A NOVEL PURINE TO 1-DEAZAPURINE TRANSFORMATION REACTION: SYNTHESIS OF 1-DEAZAADENOSINE DERIVATIVES[1]

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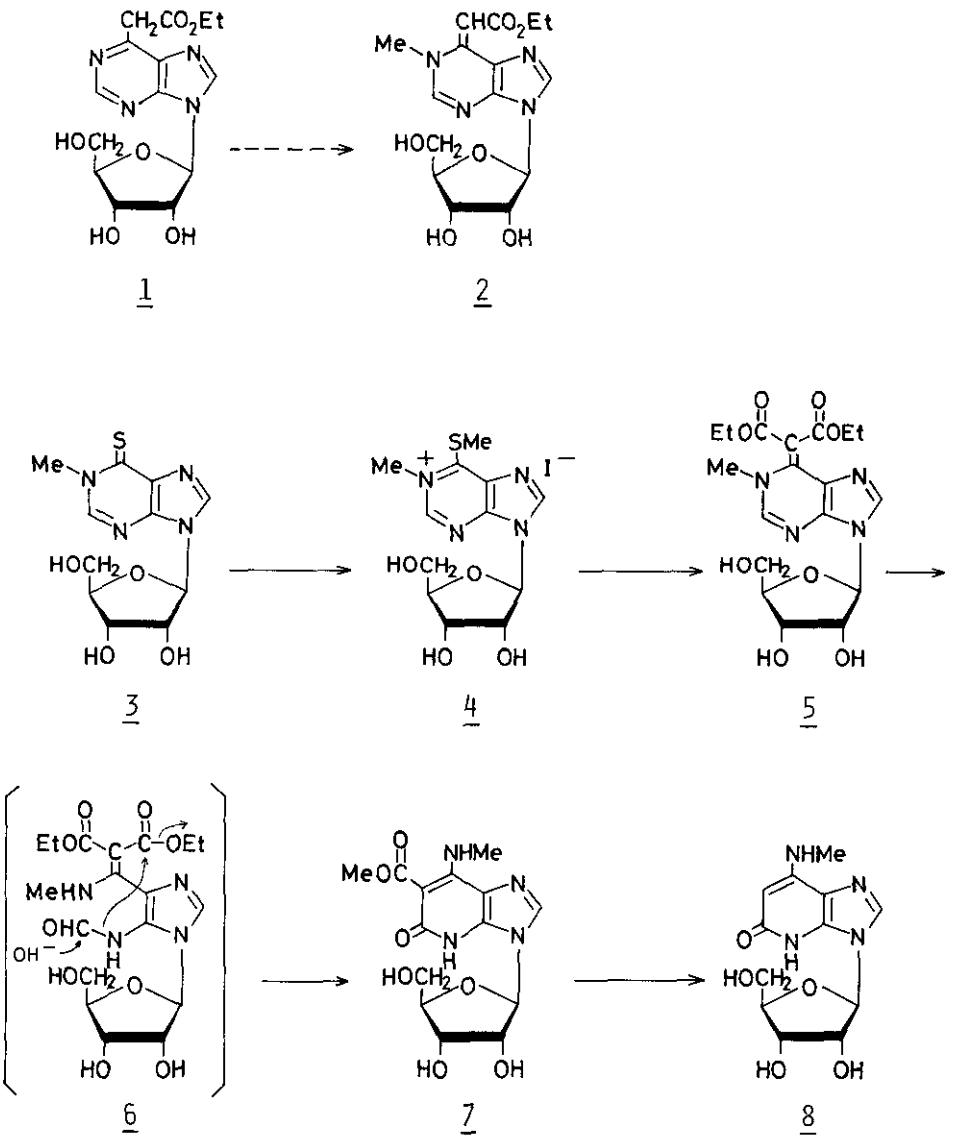
Abstract-- Sulfur-methylation of 1-methyl-6-thioinosine followed by treatment with diethyl sodiomalonate gave 1-methyl-6-bis(ethoxycarbonyl)methylene-1,6-dihydro-9-β-D-ribofuranosylpurine (5). Compound 5 underwent the Dimroth type rearrangement in methanolic potassium hydroxide to afford a 1-deazapurine derivative (7), which, on heating in aqueous alkali furnished 7-methylamino-3-β-D-ribofuranosyl-3H-imidazo[4,5-b]pyridin -5(4H)-one (8).

In recent years deazapurine nucleosides have been synthesized in the search for anticancer, antiviral and antibacterial agents or as biochemical tools in some enzymatic studies. Their synthesis involved the condensation of a properly protected deazapurine or the imidazole precursor with a sugar derivative[2]. However, this method necessarily involves the multi-step synthesis of a deazapurine and/or the formation of the regio-isomers at the glycosylation step, which made the large-scale preparation often quite difficult. This communication describes a synthesis of 1-deazaadenosine derivatives from adenosine via a unique ring transformation of a purine to a 1-deazapurine.

It has been well known that N^1-alkyl and N^1-alkoxy derivatives of 9-substituted adenines undergo the Dimroth rearrangement under alkaline conditions to afford N^6-alkyl and N^6-alkoxy adenine derivatives, respectively[3,4]. As an extension of this rearrangement we have reported a conversion of N^1-methoxy-N^6-cyanoadenosine to N^6-methoxy-2,6-diaminopurine riboside[5]. Our present approach to 1-deazaadenosines involves the preparation of N^1-alkylpurine nucleoside possessing a functional carbon chain at the C-6 and its transformation of the purine moiety into the 1-deazapurine system in which the C-1 and C-2 portions come from the exocyclic carbon atoms on the purine ring.

