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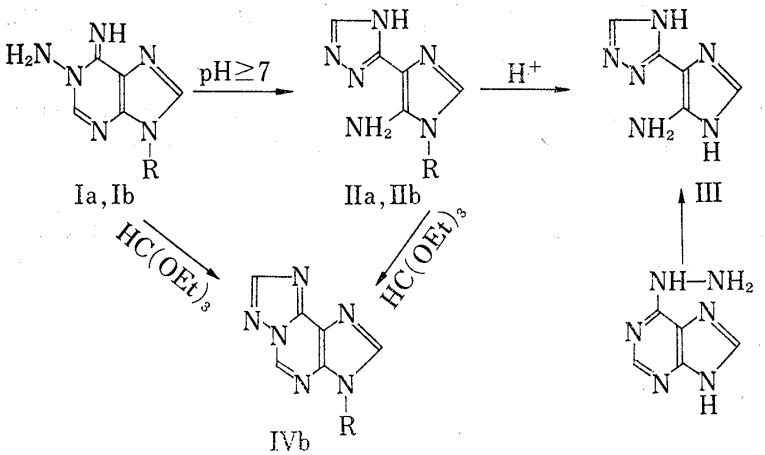
Studies on Chemical Alterations of Nucleic Acids and Their Components. VIII.[1] Alkaline Rearrangement of 1-Aminoadenosine to 5-Amino-1-β-D-ribofuranosyl-4-(1,2,4-triazol-3-yl)imidazole

It is well known as Dimroth rearrangement that 1-alkyl- and 1-alkoxy-adenine derivatives are rearranged in alkaline media to N^6-alkyl- and N^6-alkoxy-adenines, respectively, through hydrolytic cleavage of 1,2-bond, followed by dehydrative ring closure.[2,3] This paper describes alkaline rearrangement of 1-aminoadenosine (Ia) which was recently prepared in our laboratory by amination of adenosine.[1]

The solution of the hydrochloride (Ia, 1.5 g) in 10 ml of water was adjusted to pH 11 with conc. sodium hydroxide and heated at 60° for 2 hr. When the reaction mixture was kept standing at room temperature, the product IIa was precipitated as colorless material, which was almost a pure form of the product. The yield was 83%. mp 119—120° (decomp.) (from H_2O). *Anal.* Calcd. for $C_{10}H_{14}O_4N_6 \cdot 5/6\ H_2O$ (hygroscopic): C, 40.40, H, 5.27, N, 28.28. Found: C, 40.41, H, 4.82, N, 28.10. UV λ_{max} (nm): pH 1, 247 and 260 (sh.); pH 7, 260; pH 11, 250. pK_a in H_2O at 25°: 3.8 and 10.3 (measured by ultraviolet (UV) spectroscopy). The rearranged product IIa was hydrolyzed in conc. HCl at 37° for 2 days. The hydrolyzed product III purified by chromatography was found to be identical with 5(4)-amino-4(5)-(1,2,4-triazol-3-yl)-imidazole which was derived from 6-hydrazinopurine through several steps.[4] UV λ_{max} (nm): pH 1, 244 and 260; pH 7, 265; pH 13, 262. The nuclear magnetic resonance (NMR) and pK_a data also supported the structural assignment of IIa.



1-Amino-9-methyladenine (Ib) underwent alkaline rearrangement under the reaction condition chosen for the riboside to product 5-amino-1-methyl-4-(1,2,4-triazol-3-yl)-imidazole (IIb) in a quantitative yield. The treatment of either Ib or IIb with ethyl orthoformate gave 7-methyl-s-triazolo[3,2-*i*]purine (IVb), as formulated in the Chart. mp 271° (from methanol).

1) Part VI: G.-F. Huang, T. Okamoto, M. Maeda, and Y. Kawazoe, *Tetrahedron Letters*, **1973**, 4541 (Part VII: M. Maeda, K. Nushi, and Y. Kawazoe, *Tetrahedron*, **30**, in press (1974)).
2) D.J. Brown, in "Mechanism of Molecular Migrations," I, Interscience Publishers, New York, 1968 p. 209.
3) T. Fujii, T. Itaya, C.C. Wu, and F. Tanaka, *Tetrahedron*, **27**, 2415 (1971).
4) C. Temple, Jr., C. Kussner, and J.A. Montgomery, *J. Org. Chem.*, **30**, 3601 (1965).

UV λ_{mxa} (nm): pH 1, 276; pH, 7, 281; pH 13, unstable. This fact is a further confirmation of the structural identity of the rearrangement product.

It is worth noting that 6-hydrazinopurine riboside which might have been expected to be the Dimroth rearrangement product of Ia, did not convert to IIa under the reaction conditions chosen in the present study. It is considered that the rearrangement was initiated by hydrolytic cleavage of 1,2-bond, followed by migration of the formyl group to N-amino group and then, by dehydrative ring-closure to give II. Details are to be described in a forthcoming paper.

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Studies on Quinolizine Derivatives. XI.[1] Synthesis of Azacycl[3,3,3]azine Derivatives. (4)

As an extension of our studies on azacyclazine derivatives, we have investigated the syntheses of 1-azacycl[3,3,3]azine derivatives (I).[2] In this communication, we wish to describe that the stable salt of 2-methyl-1-azacycl[3,3,3]azine hydrobromide (IV) and its unstable free base (V) are prepared by the degradation from methyl 9-cyano-2-methyl-1-azacycl[3,3,3]-azine-7-carboxylate (I).

A mixture of I in polyphosphoric acid (PPA) was heated on a boilling water bath for 4 hr to give corresponding 9-carboxamide derivative (II), mp 277—278°. While a mixture of I in PPA was heated at 150° for 4 hr to give decarboxylated 9-carboxamide derivative (III), mp 237°.

Then a mixture of II or III in 48% hydrobromic acid was refluxed for 4 hr to give 2-methyl-1-azacycl[3,3,3]azine hydrobromide (IV), mp>300°. Mass Spectrum *m/e*: 182 (M^+). UV λ_{max}^{EtOH} mμ (log ε): 228 (4.23), 268 (4.43), 350 (4.05), 375 (4.06), 388 (4.05), 428 (2.99). NMR (DMSO-d_6) δ: 6.94 (1H, triplet), 6.70 (1H, triplet), 6.26 (2H, doublet), 6.17 (1H, doublet), 5.50 (1H, doublet), 4.64 (1H, singlet), 1.40 (3H, singlet), all coupling constants being *ca.* 8 Hz.

The free base, 2-methyl-1-azacycl[3,3,3]azine (V) was obtained as yellowish brown precipitate (λ_{max}^{EtOH} mμ: 270, 283 (shoulder), 387, 405, 417, 428) by treatment of IV with potassium carbonate solution but the product was unstable and could not be purified by recrystallization. Then the NMR spectrum of the crude free base (V) in $CDCl_3$ was recorded: δ 5.64 (1H, triplet),

1) Part X: H. Awaya, C. Maseda, Y. Tominaga, R. Natsuki, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, submitted.
2) H. Awaya, C. Maseda, Y. Tominaga, R. Natsuki, Y. Matsuda and G. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **22**, 1424 (1974).