupy mixture which was immediately treated with methanolic NH_3. The major components were isolated by column chromatography and fractional crystn and tentatively identified by their uv and nmr spectra as 7-amino-3-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-ν-triazolo[4,5-*d*]pyrimidine (**3**) and 7-amino-2-(2,3,5-tri-*O*-benzyl-α- and -β-D-arabinofuranosyl)-ν-triazolo[4,5-*d*]-pyrimidine (**5**). The site of glycosylation was assigned on the basis of uv spectral comparisons of **1**, **3**, and **5** with 7-amino-1-methyl,[12] -2-methyl,[13] and -3-methyl,[14] and other ring N-substituted ν-triazolo[4,5-*d*]pyrimidines (see Table I). The anomeric configurations of **1** and **3** were determined on the basis of their nmr spectra (Table II) and optical rotations.

†An account of part of this work was presented at the 162nd National Meeting of the American Chemical Society.[1]

Table I. Uv Spectral Comparison of Some *N*-Substituted-7-amino-*v*-triazolo[4,5-*d*]pyrimidines

7-Amino-*v*-triazolo[4,5-*d*]-pyrimidine	λ_{max}^{acid}, nm	$\lambda_{max}^{neutral}$, nm
1-Methyl[a]	284	285
2-Methyl[b]	281	291
3-Methyl[c]	264	277
2-β-D-Ribofuranosyl[d]	286	297
3-β-D-Ribofuranosyl[d,e]	263	278
3-α- and β-D-Xylofuranosyl[f]	263	279
1, 2, 3, and 4	262	279
5	286	295

[a] See ref 12. [b] See ref 13. [c] See ref 14. [d] See ref 6 and 8. [e] See ref 5. [f] See ref 7.

Table II. H-1′ Chemical Shifts of Various Anomeric *v*-Triazoles or *v*-Triazolo[4,5-*d*]pyrimidine Nucleosides

Compd	Chemical shift, ppm, of the anomeric proton (H-1′) α	β
7-Amino-3-(2,3,5-tri-*O*-benzyl-D-arabinofuranosyl)-*v*-triazolo[4,5-*d*]pyrimidine	6.50	6.75
3-(2,3,5-Tri-*O*-benzyl-D-arabinofuranosyl)-*v*-triazolo[4,5-*d*]pyrimid-7-one	6.45	6.70
5-Amino-1-(2,3,5-tri-*O*-benzyl-D-arabinofuranosyl)-4-carbamoyl-*v*-triazole	6.05	6.50
5-Amino-1-(2,3,5-tri-*O*-benzyl-D-arabinofuranosyl)-4-cyano-*v*-triazole	6.05	6.55
7-Amino-3-D-arabinofuranosyl-*v*-triazolo[4,5-*d*]pyrimidine[a]	6.15	6.50
3-D-Arabinofuranosyl-*v*-triazolo-[4,5-*d*]pyrimid-7-one[a]	6.15	6.65
5-Amino-1-D-arabinofuranosyl-4-carbamoyl-*v*-triazole[a]	5.80	6.10

[a] Solvent: DMSO-d_6 (with internal reference DSS); all others, solvent $CDCl_3$ (with internal reference TMS); measurements were taken on a Hitachi R20a nmr spectrometer.

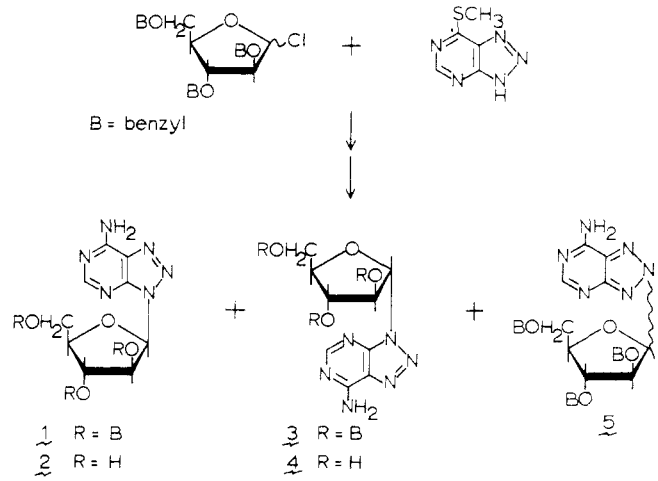
In an effort to improve the yield of the desired nucleosides (**1** and **3**) and to provide an unequivocal structure proof, an alternate synthesis was investigated. Glycofuranosyl azides have been prepared[15,16] from the corresponding glycosyl halides by nucleophilic displacement with azide. These azido sugars can be cyclized with suitable reagents to *v*-triazoles[17-19] and then to *v*-triazolo[4,5-*d*]pyrimidines.[8]

Treatment of 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride with sodium azide in acetonitrile gave an anomeric mixture of the corresponding azides. Silica gel column chromatographic separation gave 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl azide (**6**) and the β-anomer (**7**) (1:3). The anomeric configurations of the products were determined by comparison of their nmr spectra (Table II) and optical rotations.

