An Unexpected Product from the Cyclodesulfurization of 5-[1-(3-Methoxycarbonyl)thioureido]-1-(β-D-ribofuranosyl)imidazole-4-carboxamide with Dicyclohexylcarbodiimide [1]

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The treatment of 5-[1-(3-methoxycarbonyl)thioureido]-1-(β-D-ribofuranosyl)imidazole-4-carboxamide with *N,N'*-dicyclohexylcarbodiimide in *N,N*-dimethylformamide has afforded 4-cyano-5-[1-(3-methoxycarbonyl)-ureido]-1-(β-D-ribofuranosyl)imidazole.

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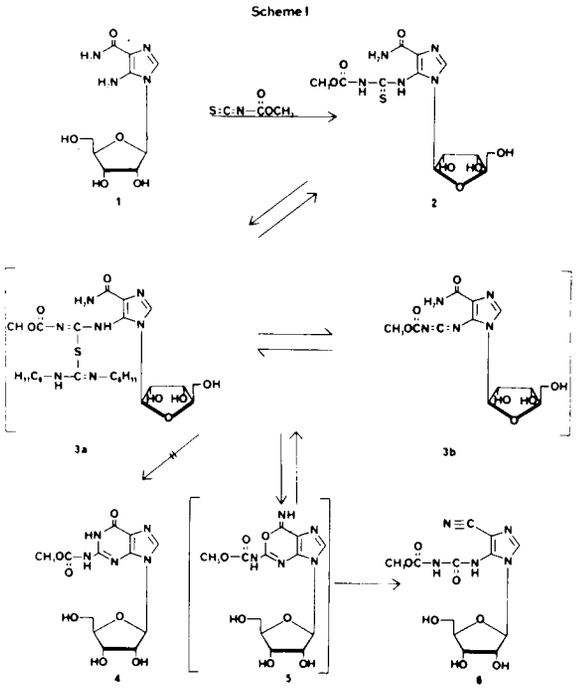
Alkoxycarbonyl isothiocyanates are highly reactive functional compounds which undergo a wide range of condensation and ring cyclization reactions in modern synthetic organic chemistry [2,3]. We have recently reported on a facile synthesis of methyl oxazolo[5,4-*d*]pyrimidin-2-carbamates which involves the cyclodesulfurization of a methoxycarbonylated thiourea derivative with *N,N'*-dicyclohexylcarbodiimide (DCC) [4]. It has been assumed that this cyclization reaction proceeds *via* the formation of a reactive carbodiimide intermediate, similar to that reported [5] for the cyclization of *o*-aminophenyl aryl and alkyl thioureas.

In order to explore the scope of this synthetic methodology, we attempted the preparation of a guanosine derivative by a condensation of 5-amino-1-(β-D-ribofuranosyl)-imidazole-4-carboxamide (AICA-riboside) (**1**) with methoxycarbonyl isothiocyanate followed by a treatment of the resulting thiourea derivative 5-[1-(3-methoxycarbonyl)thioureido]-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (**2**) [6] with DCC (Scheme I) [7]. A literature survey revealed that, although a variety of cyclization reactions have provided synthetic routes to guanosine [8], this specific method (*vide supra*) had not been examined. Since DCC is known to form *N,N'*-disubstituted carbodiimides from *N,N'*-disubstituted thioureas in a reversible equilibrium reaction [9], we reasoned that an intramolecular attack of the amide nitrogen atom on the carbodiimide carbon atom of intermediate **3b** might shift this equilibrium towards the formation of a methoxycarbonylated guanosine derivative (**4**).

A solution of AICA-riboside (**1**, 1.05 g, 2.0 mmoles) in 20 ml of DMF was treated with a solution of methoxycarbonyl isothiocyanate [10] (prepared from 4 mmoles of potassium thiocyanate and 4 mmoles of methyl chloroformate) in acetonitrile. The mixture was stirred at room temperature for 12 hours and then rotary evaporated to dryness *in vacuo* at 30°. The residue was dissolved in anhydrous DMF (10 ml) and treated with DCC (1.0 g). The reaction mixture was stirred at room temperature overnight, then rotary evaporated *in vacuo* at 60°. The residue was washed with hot toluene and then purified by column chromatography (20 g silica gel, 9:1 chloroform-methanol as eluent) to afford 260 mg (38%) of a compound (mp 176.5-177.5°) which initially appeared to be the desired *N*-3-methoxycarbonylated guanosine derivative **4** based on the ^{1}H nmr spectrum and elemental analysis. Based upon these criteria alone, however, the product could not only be compound **4**, but also 1-[4-carboxamido-1-(β-D-ribofuranosyl)imidazol-5-yl]-3-methoxycarbonylcarbodiimide (**3b**), 7-imino-5-(methoxycarbonyl)amino-3-(β-D-ribofuranosyl)imidazo[4,5-*d*][1,3]oxazine (**5**) or 4-cyano-5-[1-(3-methoxycarbonyl)ureido]-1-(β-D-ribofuranosyl)imidazole (**6**). The uv spectral data and the ^{13}C-nmr data were not consistent with those expected for an *N*-3-acylated guanosine derivative [11,12]. It was of consi-

