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THE MECHANISMS OF FORMATION AND REACTIONS OF 6-CYANO-1,3-DIMETHYLURACIL

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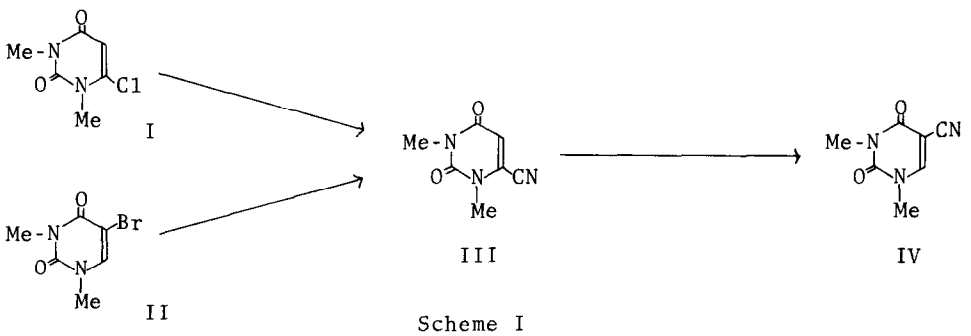
It has been reported[1] that the treatment of 5-bromouridine with KCN at 80° in DMF gave 5- and 6-cyanouridines with a by-product. Liebenow has recently reported[2] that 6-chloro-1,3-dimethyluracil(I) was treated with 2.5 equivalents of NaCN at 90-110° in DMSO to give 5-cyano-1,3-dimethyluracil(IV), which would form via a hetaryne as a intermediate.

In this connection, we carried out as follows : when the 6-chloro compound (I) was stirred with an equivalent of NaCN in DMF at room temperature for 2 hours, the sole product that we could isolate in high yield(88%), was not IV but 6-cyano-1,3-dimethyluracil(III), [mp 169°; NMR($CDCl_3$) δ 6.33(ring H-5), 3.62, 3.38(N-CH_3); IR(KBr) cm^{-1} 2240(C≡N), 1710, 1660(C=O). According to the procedure of Ueda[1], 5-bromo-1,3-dimethyluracil(II) was allowed to react with an equivalent of NaCN in DMF at room temperature for 2 hours to afford a 95% yield of the 6-cyano compound(III), which was identified by comparing with III obtained above. And then, the treatment of III with 0.1 equivalent of NaCN in DMF at 80° for 5 hours smoothly yielded a 68% of the 5-cyano compound(IV), [mp 165°; NMR($CDCl_3$) δ 7.98(ring H-6), 3.54, 3.40(N-CH_3); IR(KBr) cm^{-1} 2220(C≡N),

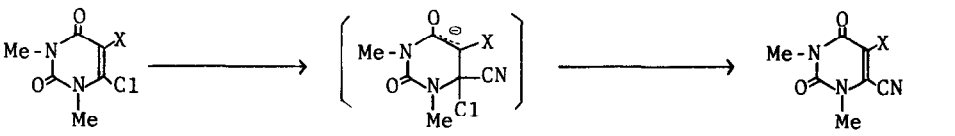


Scheme I

1720, 1650(C=O)], which was confirmed by direct comparison with an authentic sample[3].

The fact that III was derived from both I and II, suggests[4] two mechanisms in which one is an elimination-addition(E-A) involving a hetaryne, and another is an addition-elimination(A-E) involving a 5,6-dihydrouracil. In order to elucidate which of the two mechanisms is efficacious, the behavior of a deuterium at 5- or 6-position on a uracil ring was investigated.

When 6-chloro-5-deutero-[5,6] and 5-bromo-6-chloro-[7] 1,3-dimethyluracils (V and VI) in stead of I were made to react with an equivalent of NaCN under the same conditions, 6-cyano-5-deutero-1,3-dimethyluracil(VIII) and 5-bromo-6-cyano-1,3-dimethyluracil(IX: mp 125°) were obtained in 63% and 70% yields respectively without loss of 5-substituents(D and Br). The results mean that the reaction of I to III is a simple nucleophilic aromatic substitution reaction which proceeds via A-E mechanism involving the intermediate(VII).