When the α-azide (**6**) was treated with KOH and cyanoacetamide in aqueous DMF at room temp, there was only one isolable product (**10**). The β-azide (**7**) underwent a similar reaction to give two products, **10** and **13**, which were separated by silica gel column chromatography in a ratio of 14:1. The major product (**10**) was identical in all respects with the product of the α-azide cycloaddition reaction. This unusual rearrangement and its mechanism is the subject of a separate investigation.[20]

Comparison of the uv maxima of **10** and **13** with the spectral maxima of 5-amino-4-carbamoyl-1-methyl-*v*-triazole[13] and 5-amino-4-carbamoyl-3-methyl-*v*-triazole[12] permitted identification of both nucleosides as N^1-glycosyl triazoles. Since isomerization to the pyranose sugar could not

Scheme I



have occurred in the presence of the benzyl blocking groups the two products of the β-azide addition reaction were assigned the structures of 5-amino-1-(2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl)-4-carbamoyl-*v*-triazole (**10**) and the corresponding β-anomer (**13**).

Ring closure of **10** with diethoxymethyl acetate[21] gave 3-(2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl)-*v*-triazolo[4,5-*d*]pyrimid-7-one (**8**) in good yield. Similarly, the β-azide (**13**) could be converted to **15**.

The uv maxima of **8** and **15** were in good agreement with the spectral maxima published for the ribocongener, 8-azainosine.[8,22]

Dehydration of the carboxamides, **10** and **13**, to the corresponding nitriles, **17** and **20**, was attempted using several different reagents, (*e.g.*, pyrophosphoryl chloride,[23] phosphoryl chloride[24]) but the highest yield of product was obtained by treatment with *p*-toluenesulfonyl chloride in pyridine at room temp.[24]

Cyclization of either **17** or **20** with diethoxymethyl acetate and methanolic NH_3 furnished the corresponding 7-amino-3-(2,3,5-tri-*O*-benzyl-D-arabinofuranosyl)-*v*-triazolo[4,5-*d*]pyrimidine (**3** or **1**, respectively), which were identical in every respect with the nucleosides obtained from the fusion reaction, thus confirming the site of glycosylation assigned tentatively on the basis of the uv spectra.

