A Convenient Synthesis of 8-Azaadenosine (1)

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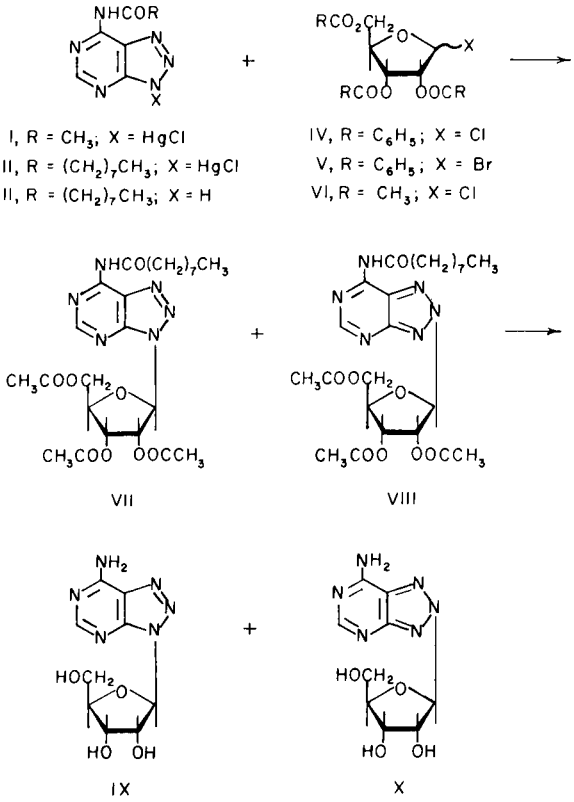
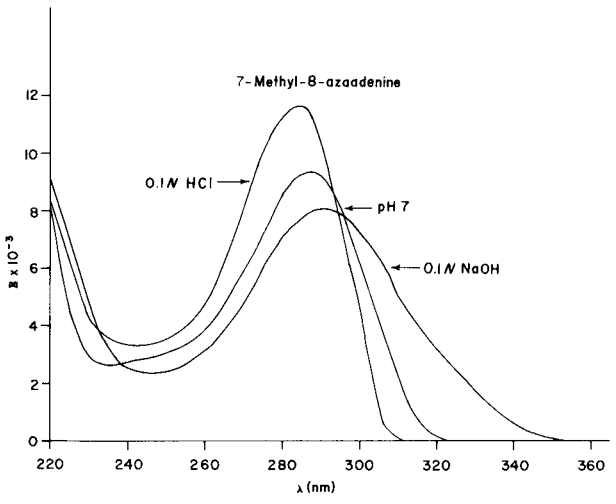
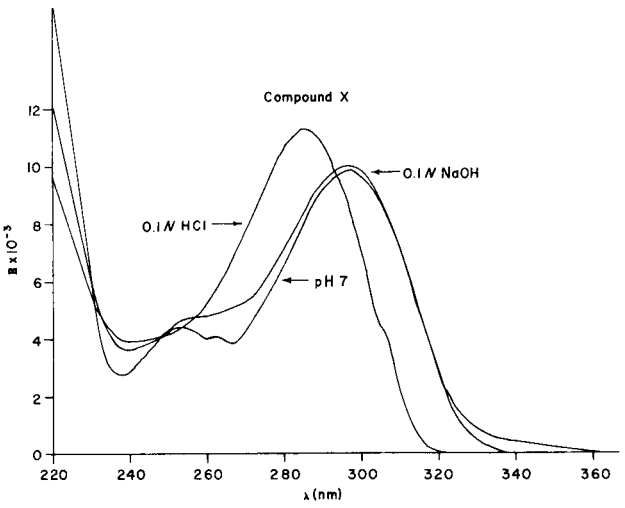
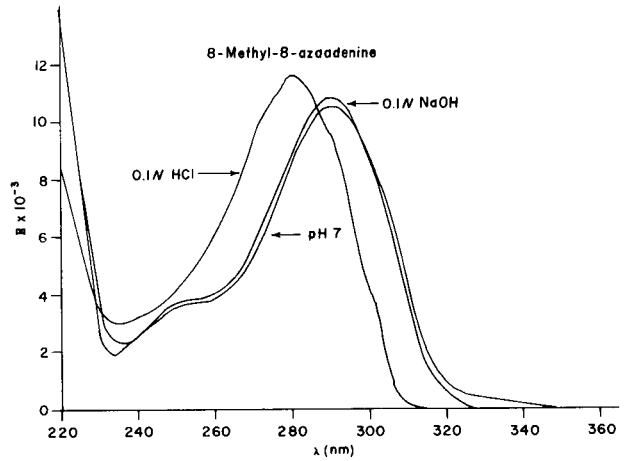
Derivatives of *v*-triazolo[4,5-*d*]pyrimidine, particularly 8-azaguanine (5-amino-7-hydroxy-*v*-triazolo[4,5-*d*]pyrimidine), have received considerable attention as purine antagonists in biological systems including viruses and cancer (2). More recently the differences in biologic activity of purine analogs and their nucleosides have become appreciated (2-4) and have made the study of the biologic effects of 8-azaadenosine (7-amino-3-β-D-ribofuranosyl-*v*-triazolo-[4,5-*d*]pyrimidine) and its derivatives important. The synthesis of 8-azaadenosine (IX) was first reported by Davoll (5), who prepared it by the conventional chloromercuri procedure from *N*-acetyl-8-azaadenine. Although he did not give a yield of pure material, it was less than 16% (6). In our hands the reaction inconsistently gave yields of pure IX on the order of 10%, and chromatography on silica gel indicated the presence of an isomer not detected by Davoll. Substitution of the chloromercuri derivative of *N*-nonanoyl-8-azaadenine (II) for the *N*-acetyl derivative I in this reaction gave, surprisingly, a 13% yield of the other isomer and only a very small yield of the blocked 8-azaadenosine (VII). An analytically pure sample of the other isomer was prepared, and a comparison of its uv spectrum with that of the 7- and 8-methyl-8-azaadenines (9) (see Figure) clearly shows that the isomer is the 8-substituted-8-azaadenine (7-amino-2-β-D-ribofuranosyl-*v*-triazolo[4,5-*d*]pyrimidine, X). This assignment is supported by the infrared and proton magnetic resonance spectra of the three compounds. Because of the hydroxyl absorption of X comparisons cannot be made of the NH stretching region of the infrared spectra, but in the region of NH deformation and double bond stretching such comparisons can be made. The spectrum of the 7-isomer shows a double peak at 1655 and 1635 cm^{-1}, whereas the spectra of the 8-isomer and X show only a single peak at 1660 cm^{-1}. Furthermore, although the absorption due to C_2 in the pmr spectra occurs at about 8.3 δ for all three compounds, the NH absorption is much further downfield from TMS in the case of X (8.23) and the 8-isomer (8.01) than in the case of the 7-isomer (7.68), due no doubt to the greater shielding effect of the methyl group in the latter case.