An initial attempt was made to prepare 1-methyl-6-ethoxycarbonylmethylene-9-β-D-ribofuranosylpurine (2) by methylation of 6-ethoxycarbonylmethylpurine riboside (1)[6]. However, the methylation occurred mainly at the N^3 of 1 with many side products. Therefore, other route involving the substitution of a N^1-methylpurine at the C-6 with carbon nucleophiles was next undertaken.

1-Methyl-6-thioinosine (3), which was readily derived from adenosine[7], was treated with 1.6 equivalents of methyl iodide in dimethylacetamide (DMA) at room temperature for 7 h. Addition of dry



ether into the reaction mixture afforded a precipitation of a syrup (4). The cationic base moiety of 4 would be susceptible to nucleophilic displacements at the C-6 position. Thus, the syrup (4), without further purification because of its instability, was treated with 2.5 equivalents of diethyl sodiomalonate in tetrahydrofuran-DMA at room temperature for 1 h. The reaction proceeded with concomitant evolution of methyl mercaptan. After separation by a silica gel column chromatography, 1-methyl-6-bis(ethoxycarbonyl)methylene-1,6-dihydro-9-β-D-ribofuranosylpurine (5) was obtained as a yellow foam in 58% yield; nmr (DMSO-d_6-D_2O) δ: 1.13 (6H, t, $CH_2\underline{CH_3}$), 3.65 (3H, s, NCH_3), 4.04 (4H, q, $\underline{CH_2}CH_3$), 5.92 (1H, d, 1'-H), 3.4-4.6 (other sugar protons), 8.50 and 8.65 (each 1H, s, 2-H, 8-H);

uv (H_2O) λmax nm: 251, 388, λmin: 236, 295-325 (plateau). The appearance of the absorption maximum at longer wavelength region (388 nm) was indicative of conjugation of the chromophores through the exo-methylene group. Similar treatment of 4 with ethyl sodioacetoacetate gave the 6-acetoacetate derivative in high yield.

Treatment of 5 with 2 equivalents of KOH in absolute methanol at 50° C for 3 h followed by separation of the reaction mixture on a silica gel column gave 6-methoxycarbonyl-7-methylamino-3-β-D-ribofuranosyl-3H-imidazo[4,5-b]pyridin-5(4H)-one (7)[8] in 36% yield; mp 216-217° C; m/e: 354 (M^+), 222 (B+1); nmr (DMSO-d_6)δ: 3.50 (3H, d, NCH_3), 3.86 (3H, s, OCH_3), 5.1-5.6 (sugar hydroxyl protons), 5.81 (1H, d, 1'-H), 3.4-4.6 (other sugar protons), 8.12 (1H, s, 2-H), 8.3 (1H, br, N^7-H); uv (H_2O) λmax nm (ε): 243 (28800), 288 sh (10800), 297 (11100), λmin: 267 (7800). The similar reaction of 5 with KOH in ethanol gave the ethyl ester of 7 in 23% yield.

A mechanism of the reaction could be explained as follows. Hydroxide ion attacks initially on the C-2 of 5 to give the ring-opened intermediate (6), and subsequently removes the N-formyl group from 6. The resulting free amino group reacts with the ester function to cause ring closure into 1-deazapurine. Successive transesterification at the ethoxycarbonyl group of the product gives 7.

When 7 was heated at 80° C for 2 h in 1 N NaOH to hydrolyze the ester group, a crystalline compound was obtained which turned out to be the desired decarboxylated product, 7-methylamino-3-β-D-ribofuranosyl-3H-imidazo[4,5-b]pyridin-5(4H)-one [8, 98%, mp 251-252° C (decomp); m/e: 296 (M^+), 164 (B+1); nmr (DMSO-d_6)δ: 2.80 (3H, d, NCH_3), 4.8-5.8 (sugar hydroxyl protons), 5.42 (1H, s, 6-H), 5.79 (1H, d, 1'-H), 3.4-4.6 (other sugar protons), 6.68 (1H, q, N^7-H), 7.99 (1H, s, 2-H); uv (H_2O) λmax nm (ε): 227 (19100), 265 (20100), 282 (14900), λmin: 244 (7000), 275 (14200)].

Reactions of 4 with other carbon nucleophiles would provide various 6-carbon substituted purine nucleosides and their transformations to 1-deazapurine derivatives may also be possible by the present procedure. Studies in this direction, including the synthesis of 1-deazaadenosine itself, are currently in progress.

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REFERENCES AND NOTES

1. This paper constitutes Part XXXV of "Nucleosides and Nucleotides". Part XXXIV, K. Miura and T. Ueda, Chem. Pharm. Bull., 28, in press (1980).

2. For example, see: T. Itoh, S. Kitano, and Y. Mizuno, J. Heterocyclic Chem., 1972, 9, 465; T. Itoh, J. Inaba, and Y. Mizuno, Heterocycles, 1977, 8, 433; P. D. Cook, L. B. Allen, D. G. Streeter, J. H. Huffman, R. W. Sidwell, and R. K. Robins, J. Med. Chem., 1978, 21, 1212.

3. P. Brookes, A. D. Dipple, and P. D. Lawley, J. Chem. Soc. (C), 1968, 2026.

4. T. Fujii, C. C. Wu, T. Itaya, S. Moro, and T. Saito, Chem. Pharm. Bull., 1973, 21, 1676.

5. K. Miura, T. Kasai, and T. Ueda, Chem. Pharm. Bull., 1975, 23, 464. T. Ueda, K. Miura, and T. Kasai, Chem. Pharm. Bull., 1978, 26, 2122.

6. A. Yamane, A. Matsuda, and T. Ueda, Chem. Pharm. Bull., 1980, 28, 150.

7. K. Miura and T. Ueda, Chem. Pharm. Bull., 1975, 23, 2064.

8. Satisfactory elemental analyses were obtained for crystalline compounds 7 and 8.

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