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PTERIDINE STUDIES PART V[1]
DUAL REACTIVITY OF 2-CHLORO-4,6,7-TRIPHENYLPTERIDINE AND 6-CHLOROPYRIDO-[2,3-*b*]PYRAZINE TOWARDS KNH_2 IN LIQUID NH_3.[2]

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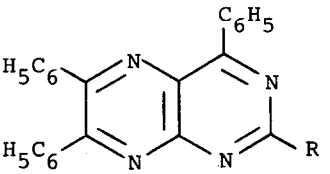
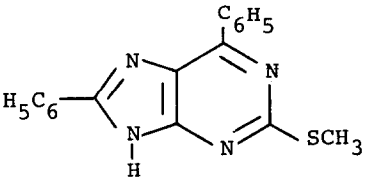
Our first report[1] on the action of strong nucleophiles on pteridines concerned the conversion of 2-methylthio-4,6,7-triphenylpteridine (1a) into 2-amino-4,6,7-triphenylpteridine (1b) and 6,8-diphenyl-2-methylthiopurine (2) (ratio 3/1) by KNH_2 in liquid NH_3 at -33°C.
Recently we proved that in these conversions all carbon positions i.e. C-2, C-4, C-6 and C-7 are attacked: formation of 1b takes place by initial attack of the nucleophile at both C-4 and C-2 and the formation of the purine derivative 2 by an attack at C-7 and, to a less extent, at C-6.
The purpose of this communication is to report that 2-chloro-4,6,7-triphenylpteridine (1c)[3] shows a rather different reactivity towards KNH_2 in liquid NH_3 than 1a. Amino-dechlorination of 1c into 1b takes place (70%) besides dechlorination into 4,6,7-triphenylpteridine[4] (1d). The formation of a purine derivative was not observed.



1a: R=SCH_3; 1b: R=NH_2

1c: R=Cl; 1d: R=H



2

By studying the amination of 2-chloro-4,6,7[^{15}N-3]pteridine[5] with unlabelled KNH_2 and in a complementary experiment, by reacting 1c with $K^{15}NH_2$ in liquid $^{15}NH_3$ it was proved that the amino-dechlorination proceeds to 100% via a ring opening ring-closure sequence [S_N(ANRORC)-mechanism]. This result means that the 2-chloro substituent in 1c has directed the attack of the nucleophile exclusively to C-4. Moreover the ^{15}N-labelling experiments indicate that neither attack on C-2, nor attack on C-6 and/or C-7 in the pyrazine ring, leading to ring contraction, takes place.

The high reactivity of position 4 in 1c is in good accordance with the general phenomenon that the presence of a chloro substituent on a carbon position adjacent to nitrogen in an aza heterocyclic ring activates the position meta to the chloro atom for amide attack[6]. Numerous reactions have been found, showing that attack on that meta position is often the introductory step in ring transformation (see, for example, the conversion of 2-chloroquinoline into 2-methylquinazoline[7]).

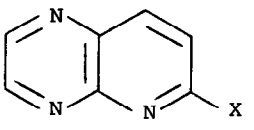
This result induced us to study the reaction of 6-chloropyrido[2,3-*b*]pyrazine[8] (3a) with KNH_2 in liquid NH_3 in order to obtain 2-methylpteridine. If this ring transformation were successful, it would provide us with a new synthesis of a pteridine ring system.

It was found, however, that when 3a (166 mg, 1.0 mmoles) was treated with KNH_2 (4 eqs.) in liquid NH_3 (50 ml) for 1 hour no trace of a pteridine derivative was obtained but two products could be isolated (60% yield), identified as pyrido[2,3-*b*]pyrazine[9] (3b) and 1H-imidazo[4,5-*b*]pyridine[10] (4b), ratio 3b/4b=1/3.

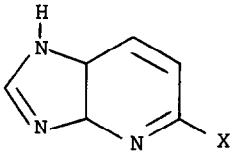
Since pteridines undergo ring contraction into purines under the applied conditions[1], the reaction mixture was carefully investigated for the presence of purines. No indication of the presence of purines was found.

The main process in this reaction i.e. the ring contraction of 3a into 4b is essentially different from the conversion of 1a into 2, since in the former reaction the leaving group participates in the ring contraction, while in the latter the leaving group remains.

The transformation of 3a into 4b bears close relationship to the conversion of 6-bromoquinoxaline into benzimidazole as reported in the literature[11].



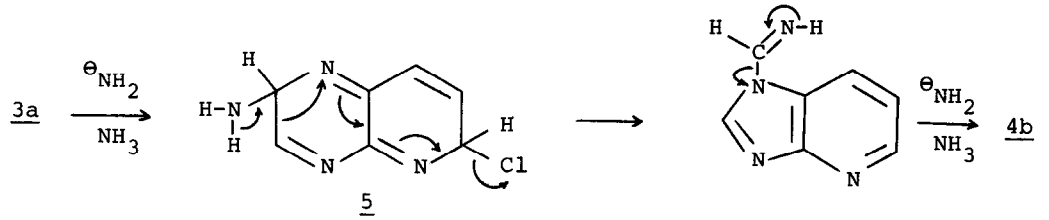
3a: X=Cl
3b: X=H



4a: X=Cl
4b: X=H
4c: X=NH_2

Concerning the mechanism of the ring contraction, the following experimental facts have been established: i) 3b is not the precurser of 4b, since 3b is stable under the reaction conditions, ii) an initial ring contraction of 3a into 5-chloro-1H-imidazo[4,5-*b*]pyridine (4a) (analogous to the conversion of 1a into 2) followed by a base-induced dechlorination is highly unlikely, since treatment of 4a[12] with KNH_2 in liquid NH_3, slowly gives 5-amino-1H-imidazo-[4,5-*b*]pyridine (4c)[12] and does not lead to the dechlorinated product 4b under these reaction conditions. These experiments suggest that the ring contraction starts by a nucleophilic attack of the amide ion at C-2 in 3a leading to 5,

which rearranges into the 1-methyleneiminoimidazo[4,5-*b*]pyridine. Under the basic reaction conditions the N-substituent is easily lost yielding 4b.



All attempts to prove the existence of the σ-adduct 5 (or its conjugate base) by means of ^{1}H-NMR[13] and ^{13}C-NMR failed[14]; the high concentration of potassium amide, being necessary for obtaining signals of reasonable intensity, causes a complete decomposition of 3a.

The influence of substituents attached to the pyrazine ring on the ring contraction and the problem of which carbon atom is then expelled are now under investigation.

Acknowledgements

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