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HETARYNES XVI (1,2)
Evidence for the occurrence of 4-t-butyl-5,6-pyrimidyne in the amination of both 6-bromo- and 5-bromo-4-t-butylpyrimidine (3)

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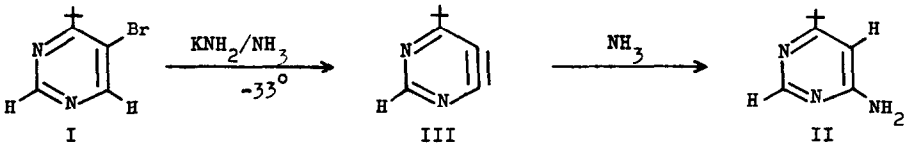
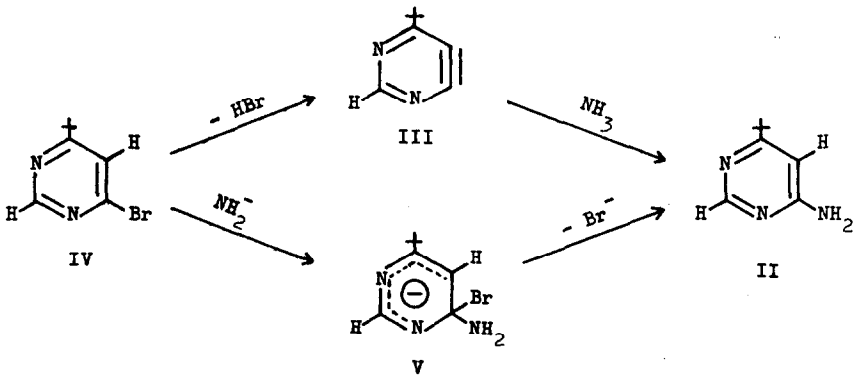
Previously it has been reported that 5-halogenopyrimidines may be dehydrohalogenated in a basic solution, yielding 4,5(=5,6)pyrimidynes (2,4-7). For example, when reacting 5-bromo-4-t-butylpyrimidine (I) with potassium amide in liquid ammonia at -33° for a few hours, a rearranged 6-amino product i.e. 6-amino-4-t-butylpyrimidine (II, yield 14%) is obtained, presumably formed via the transient 4-t-butyl-5,6-pyrimidyne (III).



I III II

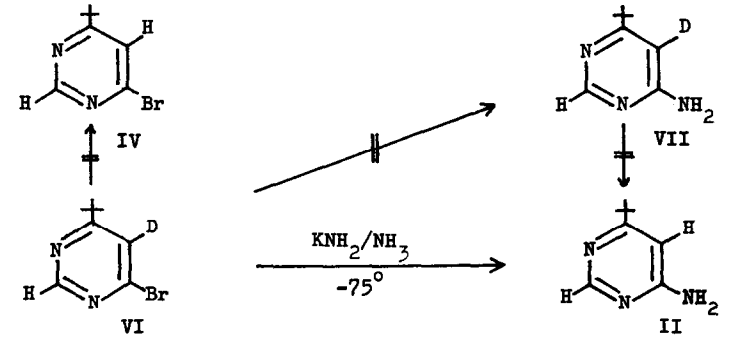
When aminating 6-bromo-4-t-butylpyrimidine (IV) at -33° for 5 min, 6-amino-4-t-butylpyrimidine (II) is formed in a nearly quantitative yield. The problem arises according to which mechanism compound II is formed. Is an elimination-addition process operative, which involves the hetaryne III, or an addition-elimination mechanism, involving the resonance stabilized anion V?



IV III V II

In order to establish which of the two mechanisms is efficacious, 6-bromo-4-t-butyl-5-deuteropyrimidine (VI) was prepared (a) and its behaviour towards potassium amide was investigated. When the amination occurs according to an addition-elimination mechanism the 6-amino compound formed will contain deuterium on position 5, while in the 6-amino product no deuterium will be present if the hetaryne III is involved.

In order to investigate whether during the reaction D/H exchange would occur in the starting material VI, the amination was carried out at -75° for ½ min. Under these conditions only 50% of the 6-bromo compound VI is converted into the 6-amino product. After the reaction the 6-bromo- and the 6-amino compound were isolated and the deuterium content in both substances was determined. Very surprisingly, it was found that in the 6-amino-4-t-butylpyrimidine no deuterium was present at all and that in the recovered 6-bromo compound the amount of D-5 label was nearly the same as that in the 6-bromo compound before the reaction. To be sure that the absence of deuterium in the 6-amino compound II might not be due to D/H exchange in possibly previously formed 6-amino-4-t-butyl-5-deuteropyrimidine (VII), compound VII was prepared (b) and allowed to react with potassium amide in liquid ammonia at -75° for ½ min. No D/H exchange in VII, however, was found to occur.