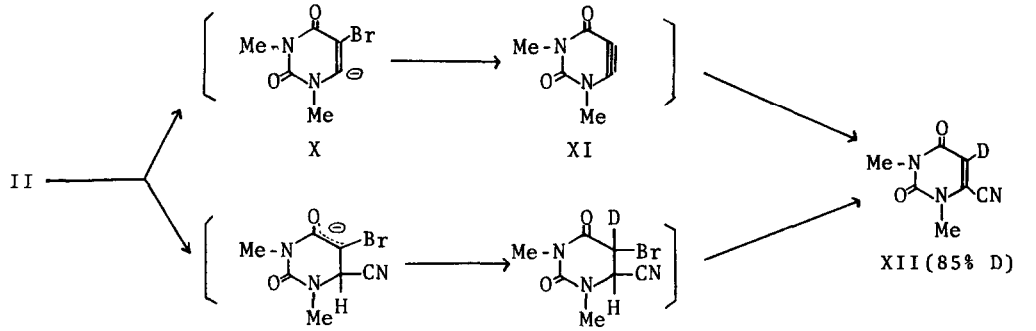
V: X=D(90% D)
VI: X=Br

VII

VIII: X=D(84% D)
IX: X=Br

Scheme 2

On the other hand, the conversion of II into III was carried out in the presence of 10 equivalents of D_2O under the same conditions to give 6-cyano-5-deutero-1,3-dimethyluracil(XII)[6]. If the hetaryne(XI) were involved in the reaction, addition of D_2O(or H_2O), a good protonating agent for the carbanion



X

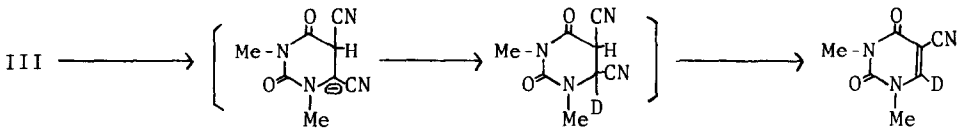
XI

XII(85% D)

Scheme 3

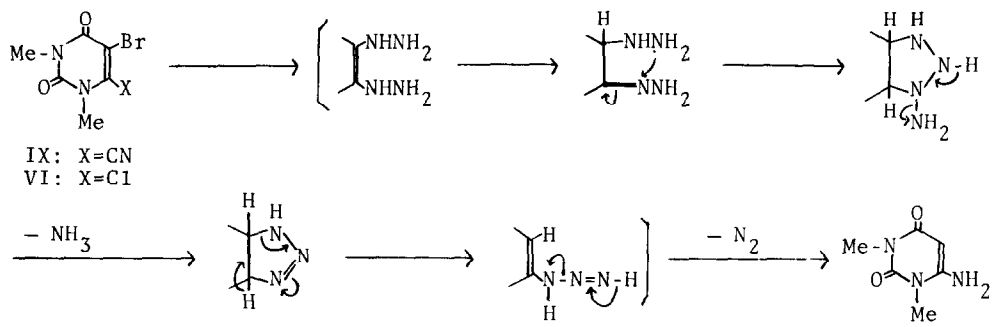
precursor(X) of XI, would inhibit the reaction[8]. Whereas the facts that D_2O had no influence on the proceeding of reaction and a deuterium was incorporated into 5-position, support the view that the conversion of II into III occured according to a well-known A-E mechanism[9] whose starting step was nucleophilic attack at 6-position (see Scheme 3).

As to the isomerisation of 6- to 5-cyano-1,3-dimethyluracil, III was allowed to react with a catalytic amount of NaCN in the presence of 10 equivalents of D_2O to give the 6-deutero-5-cyano compound(XIV)[6]. This result provides good evidence that the reaction proceeds via A-E mechanism. That is, a reasonable mechanism for the rearrangement of a cyano group involves an initial attack by a cyanide ion on 5-position followed by abstraction of a deuterium from D_2O at 6-position. Upon removal of hydrogen cyanide from 5,6-dihydro intermediate (XIII), the 5-cyano-6-deutero product(XIV) would form. This A-E mechanism caused by "5-C attack"[10] is unusual in uracil derivatives, compared with that caused by "6-C attack".



Scheme 4

Futhermore, the interesting reactivity of a 6-cyano group on a uracil ring towards a nucleophile was showed in the following experiments. When the 6-cyano compound(III) was heated at 100° for a few minutes in hydrazine hydrate, the



Scheme 5

substituted product, 6-hydrazino-1,3-dimethyluracil(XV; mp220°)[11], was obtained in a 59% yield, While, the 5-bromo-6-cyano compound(IX) underwent vigorous exothermic reaction with the evolution of NH_3 in hydrazine hydrate at room temperature to afford an abnormal product, the 6-amino-1,3-dimethyluracil(XVI; mp>300°, 44%)[12], which was also prepared in a 64% yield from 5-bromo-6-chloro compound (VI) with hydrazine hydrate under the same conditions. Compounds XV and XVI were confirmed by comparison with authentic samples[11,12]. We tentatively suggest the reaction mechanism outlined in Scheme 5.

References and Footnotes

* Satisfactory analytical data have been obtained for all crystalline compounds described in this communication.

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5. The compound V was prepared by chlorination of 5,5-dideutero-1,3-dimethylbarbituric acid with phosphorous oxychloride.
6. The position of the deuterium and the amount of deuterium present were established by NMR spectroscopy. For determination of the deuterium content in 5- or 6-position the integrated peak area of the 5- or 6-H signal was compared with that of the $N\text{-}CH_3$ signal, used as internal standard.
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