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

Reactions of some 5-substituted 4-chloro-2-phenylpyrimidines with potassium amide in liquid ammonia at -33°(2)

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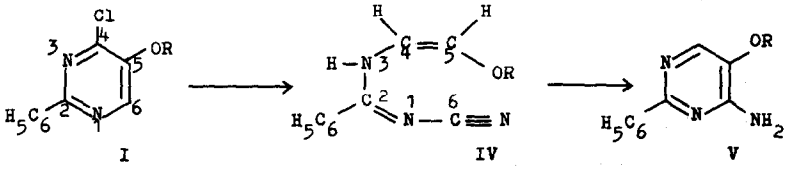
In this laboratory the reactivity of 3-substituted derivatives of 2-bromopyridine with potassium amide in liquid ammonia has recently been investigated. It was found that whereas 2-bromo-3-ethoxypyridine and 2-bromo-3-methylpyridine react with potassium amide yielding the corresponding 2-amino compounds, 3-amino-2-bromopyridine is converted into 3-cyanopyrrole (3). In this paper we wish to report some preliminary results obtained in the study of the course of reactions of 5-substituted 4-chloro-2-phenylpyrimidines i.e. 5-alkoxy-(I,R= C_2H_5,CH_3), 5-amino-(II) and 5-methyl-4-chloro-2-phenylpyrimidine (III).

When I (R= C_2H_5) was reacted with 4 equivalents of potassium amide in liquid ammonia at -33° for 4 hrs, in a 50% yield a non-aromatic open-chain compound (IV, R= C_2H_5) was obtained. This substance is isomeric with the 4-amino compound V (R= C_2H_5).



I IV V

R = CH_3, C_2H_5

The proof of the structure of IV (R= C_2H_5) was unequivocally given by the IR- and NMR-data. The IR-spectrum (potassium bromide disc) showed a strong band at 2180 cm^{-1}, the characteristic absorption of a N-C≡N group, and the out-of-plane H-C=C-H (cis) deformation vibration at 700 cm^{-1}. In the NMR-spectrum (measured in dimethylsulfoxide) the following absorptions were found: a) N_3- H, τ = - 0.54, broad doublet (J = 8 cps), b) C_5- H, τ = 3.15, doublet (J = 11 cps), c) C_4- H, τ = 2.70, quartet (J = 11 cps, J = 8 cps), d) protons of the phenyl ring at τ = 2.35, singlet, e) the absorption characteristics of the ethyl group at τ = 6.05 (quartet) and τ = 8.64 (triplet). All absorptions integrated for the correct numbers of protons. The coupling constant J = 11 cps indicates a cis-olefinic function of the hydrogens at the C_4- and C_5- positions.

Analogously, from I (R= CH_3), the open-chain compound IV (R= CH_3) was obtained in 70% yield. All IR- and NMR-data are consistent with the proposed structure IV (R= CH_3).

Above-mentioned results are the first experimental evidences that open-chain compounds can be formed from halogenopyrimidines by treatment with potassium amide in liquid ammonia. It supports strongly the hypothesis that in reactions transforming pyrimidines into s-triazines (4) and pyridines into pyrimidines (5) transient open-chain intermediates are formed.

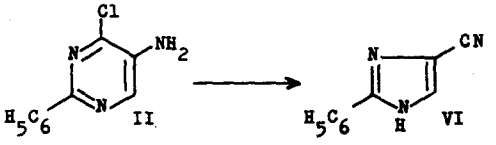
It was established by converting 4-chloro-5-methoxy-2-phenylpyrimidine-6-^{14}C into labelled IV (R= CH_3) and degradating this product that the opening of the pyrimidine ring occurs by fission of the C_5-C_6 bond and not of the C_4-C_5 bond (6).

The formation of the open-chain compounds IV (R= CH_3 or C_2H_5) from the 4-chloropyrimidine derivatives I (R= CH_3 or C_2H_5) is in marked

contrast with the result obtained in the reaction of 2-bromo-3-ethoxypyridine yielding only 2-amino-3-ethoxypyridine. Whereas in 2-bromo-3-ethoxypyridine the initial addition of the amide ion probably occurs at the bromine-bonded carbon atom (C_2), the results of the tracer experiments clearly indicate that in I the ion adds to the carbon atom to which a hydrogen atom is attached (C_6). The greater electron deficiency in position 6 of the pyrimidine ring has to be ascribed to the mesomeric and inductive effects of both nitrogens and possibly to a solvation effect at N_1 (2).

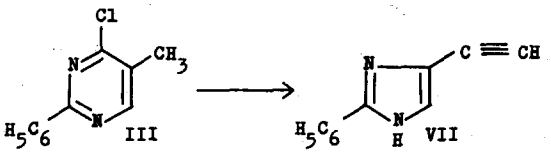
Both compounds IV (R= C_2H_5 or CH_3) have a tendency to cyclize. By heating for some minutes in boiling toluene isomerisation occurs, giving 4(=6)amino-5-alkoxy-2-phenylpyrimidines (V, R= C_2H_5 or CH_3) in excellent yields. From the results obtained in above-mentioned tracer experiments it has been established that in the recyclized product V (R= CH_3) the amino group occupies the 6-position and not the 4-position from which the chlorine atom has left.

A quite different course of the amination has been observed when treating the compounds II and III with 4 equivalents of potassium amide in liquid ammonia for 4 hrs at -33°. From II 4-cyano-2-phenyliminazole (VI) was obtained in a 35% yield, together with ~1% of 4,5-diamino-2-phenylpyrimidine. This result is in accordance with the above-mentioned formation of 3-cyanopyrrole from 3-amino-2-bromopyridine (3).



All IR- and NMR-data are consistent with the proposed structure VI. For further identification, VI has been synthesized independently, analogously to a method described for the synthesis of 2-benzyl-4-cyanoiminazole (7).

4-Ethynyl-2-phenyliminazole (VII) was isolated as the chief product (35%) together with 4-amino-5-methyl-2-phenylpyrimidine (~ 1%) when III was reacted with potassium amide as described above. This result is in complete contrast with that obtained when reacting 2-bromo-3-methylpyridine yielding nearly exclusively 2-amino-3-methyl-pyridine (3).



The IR-spectrum of VII (potassium bromide disc) was almost identical with that of VI, the C≡CH stretching vibration was found at 2105 cm^{-1} (m). The NMR-spectrum of VII (measured in acetone) showed two multiplets at τ = 1.90 and τ = 2.50; both peaks integrated for 2- resp. 4-hydrogen atoms. The absorption at τ = 1.90 has to be ascribed to the two o-hydrogens of the phenyl group, the absorption at τ = 2.50 to the m- and p-hydrogens plus the hydrogen at C_5 of the iminazole ring. The acetylenic hydrogen gave a singlet at τ = 6.28.

A detailed mechanism of the formation of the iminazoles VI and VII cannot be given. Thus far we have not established whether ring transformation occurs by fission of the C_4-C_5 bond or of the C_5-C_6 bond. It is likely, however, that both reactions are initiated by abstraction of a proton from the substituent at position 5. The enhanced

acidity of the hydrogens of the methyl group in III, compared with those of the methyl group in 2-bromo-3-methylpyridine, is due to the electron withdrawing inductive effects of both nitrogen atoms and because of the fact that the anion formed is resonance stabilized.

All products gave satisfactory analytical figures. We are indebted to Prof.Dr.H.J.den Hertog for his interest and helpful discussions and to Drs.P.Smit for recording and interpreting the IR- and NMR-spectra.

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