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DOES 2,6-DIDEHYDROPYRIDINE EXIST ? [1,2]

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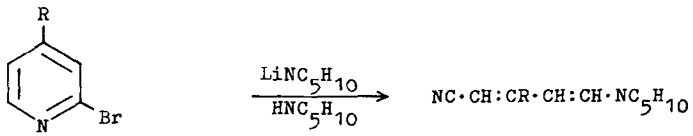
Some years ago the occurrence of 2,6-didehydropyridine (I)as an intermediate in aminations of halopyridines has been discussed from a theoretical point of view[3] and on the basis of subsequent experimental results. Kauffmann supposed that the resinification of 2-halopyridines when treated with lithium piperidide/piperidine in ethereal solution at 35°C resulted from initial formation of I[4]. Furthermore we observed that 2-bromo-3,5-diethoxypyridine reacts smoothly with potassium amide in liquid ammonia, whereas 2,6-dibromo-3,5-diethoxypyridine which cannot yield I, does not react[5].

Since then Adam, Grimison and Hoffmann concluded from extended Hückel calculations that I is the least stable of the six didehydropyridines[6], it was shown in this laboratory that 2-bromo-3,5-dialkoxypyridines react with potassium amide as well as with lithium piperidide exclusively according to an addition-elimination(AE)mechanism[5] and Kauffmann and Wirthwein withdrew the hypothesis that 2,6-didehydropyridines should occur as intermediates in the reactions they investigated[7].

We have reinvestigated the reaction of 2-bromopyridine with lithium piperidide and piperidine (molar ratio 1 : 4 : 2) in ethereal solution lowering the temperature to -60°C. It appeared that,together with an AE-substitution,ring opening occurs by fission of the 1-6 bond[8]. It seems probable that in secondary reactions the chain compound III resinifies. Analogous reactions were found to occur when reacting derivatives of 2-bromopyridine such as the 4-ethoxy- and 4-methyl compounds(II).



II

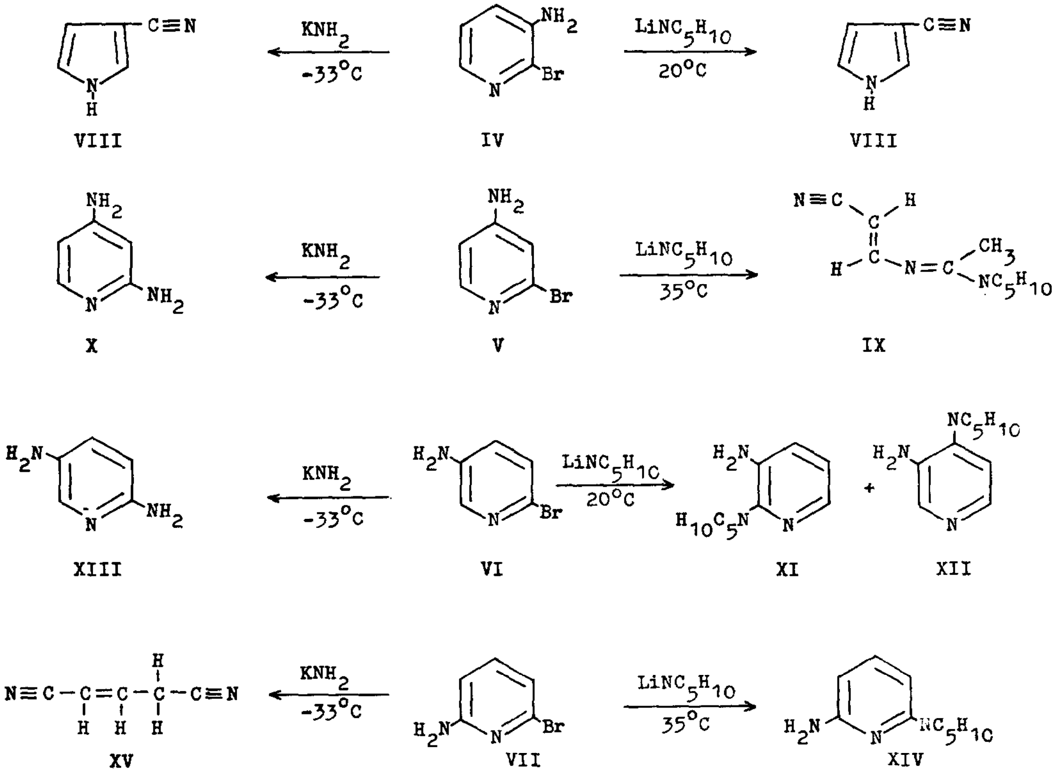
III

R = H, OC_2H_5 or CH_3

As an example data on the conversion of 2-bromo-4-ethoxypyridine are given.