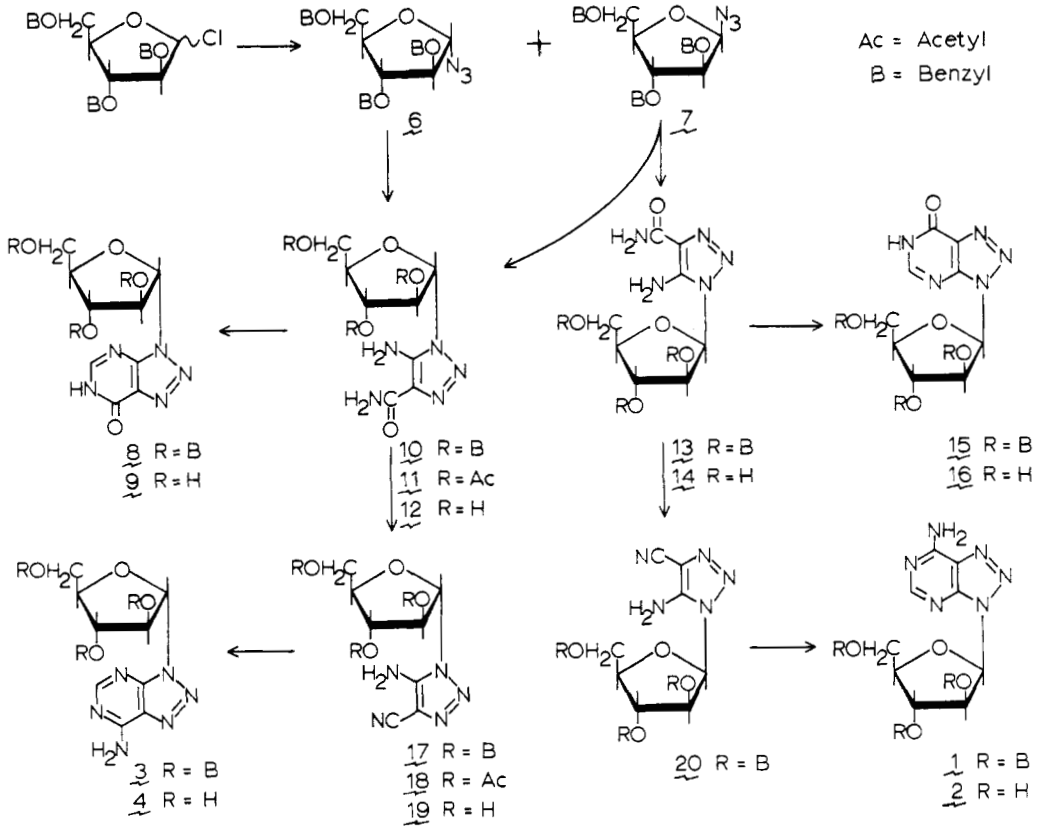
The benzyl blocking groups could be removed from the 8-azainosine analogs (**8** and **15**) by catalytic hydrogenation or Na-NH_3 (the former method is preferred) to furnish the free nucleosides, **9** and **16**. Debenzylation of the 8-azaadenosine analogs (**1** and **3**), however, was difficult‡ and gave poor and erratic yields of the free nucleosides **2** and **4**. The carbamoyl nucleosides (**10** and **13**), on the other hand, were debenzylated easily by either method to give **12** and **14**).

An alternate synthesis of **4**, suitable for large-scale preparation and avoiding the difficult debenzylation, was accomplished by acetylation of the carbamoyl nucleoside **12** to the corresponding triacetate **11** and dehydration to the triazole nitrile deriv **18** with *p*-toluenesulfonyl chloride in pyridine. Ring closure and deacetylation of **18** gave **4** in good yields. The 8-azainosine analog (**8**) could be obtained similarly by ring closure and deacetylation of **11**.

Nmr spectral comparisons of anomeric pairs of nucleo-

‡ Decomposition occurred which presumably involved cleavage of the glycosidic bond since 8-azaadenine could be isolated from the reaction mixture in small amounts.

Scheme II



sides revealed that the anomeric proton of the β-arabinofuranoside always came downfield from the anomeric proton of the α-arabinofuranoside (Table II). This observation is consistent with the reported trend in ribofuranosides[25] that the chemical shift of the anomeric proton of a C1′-C2′ trans nucleoside appears at higher field (usually around δ 0.5) than the peak observed for the anomeric proton of the corresponding C1′-C2′ cis nucleoside.

The anomeric configurations of the free ν-triazolo[4,5-*d*]-pyrimidine nucleosides were unequivocally established by periodate oxidation, followed by borohydride reduction and comparison of the optical rotations of the products with those of the ribofuranoside analogs which had been similarly oxidized and reduced.[20] Additional supportive evidence was derived from the fact that 8-aza-α-ara-A (**4**) was found *not* to be a substrate for calf intestine deaminase, whereas the β-anomer (**2**) was a substrate.[26]

Antiviral Evaluation. A 24-hr monolayer of human carcinoma of the nasopharnyx (KB) or continuous passaged rabbit kidney (RK13) cells were exposed to 100 $CCID_{50}$/ml of types 1 and 2 herpes simplex virus, type 3 adenovirus, vaccinia virus, myxoma virus, pseudorabies virus (all DNA viruses), and type 3 parainfluenza virus and type 13 rhinovirus (RNA viruses). Concentrations ranging from 1000 to 1 μg/ml of each compound were added within 15 min after the virus. Disposable plastic microplates were used for each antiviral experiment as previously described.[27] Antiviral activity was determined by observing inhibition of viral cytopathic effect (CPE) after a 72-hr incubation at 37°. Antiviral activity was given a numerical virus rating (VR) taking into account the degree of CPE inhibition and cytotoxicity as described previously.[27] Using this system, any VR of less than 0.5 was considered insignificant; a VR of greater than 0.5 was significant and indicative of definite antiviral activity. 9-β-D-Arabinofuranosyladenine (ara-A) was tested as a known active control in each experiment for comparative purposes. 7-Amino-3-α-D-arabinofuranosyl-ν-triazolo[4,5-*d*]pyrimidine (4, 8-aza-α-ara-A) had significant antiviral activity, which is summarized in Table III. This activity was essentially equal to or greater than that of ara-A against the herpes and vaccinia viruses. All other compounds tested in this series were inactive. The relative cytotoxicity for KB and RK13 cells was approximately the same as that of ara-A. Considering the fact that **4** is extremely insoluble, the antiviral activity is particularly significant.

