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TELE-SUBSTITUTIONS IN 8-CHLORO-1,7-NAPHTHYRIDINE AND 2-CHLORO-1,8-NAPHTHYRIDINE[1]

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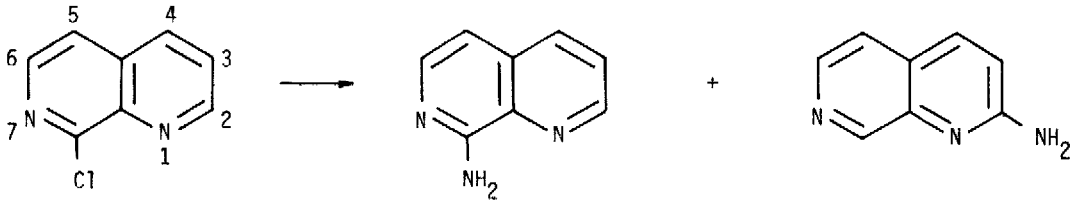
Over the years a large amount of literature has appeared on the mechanism of nucleophilic substitution reactions in azines. The two principal mechanisms established for substitution at the ring atom, to which the leaving group is attached, are the Addition-Elimination process $S_N(AE_n)$[3] and the recently discovered S_N(ANRORC) mechanism[4], involving an Addition of the Nucleophile, Ring-Opening and Ring-Closure sequence. For the cine- and tele-substitution reactions in these systems the $S_N(AE_a)$[5]- and S_N(EA)-mechanism[5,6] are presented

There is sound evidence that the amination of 4-X-pyridine (X=Cl, Br, I) by amide ions proceeds by an initial base-induced dehydrohalogenation leading to the transient 3,4-didehydropyridine[7] - whereas 4-X-pyrimidines (X=Cl, Br, I) undergo with the amide ion an addition reaction, leading to a Meisenheimer σ-complex[8]. Since we have recently found[9] that 1,5-, 1,6-, 1,7- and 1,8-naphthyridine give adducts with an amide ion, we became interested in the behaviour of halogenonaphthyridines towards potassium amide in order to study the competitive occurrence of dehydrohalogenation versus adduct formation in these systems

In this paper we wish to give the results of our study on the reaction of 8-chloro-1,7-naphthyridine (1) and 2-chloro-1,8-naphthyridine (2) with potassium amide.

When 1 is reacted with potassium amide for 4 h a mixture is obtained, from which we could recover starting material (1, 80%), and small amounts of 8-amino-1,7-naphthyridine (3,6%) and 2-amino-1,7-naphthyridine (4,5%). The formation of 3 can be proposed to occur by an $S_N(AE_n)$-process and/or by an S_N(ANRORC)-mechanism in analogy to the results, which have been established in the conversion of 3-bromo(chloro)isoquinoline into 3-aminoisoquinoline with



1 3 4

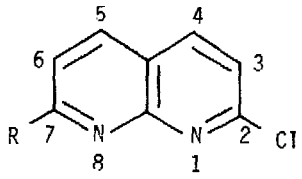
potassium amide[10,11]. The formation of 4 is of considerable interest since the nucleophile enters into a position which is different from the one which has been vacated by the leaving group. It is to our knowledge the first example of a 1,4-tele-substitution reaction in a naphthyridine system[12]. We suggest that the formation of 4 starts by an initial attack of the amide ion at C-2. The anionic σ-adduct (5) which is formed, undergoes protonation at C-8, yielding the intermediate (6), which can easily undergo a base-catalysed 1,4-dehydrohalogenation.

5 6

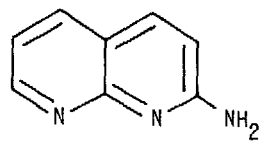
We obtained strong evidence for the formation of the adduct 5 by measuring the ^{1}H-NMR spectrum of 1 in KNH_2/NH_3 system. Whereas the spectrum of 1 in $CDCl_3$ showed the H-2 signal as a double doublet at δ9.15 ($J_{2,3}$ = 4.5 Hz, $J_{2,4}$ = 2 Hz), in KNH_2/NH_3 this signal has shifted considerably upfield to δ5.15 and appeared as a doublet (J = 4.0 Hz). All the other hydrogen signals were also shifted to a somewhat higher field and are found in the region δ6.7 - 5.3 It indicates that the negative charge in 5 is considerably delocalised over both rings. The strong upfield shifting of H-2 (Δδ = 4.0 ppm) as well as the change of the multiplicity pattern is a convincing argument for adduct formation at C-2.

Another interesting example of tele-substitution has been observed in the amination of 2-chloro-1,8-naphthyridine (2) into 2-amino-1,8-naphthyridine (8) with KNH_2NH_3 at -70°. When 2 was added to the solvent system KNH_2/NH_3, after 20 min the ^{1}H-NMR spectrum was considerably different from that of a solution of 2 in $CDCl_3$. Especially the position and multiplicity of H-7 was changed. The low field signal of H-7 characterised by a double doublet structure at δ9.10 ($J_{7,6}$ = 4.5 Hz, $J_{7,5}$ = 2 Hz) in $CDCl_3$, appeared as a doublet absorption

at δ5.10 ($J_{7,6}$ = 4.0 Hz) in KNH_2/NH_3. In addition the other proton signals of H-3, H-4, H-5 and H-6 were shifted upfield. These upfield shifts and multiplicity change clearly indicate the formation of σ-complex 9.



2, R=H
7, R=D



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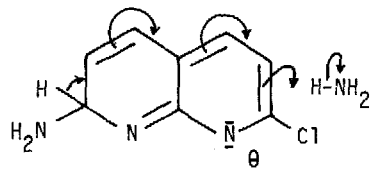

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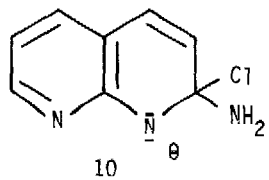

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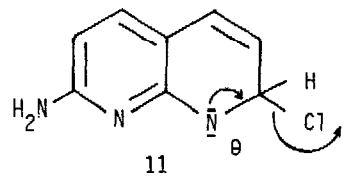

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These results give rise to the interesting question whether 8 is formed by a process in which the incoming group enters at position 7 i.e. via 9 and 11 or that the amino compound is formed via an $S_N(AE_n)$-process via 10.

Amination of 7-deutero-2-chloro-1,8-naphthyridine (7, % monodeuteration = 53.4) revealed that in the recovered starting material the deuterium content is nearly unchanged (% monodeuteration = 53.4), but that in the 2-amino compound the deuterium content is decreased (% monodeuteration = 48.7).

These results lead to the conclusion that the formation of 8 occurs by two processes i.e. the $S_N(AE_n)$-process via 10 and the $S_N(AE_a)$-process via 9. In the last-mentioned process we assume that from 9 a potassium amide induced proton shift occurs leading to 11, which aromatises by loss of the chloride ion. Whether 10 is formed by an attack of the amide ion to C-2 in the adduct 9 with a simultanuous loss of the amide ion from C_7 or from 2-chloro-1,8-naphthyridine (2) being present in a small equilibrium concentration with 9, is not known at this moment.

References and Notes

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