The Reactions of 5-Amino-4-hydrazinopyrimidines with Nitrous Acid; a New Purine Synthesis[1]

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The reaction of 5-amino-4-chloro-6-hydrazinopyrimidine (I) with nitrous acid has been shown to give 8-amino-7-chlorotetrazolo[1,5-*c*]pyrimidine (II). Reaction of II with diethoxymethyl acetate gave 4-azido-6-chloro-5-ethoxymethyleneaminopyrimidine (V), a result of tetrazole-azidoazomethine interconversion, and heating V in an inert solvent gave 6-chloro-8-ethoxypurine (IX). This sequence of reactions constitutes a new and novel purine synthesis.

The reaction of 5-amino-4-chloro-6-hydrazinopyrimidine (I) with formic acid has been shown to give 9-aminohypoxanthine,[2] apparently because the initial reaction—formylation of the 2-nitrogen of the 4-hydrazino group—provided an *in situ* generated blocking group which then directed the ring closure to the 1-nitrogen of the 4-hydrazino group. The reaction of I with nitrous acid could give any one, or combination, of four products (II, III, VI, or VII). In fact only one major product (A) was obtained. Hydrazinopyrimidines not containing an adjacent amino group have been shown to yield, on treatment with nitrous acid, tetrazolopyrimidines[3] in one case and azidopyrimidines[4] in another. 5-Amino-4-azido-6-chloropyrimidine (III) could be eliminated from consideration for the structure A by the fact that A does not exhibit azide absorption in the 2160–2120-cm.$^{-1}$ region[5] of its infrared spectrum. Actually, some of the crude reaction products did show weak azide absorption at 2145 cm.$^{-1}$ indicating the presence of the azidopyrimidine III as a minor product of the reaction.[6] However, paper chromatography indicated the presence of only one species in the purified material. Comparison of the ultraviolet spectrum of the product A with that of 7-chloro-3-ethyl-3*H*-*v*-triazolo[4,5-*d*]pyrimidine (XVIII) indicated to us that 3-amino-7-chloro-3*H*-*v*-triazolo[4,5-*d*]pyrimidine (VI) was not likely either (see Experimental).

Chemical support for the structure II was provided by the fact that this same material was obtained from the reaction of 5-amino-4,6-dichloropyrimidine (IV) and sodium azide. This reaction definitely eliminated structure VI from consideration as the initial product. Further, the reaction of II with diethoxymethyl acetate[9] at room temperature gave an ethoxymethylene derivative[10] whose infrared spectrum in solution and in the liquid state exhibited strong azide absorption indicating the structure V, which could not be formed from VI. The tetrazole-azidoazomethine equilibrium in the pyridine series has been investigated thoroughly by Boyer and co-workers[7,8] who have established that electron-donating groups (such as the amino group) stabilize the tetrazole ring system, whereas electron withdrawing groups (such as the nitro group) destabilize the tetrazole ring system and stabilize the electron donating azido group. Apparently, the electron-donating property of the amino group of II is sufficiently diminished by conversion to the ethoxymethyleneamino group to reverse the tetrazole-azidoazomethine equilibrium to such an extent that only the azido form of V is isolated.

Positive evidence for the structure II was provided also by the infrared spectrum of A. The presence of a primary amino group was indicated by typical absorption at 3430, 3395, and 3300 cm.$^{-1}$ due to NH stretching[11,12] and at 1620 cm.$^{-1}$ due to NH deformation,[12] and the presence of the tetrazole ring was indicated by bands at 1075, 1060, and 1000.[13]

Reaction of II with diethoxymethyl acetate in refluxing anisole gave a new compound IX, identified as 6-chloro-8-ethoxypurine by stepwise hydrolysis first in acid to 6-chloro-8-hydroxypurine[14] (X) and then hydrolysis of X in base to 6,8-dihydroxy-

(1) This work was supported by funds from the C. F. Kettering Foundation and from the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. SA-43-ph-1740.

(2) J. A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, **82**, 4592 (1960).

(3) C. Bülow, *Ber.*, **42**, 4429 (1909); C. Bülow and K. Haas, *Ber.*, **42**, 4638 (1909).

(4) F. R. Benson, L. W. Hartzel, and E. A. Otten, *J. Am. Chem. Soc.*, **76**, 1858 (1954).

