REACTION OF 5-NITROURACIL DERIVATIVES WITH HYDRAZINE AND POTASSIUM CYANIDE

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Treatment of 5-nitro-1,3,6-trimethyluracil (I) with potassium cyanide or hydrazines gave 6-cyano-5-nitro-1,3,6-trimethyl-5,6-dihydrouracil (III) or 5-methyl-4-nitropyrazol-3-ones (IV), respectively. A treatment of 6-bromomethyl-1,3-dimethyl-5-nitrouracil (II) with potassium cyanide gave 6-cyano-1,3-dimethyl-5-nitrocyclothymine (V). Hydrazinolysis of II gave 1,3-dimethyluracil-6-carboxaldehyde hydrazones (VII).

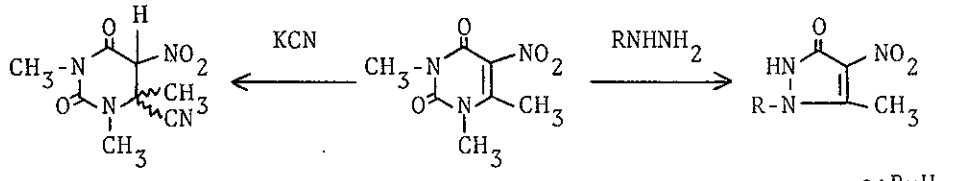
The fact that uracils are easily subjected to a 1,4-nucleophilic addition across their 5,6-double bond is recently becoming an object of attention.[1] Although 5-nitrouracils are regarded as one of the most reactive uracils undergoing a nucleophilic attack on the 6-position because of the strong electron-withdrawing nitro moiety, the resulting 5,6-dihydrouracils have been detected by spectroscopies[2] and have not hitherto been isolated in pure form. Very few attempts have been made to elucidate the mode of reactions of 5-nitrouracils with nucleophiles and, among

them, only Fox et al.[3] reported that the reaction of 5-nitrouracils with sodium azide gave v-triazolo[4,5-b]pyrimidines.

In this communication we describe a treatment of 5-nitrouracil derivatives I and II with potassium cyanide or hydrazines which lead to formation of isolatable 5,6-dihydrouracils or pyrazolones which accompanied an elimination of the nitro group; in particular the compound II showed interesting behavior.

5-Nitro-1,3,6-trimethyluracil (I) was allowed to react with potassium cyanide in DMF at room temperature for 1 hr and the reaction mixture was diluted with water and acidified with hydrochloric acid to give the diastereoisomeric mixture (in a ratio of 7 : 3)[4] of 6-cyano-5-nitro-1,3,6-trimethyl-5,6-dihydrouracil (III), mp 106-110°, in a quantitative yield. The structural assignment of III was made mainly basis on the elemental analysis and the spectral evidence. The NMR spectrum of the mixture III displayed a hygher up-field shift of the C-6 methyl signals at δ1.90 and 1.94 (the former is the main diastereoisomer) than that of I at δ2.42, and new signals of the C-5 methine proton, not observed in I, at δ5.48 and 5.57 as each singlet, respectively. Attempts to isolate each diastereoisomer by a column chromatography on silica or alumina were unsuccessful because decomposition occurred to give I. Compound III was relatively stable under usual conditions but less stable in alkaline media or on refluxing in alcohol, decomposing to I.