Table III. Comparative *in Vitro* Antiviral Activity (Virus Rating)[a] of 8-Aza-α-ara-A (4) and Ara-A

Virus	Ara-A	8-Aza-α-ara-A
Type 1 herpes simplex	0.7, 0.9	0.8, 1.0
Type 2 herpes simplex	0.8, 0.6	0.8, 0.8
Pseudorabies	0.5, 0.6	0.0, 0.0
Vaccinia	0.7, 0.9	0.8, 0.8
Myxoma	0.8, 0.8	0.0, 0.0
Type 3 adeno	0.0, 0.0	0.0, 0.0
Type 3 parainfluenza	0.1, 0.2	0.2, 0.3
Type 13 rhino	0.1, 0.1	0.0, 0.1

[a] See ref 27.

Experimental Section §

Silyl Fusion Procedure with 7-Methylthio-ν-triazolo[4,5-*d*]pyrimidine. 7-Methylthio-ν-triazolo[4,5-*d*]pyrimidine (2.5 g) was

§Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer 141 polarimeter with a 1-dm path length. Ultraviolet spectra were recorded on a Cary Model 15 spectrometer and ir spectra on a Perkin-Elmer 257 spectrophotometer (KBr pellets). Chromatography solvent mixtures were v/v. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich., and by Galbraith Laboratories, Inc., Knoxville, Tenn., and are within ±0.4% of calculated values. Evaporations were carried out under reduced pressure with bath temp below 40°.

heated under reflux with an excess of hexamethyldisilazane (HMDS) containing a catalytic amt of $(NH_4)_2SO_4$ until complete soln was achieved (0.5–1.0 hr). The excess HMDS was removed by distillation under reduced pressure, and the residual crystals were used without further purification. 2,3,5-Tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl)-D-arabinose (7.8 g) was added to 150 ml of CH_2Cl_2 presatd with anhydrous HCl at 0°. After 2 hr at 0°, the precipitated *p*-nitrobenzoic acid was removed by filtn, and the filtrate was concentrated *in vacuo* to a syrup which was dissolved in toluene and evapd to dryness *in vacuo*. The resultant 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride was added to silylated 7-methylthio-*v*-triazolo[4,5-*d*]pyrimidine, and the mixture was heated at ~120° under aspirator vacuum for 45 min. The brown syrup obtained was dissolved in methanolic NH_3 (100 ml, satd at 0°) and allowed to stand in a sealed vessel at room temp for 2 days. The soln was evapd to dryness *in vacuo*, and the syrupy residue was chromatographed on a silica gel column eluting with $CHCl_3$–acetone (4:1). The first nucleoside material eluted from the column (1.9 g) was shown by pmr and comparison with authentic compds (see below) to be a mixture of **1** and **3** from which **3** could be fractionally crystd (1.2 g, 16%). Further elution gave 7-amino-2-(2,3,5-tri-*O*-benzyl-D-arabinofuranosyl)-*v*-triazolo[4,5-*d*]pyrimidine (**5**) as a syrupy anomeric mixture (1.5 g, 21%): uv $\lambda_{max}^{pH\ 1}$ 286 nm (ϵ 9200), λ_{max}^{MeOH} 295 nm (ϵ 9400). *Anal.* ($C_{30}H_{30}N_6O_4$) C, H, N.

7-Amino-3-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-*v*-triazolo[4,5-*d*]pyrimidine (1). 5-Amino-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-4-cyano-*v*-triazole (**20**, 0.5 g) was heated under reflux in diethoxymethyl acetate (10 ml) for 4 hr. The yellow soln was evapd *in vacuo*, and the resulting syrup was dissolved in methanolic NH_3 (50 ml, satd at 0°) and allowed to stand in a sealed vessel at room temp overnight. The soln was evapd to dryness *in vacuo*, and the residue recrystd from $CHCl_3$–ligroin to give **1** as white needles: mp 165–166° (76%); $[\alpha]^{25}D$ −48.3° (*c* 1.0, $CHCl_3$); uv $\lambda_{max}^{pH\ 1}$ 262 nm (ϵ 10,300), λ_{max}^{MeOH} 278 nm (ϵ 11,300). *Anal.* ($C_{30}H_{30}N_6O_4$) C, H, N.

