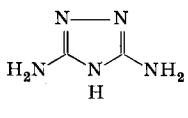
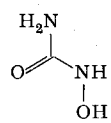
4-Hydroxyurazole[1]

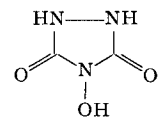
Two antileukemic agents, guanazole[2,3] (I) and hydroxyurea[4] (II), were reported to possess strikingly similar inhibitory effects on DNA synthesis and on ribonucleotide reductase in L1210 leukemia cells[5]. 4-Hydroxyurazole (III, N-hydroxybicarbamimide), a compound which incorporates both structural features of I and II, has been synthesized in this laboratory[6].



I



II



III

Stirring a mixture of 1,2-*bis* (ethoxycarbonyl)hydrazine (IV), 2 eq. of hydroxylamine and sodium hydroxide in 50% aqueous methanol at room temperature for 3 days gave, after acidification, 60% yield of 4-hydroxyurazole (III), m.p. 256–258° (from H_2O). (Calcd. for $C_2H_3N_3O_3$: C, 20.52; H, 2.58; N, 35.90; mol. wt. 117. Found: C, 20.27; H, 2.44; N, 36.06; *m/e* (M^+) 117.) Compound III, which was found to be very stable in neutral and acidic aqueous solution, gave a crimson coloration with ferric chloride solution.

It was originally postulated that compound III was formed via the *bis*hydroxamic acid VIII. Careful control of pH of the reaction mixture by titration with hydrochloric acid and isolation of the reaction intermediates revealed the reaction sequence as follows:

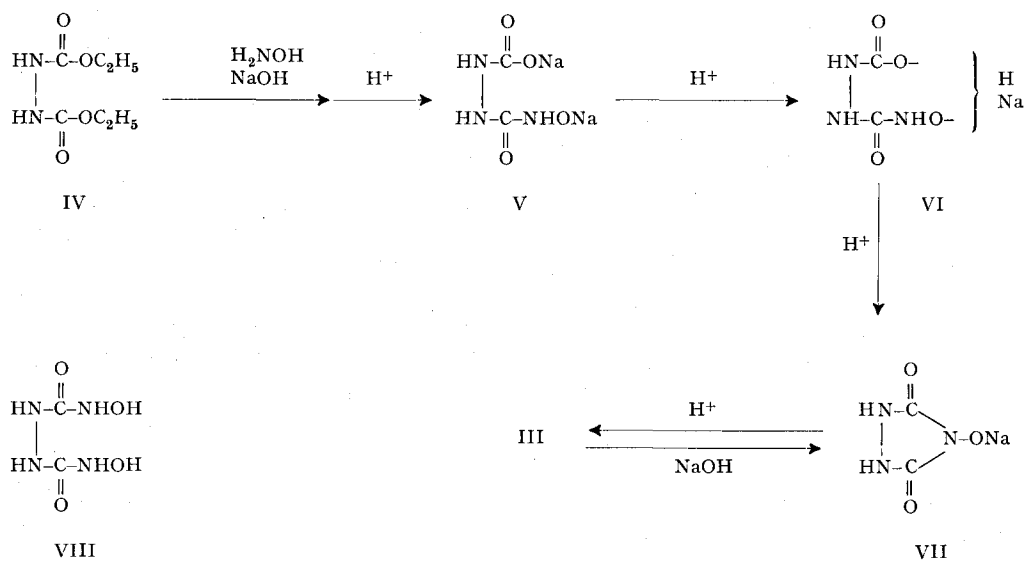
All the intermediates, which gave positive ferric chloride tests, have been isolated and characterized. The disodium salt V was obtained when the pH of the reaction mixture was adjusted to 10.2 ± 0.5 with concentrated hydrochloric acid (Calcd. for $C_2H_3N_3Na_2O_4$: C, 13.42; H, 1.69; N, 23.47. Found: C, 13.13; H, 1.52; N, 23.16). Further acidification to pH 7.2 ± 0.5 yielded the monosodium salt VI (Calcd. for $C_2H_4N_3NaO_4$: C, 15.29; H, 2.57; N, 26.76. Found: C, 15.10; H, 2.82; N, 26.57). The sodium salt of the cyclized product VII was formed at pH 3.5 ± 0.5 (Calcd. for $C_2H_2N_3NaO_3$; C, 17.28; H, 1.45; N, 30.22. Found: C. 17.36; H, 1.70; N; 30.53). Because of its acidity, 4-hydroxyurazole (III) was freed from the salt VII at pH < 1.

The intramolecular hydrogen bonding of the intermediates V and VI probably played an important role with regard to their stability since under ordinary circumstances carbamic acids and their salts decarboxylate readily. The hydrogen-bonding formation also explains the fact that only one, rather than both, ester groups of VI was replaced by the hydroxylamino function.

Zusammenfassung. Durch Hydroxylaminolyse von 1,2-*bis* (äthoxycarbonyl)hydrazin wurde Natriumsalz von 1-Äthoxycarbonyl-2-hydroxylaminocarbonylhydrazin hergestellt und mit wässeriger Salzsäure auf pH < 1 in 4-Hydroxyurazol (N-Hydroxybicarbamimid) synthetisiert.

KWANG-YUEN ZEE-CHENG and C.C. CHENG

Midwest Research Institute, 425 Volker Boulevard, Kansas City (Missouri 64110, USA), 21 June 1971.



IV V VI VII VIII

[1] This investigation was supported by Contract No. PH43-65-94 with Chemotherapy, National Cancer Institute, National Institutes of Health, U.S. Public Health Service.

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