On refluxing of I with hydrazine hydrate in 2-propanol for 2 hrs ring contraction occurred to give 5-methyl-4-nitropyrazol-



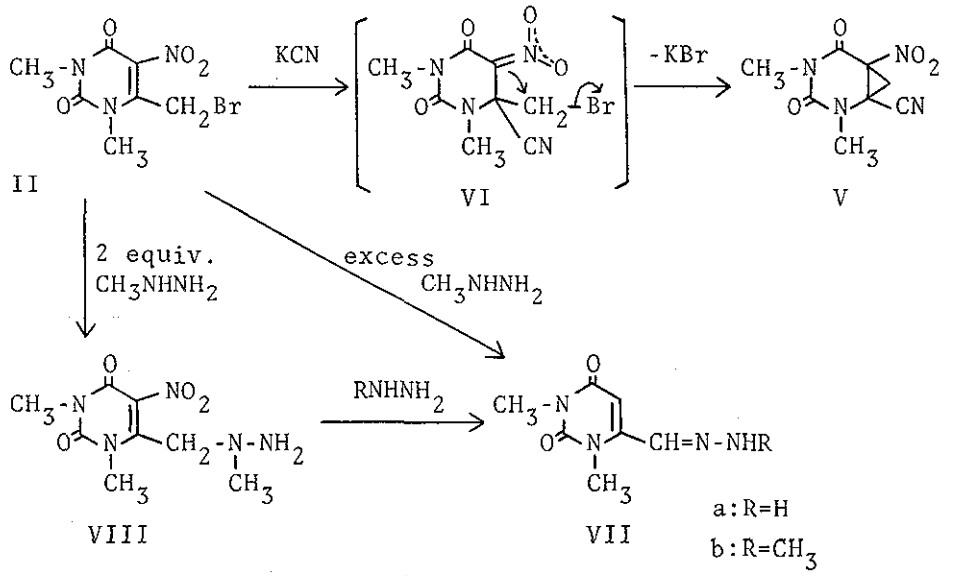
III I IV a:R=H b:R=CH_3

Scheme I

3-one (IVa), mp 224°, in 36 % yield. Similar conversion resulted from a treatment of I with methylhydrazine to give 1,5-dimethyl-4-nitropyrazol-3-one (IVb), mp 157-158°, in 55 % yield. The ring transformation probably takes place by an initial attack of hydrazines on the 6 position analogous to that of cyanide ion as described above. Subsequently, the reaction would proceed exactly according to the previously outlined mechanism,[5] thus fission of the N_1-C_6 bond gave an open-chain ureido derivative, followed by formation of a dihydropyrazole by a ring closure and further hydrolysis of the ureido moiety to give the product IV.

Then, 6-bromomethyl-1,3-dimethyl-5-nitrouracil (II)[6] was selected as a model compound to elucidate the mode of the reactions of 5-nitrouracils with nucleophiles. Treatment of II with potassium cyanide in DMF at room temperature gave 6-cyano-1,3-dimethyl-5-nitro-cyclothymine (V)[7], mp 149-150°, in 40 % yield. The NMR spectrum of V showed the characteristic signals of endo- and exo-proton of cyclopropane ring at δ1.98 and 3.11 with 8.2Hz coupling constant, respectively. The reasonable mechanism for the conversion of II to V would be as follows. An initial attack

by cyanide ion on the C-6 position of II occurs to afford an intermediate VI, which undergoes an intramolecular nucleophilic attack by the aci-nitro group on the C-6 methylene of VI with an elimination of bromo anion to give V.