In an effort to improve the yield of 8-azaadenosine (IX), we investigated the reaction of *N*-nonanoyl-8-azaadenine (6) (III) itself with tri-*O*-benzoyl-D-ribofuranosyl bromide









(V) in *N,N*-dimethylacetamide at room temperature for seven days; a 12% yield of 8-azaadenosine (IX) and a 2% yield for the other isomer were obtained. The addition of Linde molecular sieve 4-A to the reaction reduced the yield. When, however, III was allowed to react with tri-*O*-acetyl- -ribofuranosyl chloride (VI) in the presence of Linde molecular sieve AW500 (10) in refluxing benzene for 4 hours and the resulting nucleoside deacylated, a 48% conversion (based on III) to 8-azaadenosine (IX) was effected, and none of the undesired isomer was detected in the reaction mixture.

EXPERIMENTAL (11)

Chloromercuri Derivative of *N*-Nonanoyl-8-azaadenine (II).

To a boiling solution of 2.76 g. (10 mmoles) of 7-nonanamido-*v*-triazolo[4,5-*d*]pyrimidine (12) and 2.71 g. (10 mmoles) of mercuric chloride in 100 ml. of ethanol was added dropwise 10 ml. of 1 *N* sodium hydroxide. After an additional 0.5 hour of reflux the product was collected by filtration, washed with water until free of chloride ion, then with ethanol and ether and dried *in vacuo* over phosphorus pentoxide at 78° for 3 hours, yield 4.7 g. (92%).

8-Azaadenosine (7-Amino-3-β-D-ribofuranosyl-*v*-triazolo[4,5-*d*]-pyrimidine) (IX).

A solution of 2,3,5-tri-*O*-acetylribofuranosyl chloride (13) (prepared from tetra-*O*-acetyl-D-ribofuranose, 1.43 g., 4.5 mmoles) in 100 ml. of dry benzene was added to a flask containing 1.38 g. (5.0 mmoles) of *N*-nonanoyl-8-azaadenine and 10 g. of molecular sieve (AW500-1/16 in. pellets). The mixture was stirred and refluxed for 1 hour and 10 g. of molecular sieve was added. Reflux was continued an additional 3 hours. The reaction mixture was then chilled in an ice bath and filtered. The insoluble material, from which 371 mg. (27%) of *N*-nonanoyl-8-azaadenine was recovered, was washed thoroughly with dry benzene. The filtrate and washings were combined and evaporated to dryness *in vacuo*. A light orange syrup (VIII) weighing 1.68 g. was obtained. A solution of the syrup (VIII) in dry methanol (30 ml.) containing sodium methoxide (540 mg., 10.0 mmoles) was refluxed for 0.5 hour, chilled, and neutralized with concentrated acetic acid. The solution was then evaporated to dryness *in vacuo*. A solution of the residue in 100 ml. of water was washed twice with 50 ml. of chloroform. The aqueous layer was concentrated to ~20 ml., whereupon a crystalline solid was obtained. After thoroughly chilling the mixture it was filtered. A buff-colored solid was obtained; yield 451 mg. (48% conversion).

One recrystallization from water gave the analytical sample, m.p. 215-217° (Mel-Temp); $[\alpha]_D^{40}$ -79.9 ± 0.8° (*c* 0.5 H_2O); δ ppm (DMSO-d_6): 3.61 (m, $C_5'H_2$), 4.03 (t, $C_4'H$), 4.37 (t, $C_3'H$), 4.91 (t, $C_2'H$), 6.20 (d, $J_{1'2'}$ 5 Hz, $C_1'H$), 8.33 (C_2H).

Anal. Calcd. for $C_9H_{12}N_6O_4$: C, 40.30; H, 4.51; N, 31.33. Found: C, 40.12; H, 4.38; N, 31.49.

8-β-D-Ribofuranosyl-8-azaadenine(7-Amino-2-β-D-ribofuranosyl-*v*-triazolo[4,5-*d*]pyrimidine (X).

Reaction of the chloromercuri derivative II (4.7 g., 9.2 mmoles) with tri-*O*-acetyl-D-ribofuranosyl chloride (prepared from 3.18 g. of tetra-*O*-acetyl-β-D-ribofuranose) in refluxing xylene gave, after the usual work-up, 5.2 g. of a syrup which was treated with methanolic sodium methoxide. From the resulting syrup (2.4 g.) was isolated 350 mg. (13%) of a solid, m.p. 194-196° (Heizbank). Precipitation of this material from water gave the analytical sample, δ ppm (DMSO-d_6): 3.63 (m, $C_5'H_2$), 4.07 (q, $C_4'H$), 4.35 (t, $C_3'H$), 4.63 (t, $C_2'H$), 6.15 (d, $J_{1'2'}$ 4 Hz, $C_1'H$), 8.32 (C_5H); $[\alpha]_D^{40}$ -43.6 ± 3.5° (*c*, 0.52, H_2O).

Anal. Calcd. for $C_9H_{12}N_6O_4 \cdot 0.4H_2O$: C, 39.24; H, 4.68. N, 30.51. Found: C, 39.48; H, 4.74; N, 30.18.

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