(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co. Ltd., London, 1954, p. 223.

(6) Structures II and III could be in equilibrium, but, if they are, the equilibrium must lie far in the direction of the tetrazole. Boyer, and co-workers[7,8] have established the existence of the tetrazole-azidoazomethine equilibrium in the pyridine series.

(7) J. H. Boyer and E. J. Miller, Jr., *J. Am. Chem. Soc.*, **81**, 4671 (1959).

(8) J. H. Boyer and H. W. Hyde, *J. Org. Chem.*, **25**, 458 (1960).

(9) H. W. Post and E. R. Erickson, *J. Org. Chem.*, **2**, 260 (1937).

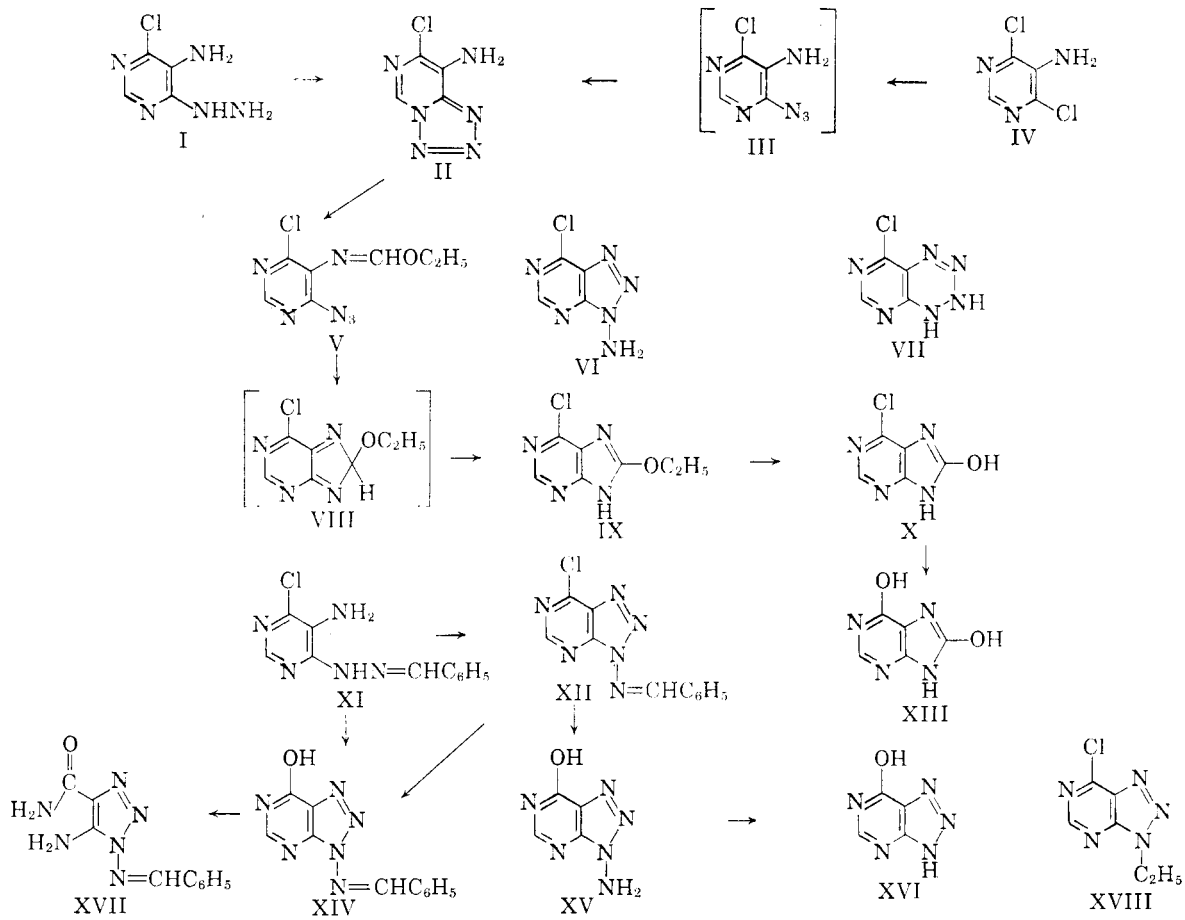
(10) Although the reaction of A with diethoxymethyl acetate at room temperature does not unequivocally eliminate the tetrazine structure VII, it is unlikely that this mild treatment would cause the rupture of such a ring.

