Synthesis of Certain 1,2,4-Thiadiazole Nucleosides

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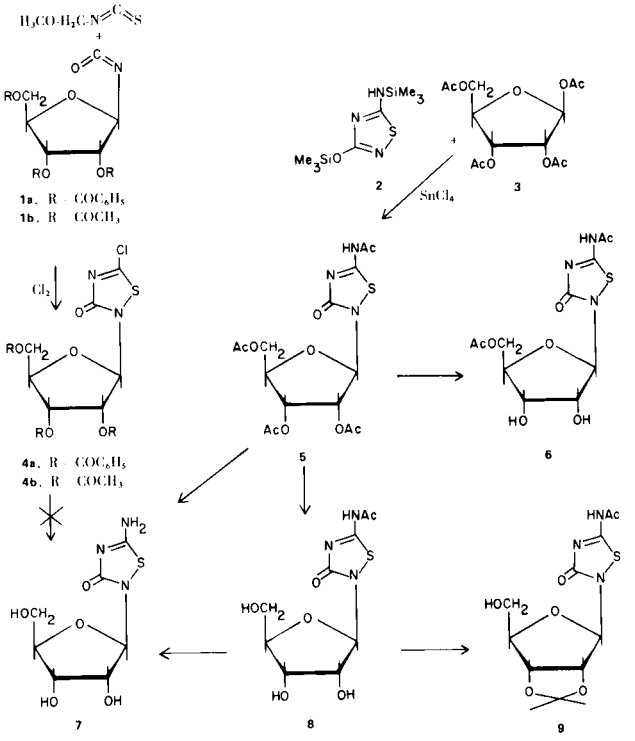
Sir:

The broad spectrum antiviral activity of the synthetic nucleoside 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (1) has generated considerable interest in the chemical synthesis of nucleosides of five-membered heterocyclic ring systems. The isosteric relationship between 1,2,4-triazole and 1,2,4-thiadiazole suggested (2) the synthesis of pyrimidine nucleoside analogs of the 1,2,4-thiadiazole ring systems. We now wish to report the first chemical synthesis of 5-amino-2-(β-D-ribofuranosyl)-1,2,4-thiadiazol-3-one (**7**), which represents a new class of cytidine analog.

The most frequently encountered procedure, originally developed by Kühle and co-workers (3) for the synthesis of 2-substituted-5-chloro-1,2,4-thiadiazol-3-ones, involves the reaction of an alkyloxymethyliminochloromethanesulfenyl chloride with isocyanates and was employed in an attempt to obtain **7**. Thus, 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl isocyanate (4) (**1a**, 1 equivalent) was treated with methoxymethylisothiocyanate (1 equivalent) in anhydrous carbon tetrachloride containing dry chlorine (1 equivalent) at 0-10° for 15 hours to obtain crystalline 5-chloro-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-thiadiazol-3-one (**4a**) in 64.5% yield, m.p. 145-146° (from ethanol); ^{1}H nmr (DMSO-d_6): δ 5.85 (d, J = 3.5 Hz, C_1'H); uv λ max (ethanol): 235 nm (ε, 3,900), 280 (1,250). Treatment of **4a** with methanolic or ethanolic ammonia or with sodium alkoxide under various conditions afforded a deep blue reaction mixture from which, in several instances 1-β-D-ribofuranosylurea and elemental sulfur were isolated. Likewise, the reaction of 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl isocyanate (5) (**1b**) with methoxymethylisothiocyanate under similar conditions furnished syrupy **4b**. Attempts to deacylate **4b** with either methanolic ammonia/hydrogen chloride or with sodium methoxide resulted in an intractable reaction mixture from which no desired product was isolated.