Scheme I



derable interest that the infrared spectrum of the product showed a strong absorption at 2230 cm^{-1} which supports the presence of a cyano group in the molecule. Therefore, on the basis of ^1H nmr, ^{13}C nmr, ir, uv spectral and elemental analysis data [13], we have assigned the structure of this unexpected product as the nucleoside **6**.

A plausible mechanism for the formation of the product involves the initial formation of the isothiourea derivative **3a**, which may afford the carbodiimide intermediate **3b** upon loss of *N,N'*-dicyclohexylthiourea. Ring closure by an intramolecular attack of the carboxamide oxygen atom on the carbodiimide carbon atom of **3b** or by an intramolecular Michael addition-elimination reaction of **3a** then affords the oxazine intermediate **5**, which ring opens to give the 4-cyanoimidazole product **6**.

Modification of this methodology towards the successful synthesis of guanosine derivatives is currently under active investigation in our laboratory.

REFERENCES AND NOTES

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[6] Identified by ^1H nmr and ir spectral data: ^1H nmr (270 MHz, DMSO-d_6): δ 11.69 (s, 1H, NH), 10.94 (s, 1H, NH), 8.02 (s, 1H, H-2), 7.27 and 7.07 (s, 1H each $CONH_2$), 5.48 (d, 1H, J = 3.5 Hz, H-1'), 4.7-5.3 (b, 3H, OH), 4.15 (br, 1H), 4.04 (m, 1H), 3.87 (m, 1H), 3.77 (s, 3H, CO_2CH_3), 3.68 (d of d, 2H, H-5'); ir (potassium bromide): 3500-3100, 3020, 2920, 1730, 1665, 1605, 1040 cm^{-1}.

[7] The conformation of the glycosidic bond of the compounds shown in Scheme I is shown as *syn* or *anti* purely for convenience; none of the conformations have been determined.

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[11] For the uv spectral data of *N*-3-benzoylguanosine, see S. Chladek and J. Smrt, *Collect. Czech. Chem. Commun.*, **29**, 214 (1964).

[12] For example, N^2-benzoyl-5'-*O*-acetylguanosine (mp 230-231°); ^{13}C nmr (90.56 MHz, DMSO-d_6): δ 170.1, 169.0, 155.0, 148.8, 148.1, 138.0, 120.7, 133.1, 132.2, 128.5, 128.4, 86.8, 81.7, 73.1, 70.3, 64.0, 20.6.

[13] ^1H nmr (360 MHz, DMSO-d_6): δ 10.80 (s, 1H, NH), 9.70 (s, 1H, NH), 8.14 (s, 1H, H-2), 5.58 (brs, 1H, OH), 5.46 (d, 1H, H-1', J = 4.2 Hz), 5.22 (d, 1H, OH), 5.09 (s, 1H, OH), 4.17 (brs, 1H, H-2'), 4.04 (q, 1H, H-3'), 3.90 (q, 1H, H-4'), 3.74 (s, 3H, OCH_3), 3.63 (q, 1H, H-5'), 3.53 (q, 1H, H-5'); ^{13}C nmr (90.4 MHz, DMSO-d_6): δ 154.5, 150.8, 134.9, 133.8, 114.4, 108.4, 88.6, 85.4, 75.0, 69.6, 60.5, 52.9; ir (potassium bromide): 3320, 3260, 2930, 2850, 2230, 1700-1730, 1600 cm^{-1}; uv (methanol): λ max nm (ε × 10^4) 227 (9.0); (pH 1): 228 (9.2); (*p*H 11): 272 (1.0).

Anal. Calcd. for $C_{12}H_{15}N_5O_7$: C, 42.23; H, 4.43; N, 20.52. Found: C, 41.97; H, 4.49; N, 20.38.