(11) The infrared spectrum of A in the X—H stretching region was practically identical with that of 8-aminopyridotetrazole.[8]

(12) Ref. 3, p. 212.

(13) E. Lieber, D. Levering, and L. Patterson, *Anal. Chem.*, **23**, 1594 (1951).

(14) R. K. Robins, *J. Am. Chem. Soc.*, **80**, 6674 (1958).



purine[14] (XIII). This reaction of II to give IX *via* V not only provided additional evidencef or the structure of II and V but also constitutes a novel purine synthesis and, in fact, permitted the preparation of a purine whose preparation is not possible by any of the conventional purine syntheses. This type of ring closure, involving intramolecular hydrogen abstraction, is known to give other heterocycles such as carbazoles,[15] carboline, and thienoindole.[16]

Nitrosation of 5-amino-4-benzylidenehydrazino-6-chloropyrimidine in aqueous acetic acid gave 3-benzylideneamino-7-chloro-3*H*-*v*-triazolo[4,5-*d*]-pyrimidine (XII), since the benzylidene blocking group precluded the tetrazole formation described above. However, a mixture of XII and II was obtained when the nitrosation reaction was carried out in a mixture of aqueous hydrochloric acid and dioxane. Apparently, II arose *via* I, formed by hydrolysis of the benzylidene group of XI. Dilute acid treatment of XII gave 3-amino-3*H*-v-triazolo-[4,5-*d*]pyrimidin-7-ol resulting from hydrolysis of both the 7-chloro group and the benzylidene group of XII. The intermediate XV was not isolated but its acid solution was treated with sodium nitrite which caused deamination to *v*-triazolo[4,5-*d*]pyrimidin-7-ol (8-azahypoxanthine) (XVI), a known compound. This sequence (XII → XV → XVI) established the identity of XII. Treatment of XI with an aqueous solution of nitrous acid in *N*,*N*-dimethylformamide and glacial acetic acid instead of water resulted in ring closure with concomitant hydrolysis of the chlorine atom of XI to give 3-benzylideneamino-3*H*-*v*-triazolo[4,5-*d*]pyrimidin-7-ol (XIV). The ultraviolet spectrum indicated that an aqueous basic solution of XII at room temperature also formed XIV while hot base treatment of XII apparently ruptured the pyrimidine ring resulting in the formation of XVII. This structure has not been established unequivocally.

Experimental

The melting points reported were determined on a Kofler Heizbank and are corrected. The ultraviolet spectra were determined in aqueous solution with a Cary Model 14 or with a Beckman DK-2 (optical densities at the maxima with a Beckman DU). The infrared spectra were determined in pressed potassium bromide disks or when indicated, in solution, with a Perkin-Elmer Model 221 spectrophotometer.

8-Amino-7-chlorotetrazolo[1,5-*c*]pyrimidine (II).—(A). A solution of sodium nitrite (450 mg., 6.52 mmoles) in water (2 ml.) was added with stirring at room temperature to a solution of 5-amino-4-chloro-6-hydrazinopyrimidine[2] (1.00 g., 6.26 mmoles) in water containing 1 equivalent of con-

(15) P. A. S. Smith and B. B. Brown, *J. Am. Chem. Soc.*, **73**, 2435 (1951).

(16) P. A. S. Smith and J. H. Boyer, *J. Am. Chem. Soc.*, **73**, 2626 (1951).

centrated hydrochloric acid (0.53 ml.). The solid that deposited was collected by filtration, washed with a small amount of water, and dissolved in dioxane (25 ml.). After removing some insoluble material, the dioxane filtrate was evaporated to dryness *in vacuo* and the residue purified by sublimation with slight decomposition at 110–115° (1 mm.); yield 600 mg. (56 %); m.p. 170–172° dec. with sublimation (when taken from 150°); λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1—282 (10.1), 311 (7.3); pH 7—282 (10.1), 311 (7.3); pH 13—285 (unstable); ν in cm.$^{-1}$: 3430, 3395, 3300, 3200, and 3110 (NH and CH)[11]; 1620 (NH); 1600, 1550, and 1480 (C=C, C=N); 1075, 1060, and 1000 (tetrazole ring).[13] In some samples a weak azido absorption band appeared at 2145 cm.$^{-1}$, indicating the presence of 5-amino-4-azido-6-chloropyrimidine.