	VI	II
Initial	64.3% D	
Final	65.2% D	0% D
	64.3% D	
	65.6% D	0% D

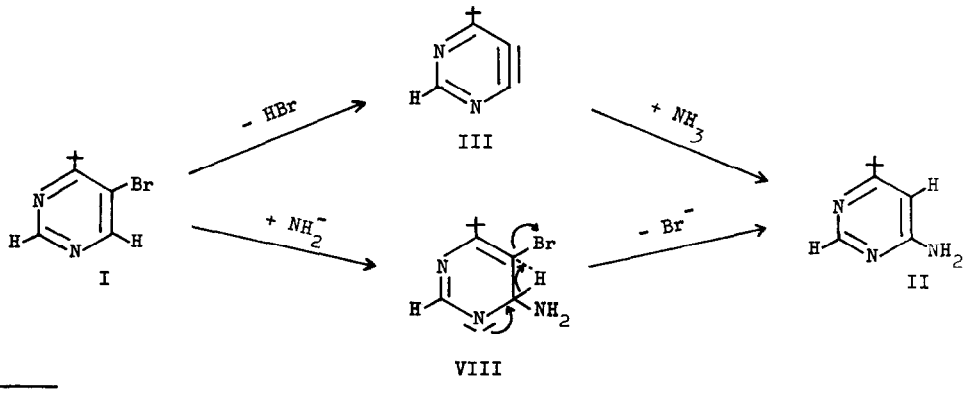
a. The preparation of VI will be published in a forthcoming paper. The position of the deuterium and the amount of deuterium present were established by PMR spectroscopy. For determination of the deuterium content in position 5 the integrated peak area of the 5-H signal (2.48 τ) was compared with that of the 2-H signal (1.12 τ), used as internal standard.

b. The synthesis of VII will be described in a forthcoming paper.

All the results obtained thus far present clear evidence that the conversion of 6-bromo-4-t-butylpyrimidine into 6-amino-4-t-butylpyrimidine by potassium amide in liquid ammonia at -75° does not occur according to an addition-elimination reaction, but via the pyrimidyne (III).

Now the occurrence of III in aminations of IV has been firmly established, we wish to present some additional support for the existence of this hetaryne III in aminations of the 5-bromo compound I. Although the hetaryne mechanism can reasonably account for the formation of the rearranged 6-amino compound II, it cannot be overlooked that II can also be formed by an initial attack of the amide ion to the electron deficient 6-position in the pyrimidine ring, yielding the resonance stabilized anion VIII followed by an internal 1,2-hydride shift with concomitant loss of a bromide ion (c).

In order to obtain more information on the mechanism of the formation of II, 5-bromo-4-t-butyl-6-deuteropyrimidine (IX) was prepared (d) and its amination was studied.

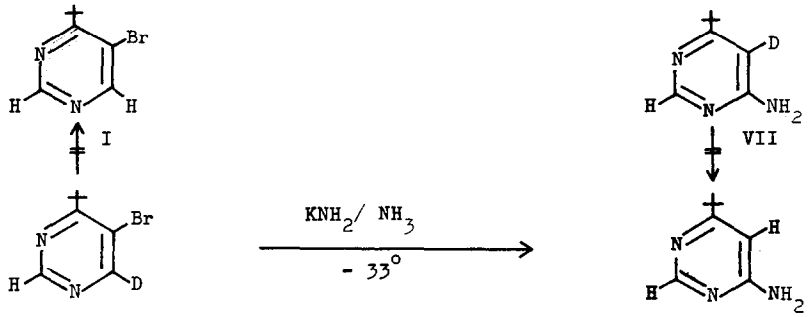


c. A similar mechanism has been proposed by Benkeser and Schroll (8) in order to explain "cine"substitutions, found in the amination of some ortho halogenated substituted benzenes with sodamide in liquid ammonia. Although it was proved (9) that these rearrangements occurred by a benzyne mechanism and not by the mechanism suggested by Benkeser and Schroll, it is possible that the conversion of I into II occurs via VIII, as the pyrimidine ring is much more susceptible to addition of nucleophiles than the benzene ring (10,11).

d. The introduction of a deuterium label in position 6 of 5-bromo-4-t-butylpyrimidine was conveniently achieved by oxidation of 5-bromo-4-t-butyl-6-hydrazinopyrimidine with silver acetate in D_2O (12). The position of the deuterium label was confirmed by PMR-spectroscopy (2-H singlet 1.10 τ; 6-H signal 1.35 τ). The integrated peak area of the 6-H signal is sharply decreased in comparison with that of the 2-H singlet, used as internal standard.

If the 6-amino compound is formed by an internal hydride shift in VIII it means that from IX a 6-amino compound is formed in which deuterium will be incorporated in position 5, while the occurrence of a hetaryne mechanism involving III would lead to the formation of an unlabelled 6-amino compound.

After reacting IX with potassium amide for 5 hrs the 5-bromo compound and the 6-aminopyrimidine derivative formed were isolated and analyzed for the deuterium content. It was found that the 6-amino compound does not contain deuterium at all and that the amount of D-6 label in the recovered 5-bromo compound was nearly the same as in the 5-bromopyrimidine derivative before the reaction.



IX

Initial	Final
57.2% D	57.6% D
57.2% D	58.8% D

II

0% D

0% D

As it has further been proved that under the reaction conditions mentioned no D/H exchange occurs in 6-amino-4-t-butyl-5-deuteropyrimidine (VII), it is clear that II is not obtained via the reaction pathway I ⟶ VIII ⟶ II; on the contrary all results can be accomodated with the occurrence of a hetaryne mechanism, involving III.

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