7-Amino-3-β-D-arabinofuranosyl-*v*-triazolo[4,5-*d*]pyrimidine (2). A soln of 7-amino-3-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-7-*v*-triazolo[4,5-*d*]pyrimidine (**1**, 1.0 g) in 2-methoxyethanol (100 ml) was hydrogenated in a Parr hydrogenator at 40 psi and 50° for 24 hr using 10% Pd/C (1.0 g) as catalyst. The mixture was filtd, and the filtrate evapd to dryness *in vacuo* and recrystd from H_2O to give 0.35 g of **2** (68%): mp 212–213°; $[\alpha]^{25}D$ −24.0° (*c* 0.5, H_2O); uv $\lambda_{max}^{pH\ 1}$ 262 nm (ϵ 11,300), $\lambda_{max}^{pH\ 7\ and\ 11}$ 277 nm (ϵ 10,700). *Anal.* ($C_9H_{12}N_6O_4 \cdot 0.5H_2O$) C, H, N.

7-Amino-3-(2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl)-*v*-triazolo[4,5-*d*]pyrimidine (3). Treatment of **17** by the same procedure as in the prepn of **1** gave **3**: mp 63–65° (27%); $[\alpha]^{25}D$ +84.5° (*c* 1.0, $CHCl_3$); uv $\lambda_{max}^{pH\ 1}$ 261 nm (ϵ 11,600), λ_{max}^{MeOH} 278 nm (ϵ 11,300). *Anal.* ($C_{30}H_{30}N_6O_4$) C, H, N.

7-Amino-3-α-D-arabinofuranosyl-*v*-triazolo[4,5-*d*]pyrimidine (4). Method 1. 5-Amino-1-(2,3,5-tri-*O*-acetyl-α-D-arabinofuranosyl)-4-cyano-*v*-triazole (**18**, 0.35 g) was heated under reflux in diethoxymethyl acetate (10 ml) for 4 hr. The orange soln was evapd to dryness *in vacuo*, and the resulting amber syrup was dissolved in methanolic NH_3 (50 ml, satd at 0°) and allowed to stand in a sealed vessel at room temp for 2 days. The soln was evapd to dryness *in vacuo*, and the residue recrystd from H_2O to give 0.13 g (75%) of **4**: mp 239–241°; $[\alpha]^{25}D$ +128.8° (*c* 0.3, H_2O); uv $\lambda_{max}^{pH\ 1}$ 261 nm (ϵ 12,900), $\lambda_{max}^{pH\ 7\ and\ 11}$ 277 nm (ϵ 12,100). *Anal.* ($C_9H_{12}N_6O_4$) C, H, N.

Method 2. Treatment of **3** (0.4 g) by the same procedure as in the preparation of **2** gave a product identical in all respects with **4** from method 1 (45%).

2,3,5-Tri-*O*-benzyl-D-arabinofuranosyl Azides (6 and 7). 2,3,5-Tri-*O*-benzyl-D-arabinofuranosyl chloride (9.8 g) was dissolved in acetonitrile (125 ml) and heated under reflux with NaN_3 (10.0 g) for 2 hr. The mixture was filtered, the residue was washed with $CHCl_3$, and the filtrate and washings were combined and evapd *in vacuo* to give a tan syrup (8.9 g). This was chromatographed on a silica gel column eluting with ligroin–EtOAc (9:1). Two major syrupy components were obtained; the first was identified as 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl azide (**6**) (1.8 g, 21%): $[\alpha]^{25}D$ +111.5° (*c* 1.0, $CHCl_3$); ir 2115 cm^{-1} (azide). *Anal.* ($C_{26}H_{27}N_3O_4$) C, H, N.

The other major component was 2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl azide (**7**, 5.5 g, 62%): $[\alpha]^{25}D$ −118.2° (*c* 1.0, $CHCl_3$); ir 2115 cm^{-1} (azide). *Anal.* ($C_{26}H_{27}N_3O_4$) C, H, N.