Anal. Calcd. for $C_4H_3ClN_6$: C, 28.15; H, 1.76; Cl, 20.80; N, 49.25. Found: C, 28.37; H, 1.66; Cl, 20.63; N, 49.36.

(B). A solution of 5-amino-4,6-dichloropyrimidine (10.0 g., 61.0 mmoles) in dimethylformamide (100 ml.) containing sodium azide (5.0 g., 77 mmoles) was heated at 95–100° for 1 hr. and poured into water (200 ml.). The solid that deposited was collected by filtration, washed with water (2 × 25 ml.), and dried *in vacuo* over phosphorus pentoxide; yield 8.9 g. (83 %); m.p. 171–173° dec. with sublimation (when taken from 150°).

4-Azido-6-chloro-5-ethoxymethyleneaminopyrimidine (V).—A suspension of 8-amino-7-chlorotetrazolo[1,5-*c*]pyrimidine (1.00 g., 5.87 mmoles) in diethoxymethyl acetate (20 ml.) was allowed to stand at room temperature under anhydrous conditions. The solid was completely dissolved after standing overnight. At the end of 3 days the solution was evaporated to a small volume *in vacuo*, and the liquid distilled at about 123–126°/2 mm.; yield 1.00 g. (75%): one sample of the liquid that was not kept under anhydrous conditions decomposed to 8-amino-7-chlorotetrazolo[1,5-*c*]pyrimidine. λ_{max} in mμ ($\epsilon \times 10^{-3}$): C_2H_5OH–298 (10.0); ν in cm.$^{-1}$ ($CHCl_3$): 3020 (aromatic CH); 2940 and 2900 (aliphatic CH); 2145 (—N_3); 1640 (exocyclic C=N); 1620, 1590, and 1530 (C=C, C=N); 1470 and 1370 (aliphatic CH); 1245 (=CHOC_2H_5).

Anal. Calcd. for $C_7H_7ClN_6O$: C, 37.10; H, 3.09; Cl, 15.66; N, 37.10. Found: C, 37.14; H, 3.17; Cl, 15.81; N, 37.17.

6-Chloro-8-ethoxypurine (IX).—A solution of 8-amino-7-chlorotetrazolo[1,5-*c*]pyrimidine (500 mg., 2.93 mmoles) in anisole (10 ml.) containing diethoxymethyl acetate (4.0 ml.) was refluxed for 1.5 hr., evaporated to dryness *in vacuo*, and the residue recrystallized from water to give impure product; yield 360 mg. (62 %). The analytical sample was obtained by recrystallization of a small amount of the above solid from petroleum ether (b.p. 85–105°) m.p. 187–190° dec with sublimation; λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1—274 (11.7); pH 7—279 (11.3); pH 13—281 (11.6); ν in cm.$^{-1}$: 3070 (aromatic CH); 2990, 2940, and 2880 (aliphatic CH); 2800–2400 (acidic H); 1630, 1585, 1550 (C=C, C=N); 1455 and 1370 (aliphatic CH).

Anal. Calcd. for C_7H_7ClNO: C, 42.30; H, 3.53; Cl, 17.88; N, 28.20. Found: C, 42.42; H, 3.73; Cl, 17.60; N, 28.25.

3-Benzylideneamino-7-chloro-3*H*-*v*-triazolo[4,5-*d*]pyrimidine (XII).—Solid sodium nitrite (300 mg., 4.35 mmoles) was added with stirring to a suspension of 5-amino-4-benzylidenehydrazino-6-chloropyrimidine (1.00 g., 4.04 mmoles) in 20% aqueous acetic acid (20 ml.) and the whole stirred at room temperature for 12 hr. The solid was collected by filtration, washed with water (5 ml.), and dried *in vacuo* over phosphorus pentoxide; yield 800 mg.; m.p. 184° dec. (with softening from 180°).