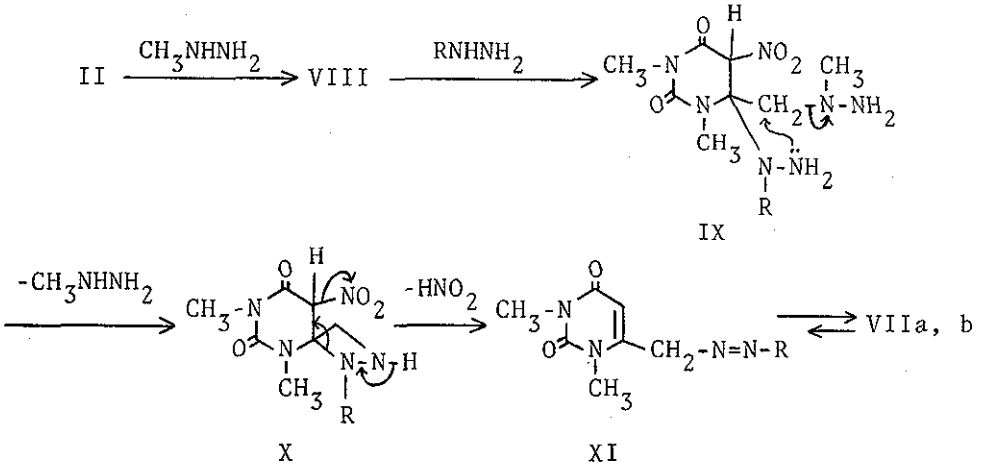


Scheme 2

On the reaction of II with excess methylhydrazine in ethyl acetate at 0°, 1,3-dimethyluracil-6-carboxaldehyde methylhydrazone (VIIb), mp 216-217°, was obtained in 83 % yield. Compound VIIb was identical in every respect with an authentic sample unequivocally prepared by the 1,3-dimethylation of uracil-6-carboxaldehyde methylhydrazone[8] with dimethyl sulfate. Careful treatment of II with 2 equiv. of methylhydrazine under the same conditions as described above led to the normal substitution product, 6-(α-methylhydrazino)methyl-5-nitro-1,3-dimethyluracil (VIII), mp 126-127°, in 46 % yield. Further treatment of VIII

with more equiv. of methylhydrazine gave VIIb in 38 % yield. Conversion of VIII into the crossed product VIIa, mp 232-233°, occurred on treatment of VIII with excess hydrazine hydrate, instead of methylhydrazine, in 76 % yield. These facts imply that the formation of VIII initially takes place during the hydrazinolysis of II to VII. The subsequent steps, in which the nucleophilic attack on the C-6 position is also a key step, can be explained as follows (Scheme 3). Thus compound VIII undergoes the nucleophilic addition by hydrazines on the C-6 position to form the resulting dihydro compound IX, which is transformed into the spiro compound X by the elimination of methylhydrazine, and then evolution of nitrous acid from X yields XI. Tautomerization of XI affords VII.

The reactions of I and II with other nucleophiles are now in progress.



Scheme 3

References and Footnotes

1) R. Shapiro, R.E. Servis, M. Welcher, J. Am. Chem. Soc., 1970, 92, 422; H. Hayatsu, Y. Wataya, K. Kai, ibid., 1970, 92, 724; G.S. Pork and I.H. Pitman, ibid., 1974, 96, 4654; F.A. Sedor, D.G. Jacobson, and E.G. Sander, ibid., 1975, 97, 5572; G.S. Pork and I.H. Pitman, ibid., 1975, 97, 5566 and 5599; L. Szabo, Y.I. Kalman, and T.J. Bardos, J. Org. Chem., 1970, 35, 1434; Y. Wataya, K. Negishi, and H. Hayatsu, Biochemistry, 1973, 12, 3992; S. Senda, K. Hirota, and T. Asao, Tetrahedron Lett., 1973, 2647, J. Org. Chem., 1975, 40, 353.

2) I.H. Pitman, M.J. Cho, and G.R. Pork, J. Am. Chem. Soc., 1974, 96, 1840.

3) H.U. Blank, I. Wempen, and J.J. Fox, J. Org. Chem., 1970, 35, 1131.

4) The ratio was calculated from the NMR spectrum by the comparison with each C-6 methyl signal.

5) H.C. van der Plas, "Ring Transformations of Heterocycles", Academic Press, New York, N.Y., 1973, Vol. 2, p 116.

6) Compound II was prepared by bromination of I with bromine in acetic acid in 86 % yield, mp 143-144°.

7) The name of "cyclothymine" was introduced by Witkop et al., cf. T. Kunieda and B. Witkop, J. Am. Chem. Soc., 1971, 93, 3478.

8) K. Zee-Cheng and C.C. Cheng, J. Heterocycl. Chem., 1967, 4, 163.

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