Because of the lability of **4a** and **4b**, particularly to acid and base, the synthesis of **7** was approached by an alternate route. 5-Amino-1,2,4-thiadiazol-3-one (6) (1 equivalent) was silylated with hexamethyldisilazane according to the general procedure of Wittenburg (7). The crystalline



bistrimethylsilyl derivative (**2**) thus obtained was then treated with 1 equivalent of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**3**) in the presence of 1.4 equivalent of stannic chloride (8) in 1,2-dichloroethane at 25° for 5 hours which, after purification by silica gel column chromatography, provided a single, crystalline nucleoside product, identified as 5-acetamido-2-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-thiadiazol-3-one (**5**) in 60% yield, m.p. 229-230° (ethanol); $[\alpha]_D^{25}$ -41.5° (c 1, ethanol); ^{1}H nmr (deuteriochloroform): δ 2.17 (d, 9H, -OAc), 2.56 (s, 3H, -NAc), 6.06 (d, J = 4.5 Hz, C_1'H); uv λ max (*p*H 1): 236 nm (ε, 12,000), 275 sh (4,000); (*p*H 7 and 11): 256 nm (ε, 13,000), 278 sh (6,500). The ^{13}C nmr spectrum is also in agreement with this structure. The formation of **5** is of particular interest since the 5-amino group of the aglycon becomes acylated under the conditions employed. Although the determination of the site of ribosylation at N-2 is favorable on the basis of conventional valence bond considerations, the

large upfield ^{13}C chemical shift of C-3 in **5** (δ 162.3 ppm) as compared to that of the base anion (δ 176.5 ppm) furnished (9) strong support for the ribosylation site as N-2.

Selective deacylation of the secondary *O*-acetyl groups of **5** with either methanolic ammonia (10) at 0°, or with catalytic amount of sodium methoxide in methanol (*p*H 8.5) at room temperature for 30 minutes followed by silica gel column chromatography (to separate the minor product **8**) provided crystalline 5-acetamido-2-(5-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-thiadiazol-3-one (**6**) in 58% yield, m.p. 212-213° (25% aqueous ethanol); $[\alpha]_D^{25}$ -30.1° (c 1, water); ^1H nmr (DMSO-d_6): δ 2.13 (s, 3H, -OAc), 2.28 (s, 3H, -NAc), 5.70 (d, J = 4.5 Hz, $C_1'H$); uv λ max (*p*H 1): 235 nm (ε, 8,300), 270 sh (3,500); (*p*H 7 and 11): 255 nm (ε, 8,800), 276 sh (4,700). Further saponification of **6** or the direct deacylation of **5** with sodium methoxide (*p*H 8.5 for 2.5 hours at 28°) followed by column chromatography on silica gel provided 5-acetamido-2-(β-D-ribofuranosyl)-1,2,4-thiadiazol-3-one (**8**) in 67% yield, m.p. 202-203° dec., (25% aqueous ethanol); $[\alpha]_D^{25}$ -50.1° (c 1, water); ^1H nmr (DMSO-d_6): δ 2.28 (s, 3H, -NAc), 5.65 (d, J = 5.0 Hz, $C_1'H$); uv λ max (*p*H 1): 235 nm (ε, 10,600), 275 (3,500); (*p*H 7): 254 nm (ε, 9,900), 277 sh (5,400); (*p*H 11): 254 nm (ε, 12,700), 277 sh (5,900). Isopropylidenation of **8** with 2,2-dimethoxypropane in the presence of perchloric acid in acetone gave 5-acetamido-2-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1,2,4-thiadiazol-3-one (**9**) in quantitative yield, m.p. 220-221° dec., (aqueous methanol). The ^1H nmr spectrum of **9** in DMSO-d_6 revealed a doublet centered at δ 5.76 with a $J_{1,2}$ of 3.0 Hz indicating (11) the β-configuration. The spectrum also revealed the difference in proton chemical shifts between the methyl signals of isopropylidene group to be 0.19 ppm, a difference characteristic of the β-configuration (12). Thus, the β-configuration for **9** and hence **5**, **6**, **7** and **8** were assigned unequivocally.

Prolonged treatment of **8** or **5** with sodium methoxide in methanol (*p*H 8.5 to 9.0 at 30°) furnished a 48% yield of 5-amino-2-(β-D-ribofuranosyl)-1,2,4-thiadiazol-3-one (**7**), m.p. > 240° dec., (aqueous ethanol); ^1H nmr (DMSO-d_6): δ 5.63 (d, J = 4.5 Hz, $C_1'H$); uv λ max (*p*H 1): 220 nm (ε, 14,950), 273 (5,000); (*p*H 7): 220 nm (ε, 13,950), 255 (6,250); (*p*H 11): 230 nm (ε, 11,200), 278 sh (7,500).

All new compounds gave proper elemental analyses and the spectral data are in agreement with the structures assigned.

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