A sample was purified by boiling in 1:1 ethanol–water and drying the insoluble solid *in vacuo* over phosphorus pentoxide; m.p. 191–192° dec. with sublimation. The ultraviolet spectrum indicated that this compound was converted to the corresponding 7-hydroxy compound in 0.1 *N* sodium hydroxide; λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1,13—(unstable); pH 7—267 (20.4), 309 (15.7); $\bar{\nu}$ in cm.$^{-1}$: 1600, 1590, 1575, and 1510 (C=C, C=N); 765 and 690 (monosubstituted phenyl).

Anal. Calcd. for $C_{11}H_7ClN_6$: C, 51.00; H, 2.71; Cl, 13.72; N, 32.50. Found: C, 50.93; H, 2.83; Cl, 13.65; N, 32.59.

***v*-Triazolo[4,5-*d*]pyrimidin-7-ol (XVI) from 3-Benzylideneamino-7-chloro-3*H*-*v*-triazolo[4,5-*d*]pyrimidine (XII).**—The ultraviolet spectrum of an aliquot from a suspension of 3-benzylideneamino-7-chloro-*v*-triazolo[4,5-*d*]-pyrimidine in 1 *N* hydrochloric acid which had been refluxed for 1 hr. indicated that the chlorine atom had been replaced by a hydroxy group. Steam distillation of the acidic solution removed the benzal group as benzaldehyde.

The acidic solution was next concentrated on the hot plate, the insoluble material removed by filtration, and the filtrate treated with excess sodium nitrite. After warming for 30 min., the solution was evaporated to dryness *in vacuo*. The residue was shown to be impure *v*-triazolo-[4,5-*d*]pyrimidin-7-ol by comparison of its ultraviolet spectrum and chromatographic characteristics with that of an authentic sample.

3-Benzylideneamino-3*H*-*v*-triazolo[4,5-*d*]pyrimidin-7-ol (XIV).—A solution of sodium nitrite (600 mg., 8.70 mmoles) in water (5 ml.) was added with stirring at room temperature to a solution of 5-amino-4-benzylidenehydrazino-6-chloropyrimidine[2] (2.00 g., 8.08 mmoles) in 3:1 dimethylformamide–glacial acetic acid (40 ml.). At the end of 1 hr. the mixture was diluted with water (100 ml.), and the solid (1.35 g.) collected and recrystallized from 1:1 water–dimethylformamide (120 ml.); yield 970 mg. (50%); m.p. > 260°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1—252 (15.0), 298 (20.4), 305 (sh.) (19.9); pH 7—252 (13.1), 300 (sh.) (22.3), 305 (22.4); pH 13–251 (17.4), 275 (11.3), 317 (3.02); $\bar{\nu}$ in cm.$^{-1}$: 3420, 3180, and 3140 X—H); 3065 (aromatic CH); 1715 (C=O); 1610, 1600, 1590, 1565, and 1490 (C=C, C=N); 770 and 690 (monosubstituted phenyl).

Anal. Calcd. for $C_{11}H_8N_6O$: C, 55.00; H, 3.33; N, 35.00. Found: C, 54.84; H, 3.37; N, 34.64.

7-Chloro-3-ethyl-3*H*-*v*-triazolo[4,5-*d*]pyrimidine (XVIII).—To a solution of 5-amino-6-chloro-4-ethylaminopyrimidine (500 mg., 2.90 mmoles) in 10:1 water–acetic acid (5 ml.) was added with stirring at room temperature a solution of sodium nitrite (220 mg., 3.18 mmoles) in water (1.0 ml.). After four minutes the white solid that deposited was collected by filtration, washed with water (3 × 3 ml.), and dissolved in ether (25 ml.). The ether solution was treated with magnesium sulfate, the ether removed *in vacuo* (room temperature), and the white solid dried *in vacuo* over phosphorus pentoxide; yield 280 mg. (52.5 %); m.p. 77–78°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1–264 (9.3); pH 7–263 (9.2); pH 13—unstable; $\bar{\nu}$ in cm.$^{-1}$: 2985 and 2940 (aliphatic CH); 1590 and 1570 (C=C, C=N, N=N).

Anal. Calcd. for $C_6H_6ClN_5$: C, 39.25; H, 3.27; Cl, 19.35. Found: C, 39.40; H, 3.38; Cl, 19.22.

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