3-(2,3,5-Tri-*O*-benzyl-α-D-arabinofuranosyl)-7-oxodihydro-*v*-triazolo[4,5-*d*]pyrimid-7-one (8). 5-Amino-1-(2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl)-4-carbamoyl-*v*-triazole (**10**, 1.0 g) was heated under reflux in diethoxymethyl acetate (20 ml) for 4 hr. The orange soln was evapd *in vacuo*, and the resulting amber syrup was dissolved in methanolic NH_3 (100 ml, satd at 0°) and allowed to stand in a sealed vessel at room temp for 18 hr. The soln was evapd to dryness *in vacuo*, and the residue was recrystd from MeOH–H_2O to give white crystals of **8** (0.8 g, 79%): mp 109–110°; $[\alpha]^{25}D$ +89.8° (*c* 1.0, $CHCl_3$); uv λ_{max}^{MeOH} 256 nm (ϵ 9200), $\lambda_{max}^{pH\ 11}$ 278 nm (ϵ 10,200). *Anal.* ($C_{30}H_{29}N_5O_5$) C, H, N.

3-α-D-Arabinofuranosyl-7-oxodihydro-*v*-triazolo[4,5-*d*]pyrimid-7-one (9). Method 1. 5-Amino-1-(2,3,5-tri-*O*-acetyl-α-D-arabinofuranosyl)-4-carbamoyl-*v*-triazole (**11**, 0.8 g) was heated under reflux in diethoxymethyl acetate (10 ml) for 4 hr. The yellow soln was evapd to dryness *in vacuo*, and the syrupy residue was dissolved in methanolic NH_3 (50 ml, satd at 0°) and allowed to stand in a sealed vessel at room temp for 2 days. The soln was evapd to dryness *in vacuo*, and the residue then was recrystd from EtOH–ligroin to give crystals of **9** (64%): mp 174–176°; $[\alpha]^{25}D$ +106.5° (*c* 1.0, H_2O); uv $\lambda_{max}^{pH\ 1}$ 255 nm (ϵ 9500), $\lambda_{max}^{pH\ 7}$ 254 nm (ϵ 9500), $\lambda_{max}^{pH\ 11}$ 276 nm (ϵ 10,500). *Anal.* ($C_9H_{11}N_5O_5$) C, H, N.

Method 2. Treatment of **8** (0.5 g) by the same procedure as in the preparation of **2** gave a product identical in all respects with **9** from method 1 (80%).

5-Amino-1-(2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl)-4-carbamoyl-*v*-triazole (10) and the β-Anomer (13). 2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl azide (**7**, 17.0 g) was added to a cooled soln of KOH (3.2 g) and cyanoacetamide (4.8 g) in H_2O (25 ml) and DMF (250 ml). The yellow soln was allowed to slowly warm to room temp over 3 hr and then evapd to dryness *in vacuo*. The residue was dissolved in MeOH (100 ml) and the soln was neutralized with Dowex 50 (H^+), 100–200 mesh. After filtn, the filtrate was evapd to dryness *in vacuo* and the residue partitioned between H_2O and EtOAc. The organic layer was evapd to dryness *in vacuo*, and the residual syrup chromatographed on a silica gel column eluting with $CHCl_3$–acetone (9:1). 5-Amino-1-(2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl)-4-carbamoyl-*v*-triazole (**10**) was obtained as white crystals (14.7 g, 72%): mp 69–71°; $[\alpha]^{25}D$ +60.3° (*c* 1.0, $CHCl_3$); uv $\lambda_{max}^{pH\ 1}$ 262 nm (ϵ 11,100), λ_{max}^{MeOH} 235 (ϵ 9500) and 259 nm (9300), $\lambda_{max}^{pH\ 11}$ 237 (ϵ 11,700) and 262 nm (11,400). *Anal.* ($C_{29}H_{31}N_5O_5$) C, H, N.

The minor product, which was the first component to be eluted from the column, was obtained as a syrup and identified as 5-amino-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-4-carbamoyl-*v*-triazole (**13**, 0.9 g, 5%): $[\alpha]^{25}D$ −43.0° (*c* 1.0, $CHCl_3$); uv $\lambda_{max}^{pH\ 1}$ 261 nm (ϵ 10,800), λ_{max}^{MeOH} 236 (ϵ 9100) and 259 nm (8300), $\lambda_{max}^{pH\ 11}$ 237 (ϵ 9950) and 261 nm (9100). *Anal.* ($C_{29}H_{31}N_5O_5$) C, H, N.

Compound **10** was obtained as the sole product on treatment of **6** with cyanoacetamide by the above method (85%).

