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RING TRANSFORMATIONS IN REACTIONS OF HETEROCYCLIC HALOGENO COMPOUNDS WITH NUCLEOPHILES (VII) (1)

Conversion of bromo derivatives of 3-aminopyridine into cyanopyrroles

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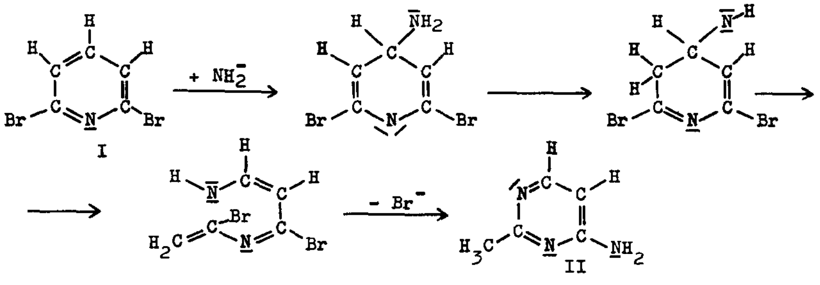
Halogenopyridines and derivatives of these substances react with potassium amide in liquid ammonia according to various patterns. Together with normal substitutions of halogen atoms by the amino group, replacements with ortho-, meta- and para-rearrangements have been observed (2), whereas by way of exception 3-fluoropyridine is converted into a mixture of fluorinated bipyridines (3). A ring transformation occurs when a 6-substituted derivative of 2-bromopyridine e.g. 2,6-dibromopyridine (I) is treated with potassium amide. This reaction is initiated by addition of the amide ion to the 4-carbon atom. Then, an unusual opening of the pyridine nucleus by fission of the C_3-C_4 carbon bond takes place, whereupon by subsequent ring closure a pyrimidine derivative, e.g. 4-amino-2-methylpyrimidine (II) is formed (4,5).



The last result induced us to study the effect of substituents occupying the 3-position in 6-substituted derivatives of 2-bromopyridine on the course of reactions of these substances with potassium amide.

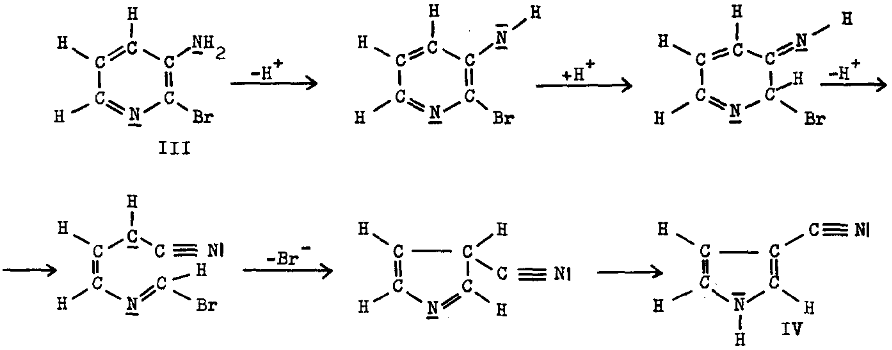
First the conversion of 3-amino-2,6-dibromopyridine was investigated. From the complicated reaction mixture obtained, a colourless solid, melting at 124-125° after recrystallisation from water, was isolated. It was considered to be a bromocyanopyrrole from its analysis (found: C 35.3, H 1.5, N 16.9; calc. for $C_5H_3BrN_2$ (171.01): C 35.11, H 1.77, N 16.38) and its infrared spectrum (measured in chloroform, showing NH- and CN-stretching frequencies at 3460 and 2240 cm^{-1} respectively) (6).

As the pyridine ring is transformed into a pyrrole nucleus, the mechanism of this reaction differs completely from the ring transformation of 2,6-dibromopyridine. It is likely that the reaction is not initiated by the addition of an amide ion to carbon atom 4, but is started by abstraction of a proton from the amino group. Therefore, it was expected that a <u>mono</u>bromo derivative of 3-aminopyridine might be converted into a pyrrole derivative exclusively.

As it was known that 3-amino-6-bromopyridine was converted very slowly with potassium amide, yielding only 3,6-diaminopyridine (7), we reacted 3-amino-2-bromopyridine (III) with a solution of the fourfold molecular amount of potassium amide in liquid ammonia for 24 hrs at -33°. From the reaction mixture a cyanopyrrole (m.p. 54-55°; analysis: found: C 65.4, H 4.3, N 30.6; calc. for $C_5H_4N_2$ (92.10): C 65.20, H 4.38, N 30.42) was isolated. Infrared spectrum measured in chloroform: absorptions at 2239 and 3480 cm^{-1}; N.M.R.-spectrum in $CDCl_3$: one broad singl

(τ = 0.4 ppm); three multiplets (τ = 2.68, 3.20 and 3.55 ppm; ratio of peak areas = 1 : 1 : 1). From these data it appears that the substance in question is a cyanopyrrole and from the fact that it is not identical with 2-cyanopyrrole (a liquid, prepared from pyrrole aldehyde (8), N.M.R.-spectrum: absorptions at τ = 3.1 and 3.8 ppm; ratio of peak areas = 2 : 1) that it must be considered to be 3-cyanopyrrole (IV) (9).

For the formation of IV from 3-amino-2-bromopyridine (III) tentatively the following mechanism is given:



In this sequence the pyridine ring is opened by fission of the C_2-C_3 bond, which is as unusual as that of the C_3-C_4 bond during the conversion of 2,6-dibromopyridine (I) into 4-amino-2-methylpyrimidine (II).

From 3-amino-2-chloropyridine under the same reaction conditions no more than 1% 3-cyanopyrrole is formed.

The investigation is being continued by comparing the reactivity of other 3-substituted 2-bromopyridines. It has already been found that whereas from 2-bromo-3-ethoxypyridine in a fast reaction 2-amino-3-ethoxypyridine is formed (yield>80%) (10), from 2-bromo-3-methylpyridine in 10 hrs 2-amino-3-methylpyridine is formed in a yield of only 25%. Neither a pyrimidine nor a pyrrole derivative which might be formed from 2-bromo-3-methylpyridine was detected in the reaction mixture (9).

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