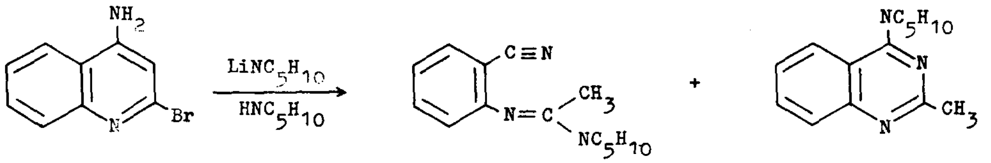
The reaction mixture was separated by GLC into fractions A and B (weight ratio 1: > 4) with retention times = 5.5 and 11.0 min from a column (length 100 cm, diameter 4 mm) filled with Apiezon-L (1.0 g) and anhydrous soda (0.4 g) on Kieselguhr 60-80 (5 g) at 220°C, using hydrogen as carrier gas (rate 100 ml/min). Fraction A was identified with an authentic specimen of 4-ethoxy-2-piperidinopyridine (IR-spectrum);the structure of fraction B was determined by spectrometry:IR : CN, C = C; MS : M = 206, characteristic fragmentation 206 → 166; PMR (CDCl$_3$) τ = 3.0 (d, J = 13.5 cps), 4.7 (d, J = 13.5 cps), 6.1 (s) (for vinylic protons).

In the reactions of the compounds mentioned above only substitution without rearrangement and ring opening by fission of the 1-6 bond were found to occur. Continuing our study we established that there is a remarkable variety in the course of the reactions of derivatives of 2-bromopyridine with bases depending on the substituent, its position in the nucleus and the reagent chosen. In the subsequent scheme chief products of reactions of isomeric amino-2-bromopyridines with lithium piperidide and with potassium amide in liquid ammonia are summarized[9].



The transformation of IV by lithium piperidide proceeds similarly to that by potassium amide; fission of the 2-3 bond leads to the formation of 3-cyanopyrrole (VIII).

In the reaction of V with lithium piperidide substitution without rearrangement is not the chief process as is the case in the amination with potassium amide. Mainly IX was shown to be formed as the result of a ring opening with fission of the 3-4 bond. This reaction is analogous to the conversion of 4-amino-2-bromoquinoline (XVI) with lithium piperidide which yields the ring opening product XVII together with an equal amount of 2-methyl-4-piperidinoquinazoline (XVIII), however.



XVI XVII XVIII

When 6-amino-2-bromopyridine (VII) is reacted with lithium piperidide, no ring opening takes place;only XIV is produced in high yield as the result of an AE substitution.

In our opinion the conversion of VI with lithium piperidide is the most remarkable one. XI and XII are formed in good yields (ratio = 10 : 1), whereas the presence of 5-amino-2-piperidinopyridine could not be detected. The elucidation of these cine-substitutions asks for further investigation. In the conversion of VI into XI certainly no bromine migration yielding IV is involved as IV would be transformed into VIII. Thus, we will have to establish whether the chief reaction of VI proceeds via an anomalous adduct or the 5-amino derivative of 2,6-didehydropyridine[*].

Acknowledgement

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[*] Cf. in this connection the result of an unpublished experiment that from the reaction of 2,3-dibromopyridine with lithium piperidide/piperidine at -60°C, small amounts of both 2-piperidino-3-bromo- and 6-piperidino-3-bromopyridine were found to be formed.

References

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2. This investigation has been carried out under the auspices of the Netherlands Foundation for Chemical Research (SON) and with financial aid from the Netherlands Organisation for the Advancement of Pure Research (ZWO).
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4. Th.Kauffmann, Angew.Chem.Int.Ed. 4, 543 (1965).
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7. Th.Kauffmann and R.Wirthwein, Angew.Chem.Int.Ed. 10, 20 (1971).
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9. The course of the aminations with potassium amide was established by J.W.Streef and H.J.den Hertog (See Rec.Trav.Chim. 85, 803 (1966) and 88, 1391 (1969)).