5-Amino-1-(2,3,5-tri-*O*-acetyl-α-D-arabinofuranosyl)-4-carbamoyl-*v*-triazole (11). 5-Amino-1-α-D-arabinofuranosyl-4-carbamoyl-*v*-triazole (**12**, 0.25 g) was acetylated by standard procedures using acetic anhydride in pyridine to give, after recrystn from $CHCl_3$–ligroin, 0.27 g (75%) of **11**: mp 89–91°; $[\alpha]^{25}D$ +59.5° (*c* 1.0, $CHCl_3$); uv $\lambda_{max}^{pH\ 1}$ 234 (ϵ 9300) and 261 nm (8300), λ_{max}^{MeOH} 236 (ϵ 9500) and 258 nm (8500), $\lambda_{max}^{pH\ 11}$ 236 (ϵ 8500) and 261 nm (8100). *Anal.* ($C_{14}H_{19}N_5O_8$) C, H, N.

5-Amino-1-α-D-arabinofuranosyl-4-carbamoyl-*v*-triazole (12). Method 1. Sodium was added, in small portions, to a stirred suspension of 5-amino-1-(2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl)-4-carbamoyl-*v*-triazole (**10**, 4.0 g) in liquid NH_3 (100 ml) until the deep blue color persisted. The color was discharged by careful addn of NH_4Cl, and the reaction mixture was allowed to evaporate to dryness under a stream of N_2. The solid residue was triturated with C_6H_6 (50 ml) and then was suspended in elution solvent [EtOAc–*n*-PrOH–H_2O (4:1:2, upper phase)], and the inorganic salts were removed by elution from a silica gel column. Recrystn from EtOH gave 1.2 g (61%) of **12**: mp 147–149°; $[\alpha]^{25}D$ +131.7° (*c* 1.0, H_2O); uv $\lambda_{max}^{pH\ 1}$ 235 (ϵ 8100) and 260 nm (7700), $\lambda_{max}^{pH\ 7\ and\ 11}$ 234 (ϵ 8600) and 258 nm (8000). *Anal.* ($C_8H_{13}N_5O_5$) C, H, N.

Method 2. Treatment of **10** (1.0 g) by the same procedure as in the preparation of **2** gave 0.47 g (95%) of **12** identical in all respects with the product obtained by method 1.

5-Amino-1-β-D-arabinofuranosyl-4-carbamoyl-*v*-triazole (14). The same procedure as for **12** (method 1) was used starting with **13**: yield 75% as a freeze-dried solid; $[\alpha]^{25}D$ −19.3° (*c* 1.2, DMF); uv $\lambda_{max}^{pH\ 1,7,11}$ 234 (ϵ 8000) and 258 nm (7800). *Anal.* ($C_8H_{13}N_5O_5$) C, H, N.

3-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)-7-oxodihydro-*v*-triazolo[4,5-*d*]pyrimid-7-one (15). The same procedure as for **8** was used starting with **13** (79% as a syrup): $[\alpha]^{25}D$ − 39.8° (*c* 1.0, $CHCl_3$); uv

$\lambda_{max}^{pH\ 1}$ 255 nm (ϵ 8100), λ_{max}^{MeOH} 255 nm (ϵ 8400), $\lambda_{max}^{pH\ 11}$ 277 nm (ϵ 9200). *Anal.* ($C_{30}H_{29}N_5O_5$) C, H, N.

3-β-D-Arabinofuranosyl-7-oxodihydro-*v*-triazolo[4,5-*d*]pyrimid-7-one (16). The same procedure as for **2** was used starting with **15** (60%): mp 195° dec; $[\alpha]^{25}D$ +75.0° (*c* 1.0, H_2O); uv $\lambda_{max}^{pH\ 1}$ 255 nm (ϵ 6800), $\lambda_{max}^{pH\ 11}$ 275 nm (ϵ 7500). *Anal.* ($C_9H_{11}N_5O_5$) C, H, N.

5-Amino-1-(2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl)-4-cyano-*v*-triazole (17). 5-Amino-1-(2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl)-4-carbamoyl-*v*-triazole (**10**, 1.1 g) was dissolved in dry pyridine (20 ml) and treated with *p*-toluenesulfonyl chloride (1.5 g). The soln was left at room temp overnight, then H_2O was added, and the soln was extd with EtOAc. The organic layer was washed with H_2O, dried (Na_2SO_4), and then evapd *in vacuo* to give a syrup which crystd after standing several days. Recrystn from MeOH gave the analytical sample (0.8 g, 75%): mp 114–115°; $[\alpha]^{32}D$ +72.3° (*c* 1.0, $CHCl_3$); ir 2220 cm^{-1} (C≡N); uv λ_{max}^{MeOH} 231 (ϵ 10,800) and 251(sh) nm (8300). *Anal.* ($C_{29}H_{29}N_5O_4$) C, H, N.

5-Amino-1-(2,3,5-tri-*O*-acetyl-α-D-arabinofuranosyl)-4-cyano-*v*-triazole (18). Method 1. 1-(2,3,5-Tri-*O*-acetyl-α-D-arabinofuranosyl)-5-amino-4-carbamoyl-*v*-triazole (**11**, 0.5 g) was dissolved in dry pyridine (10 ml) and treated with *p*-toluenesulfonyl chloride (0.75 g). The soln was left at room temp overnight, then H_2O was added, and the soln was extd with EtOAc. The organic layer was washed with H_2O, dried (Na_2SO_4), and then evapd *in vacuo* to give **18** (0.34 g, 72%) as a syrup: $[\alpha]^{25}D$ +51.7° (*c* 1.3, $CHCl_3$); ir 2220 cm^{-1} (C≡N); uv $\lambda_{max}^{pH\ 7}$ 227 (ϵ 10,500) and 250(sh) nm (6600), $\lambda_{max}^{pH\ 11}$ 232 (ϵ 8100) and 250(sh) nm (6600). *Anal.* ($C_{14}H_{17}N_5O_7$) C, H, N.

Method 2. 5-Amino-1-α-D-arabinofuranosyl-4-cyano-*v*-triazole (**19**) was acetylated by standard procedures using acetic anhydride in pyridine to give syrupy **18** identical in all respects with the product from method 1.

5-Amino-1-α-D-arabinofuranosyl-4-cyano-*v*-triazole (19). The same procedure as in the preparation of **12** (method 1) was used starting with **17** to furnish **19** (32%): mp 167–168°; $[\alpha]^{25}D$ +141.3° (*c* 1.0, H_2O); ir 2220 cm^{-1} (C≡N); uv $\lambda_{max}^{pH\ 1\ and\ 7}$ 228 (ϵ 9900) and 252 nm (6800), $\lambda_{max}^{pH\ 11}$ 231 (ϵ 9000) and 252 nm (6800). *Anal.* ($C_8H_{11}N_5O_4$) C, H, N.

5-Amino-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-4-cyano-*v*-triazole (20). The same procedure as for **17** was used starting with **13** (77%): $[\alpha]^{25}D$ −31.3° (*c* 1.0, $CHCl_3$); ir 2220 cm^{-1} (C≡N); uv λ_{max}^{MeOH} 230 (ϵ 10,200) and 250(sh) nm (6700). *Anal.* ($C_{29}H_{29}N_5O_4$) C, H, N.

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2,5-Dihydro-1,2,4-benzothiadiazepine 1,1-Dioxides. Synthesis and Pharmacological Evaluation†

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A new method of synthesis of 2,5-dihydro-1,2,4-benzothiadiazepine 1,1-dioxide derivatives *via* nitrilium salts is described. A number of the compounds were tested for acute toxicity and CNS activity in mice, and it was found that *n*-hexyl-substituted derivatives effectively antagonized MES seizures.

In recent years considerable attention has been paid to the synthesis and biological study of 1,2,4-benzothiadiazine 1,1-dioxide derivatives and related compounds, owing mainly to the interesting diuretic activities found in some of them.[1] In marked contrast, the homolog heterocyclic system, 1,2,4-benzothiadiazepine 1,1-dioxide, has been scarcely considered. Cignarella and Teotino,[2] by condensation of ethyl orthoformate with *o*-aminomethylbenzenesulfonamide in propylene glycol, obtained in 51% yield a product to which they assigned the structure of 2,5-dihydro-1,2,4-benzothiadiazepine 1,1-dioxide. The reaction, however, was not applicable to other N^1-substituted sulfonamides such as *o*-aminomethylbenzenesulfonmethylamide or -sulfonphenylamide. More recently, another group[3] has successfully applied this scheme of synthesis to obtain 7-chloro-2,5-dihydro-1,2,4-benzothia-

†This paper should be considered as paper 10 of our series on nitrilium salts. For paper 9 see ref 14.