Pteridine Studies (IV)[1]

On the mechanism of the conversion of 2-(methylthio)-4,6,7-triphenylpteridine into 2-amino-4,6,7-triphenylpteridine and 6,8-diphenyl-2-(methylthio)purine[2]

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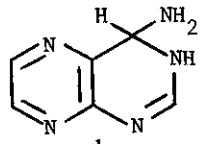
The ring contraction of 2-(methylthio)-4,6,7-triphenylpteridine (3) into 2-(methylthio)-6,8-diphenylpurine (5a) by KNH_2 in NH_3 at -33° has been studied using selectively deuterium labelled pteridines. It was found that the purine obtained from 2-(methylthio)-4,6-diphenyl-7-(pentadeuterophenyl)pteridine - prepared by phenylation of 2-(methylthio)-4,6-diphenylpteridine with pentadeuterophenyllithium - only contained 13% of the deuterium label, indicating that C-7 is mainly expelled during the ring contraction. The mechanism is discussed. Furthermore the amination of 3 was studied using both ^{15}N-3 labelled compounds as well as $K^{15}NH_2$ in $^{15}NH_3$. It was found that the amination of 3 takes place for 50-85% - depending on $[KNH_2]$ - according to a ring opening-ring closure mechanism (S_N(ANRORC)) forming 2-amino-4,6,7-triphenylpteridine (4). Thus in 3 the pteridine nucleus is found to be attacked by the amide ion on C-4, C-2, C-6 and C-7 in the approximate order of reactivity: C-4 ≥ C-2 > C-7 > C-6.

Introduction

In an earlier investigation we reported on the addition of liquid ammonia to pteridine and some of its derivatives[4]. ^1H-nmr evidence was presented for the formation of two different species i.e. the 1 : 1 σ-adduct 4-amino-3,4-dihydro-

pteridine (1) and the thermodynamically favoured 2 : 1 σ-adduct 6,7-diamino-5,6,7,8-tetrahydropteridine (2). Furthermore, we observed that when 2-(methylthio)



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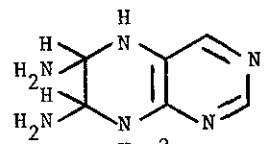

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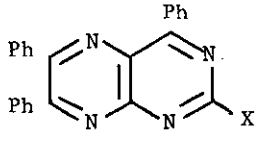
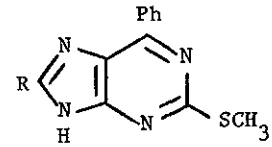
-4,6,7-triphenylpteridine (3) is reacted with potassium amide, amino-de(methylthio)-lation into 2-amino-4,6,7-triphenylpteridine (4) and ring contraction into 6,8-diphenyl-2-(methylthio)purine (5a) takes place[5]. The same purine derivative is also obtained from 4,6-diphenyl- and 4,7-diphenyl-2-(methylthio)pteridine[5]. As an



3 X = SCH_3

4 X = NH_2



5a R = C_6H_5

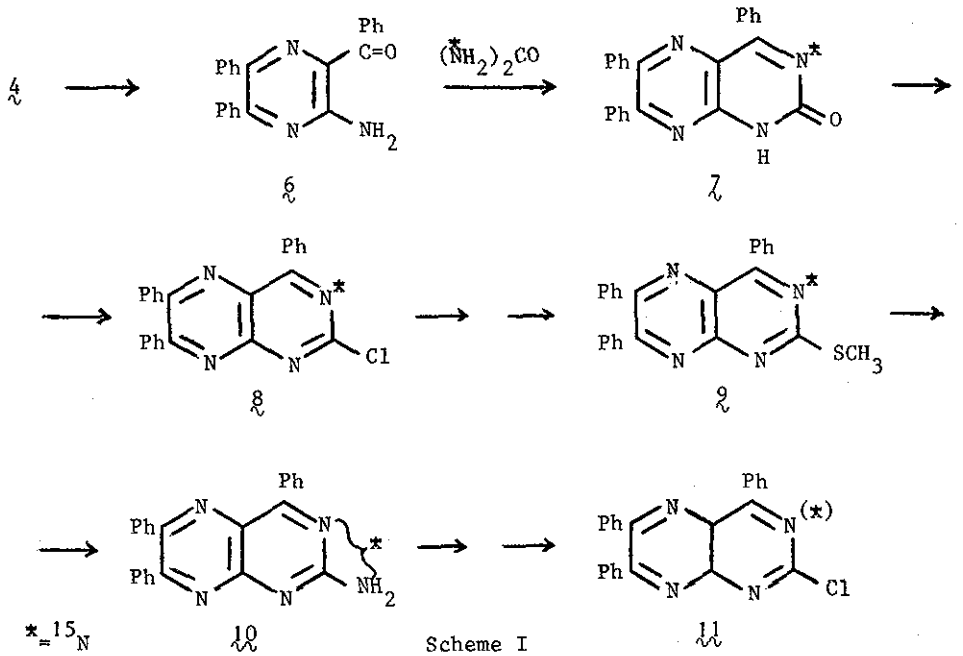
5b R = C_6D_5

amide-cataly ed ring contraction of pteridines into purines has never been observed before[6] we became interested in the scope and mechanism of this conversion. In this paper we concentrate us on the intriguing problem whether C-6 and/or C-7 is expelled from the pyrazine ring (see section b). There is ample evidence that the nucleophilic displacement in 2-substituted pyrimidines by an amide ion occurs via a ring opening-ring closure (S_N(ANRORC)) mechanism[7]. It induced us to study the occurrence of this process in the amino-de(methylthio)lation (3 → 4) (see section a).

a) On the amino-de(methylthio)lation

In order to study the occurrence of the S_N(ANRORC)-mechanism we prepared 2-(methylthio)-4,6,7-triphenylpteridine (9) which is enriched with ^{15}N in N-3 of the pyri-

midine ring. If the amino-de(methylthio)lation occurs without ring opening, all ^{15}N remains in the ring, while in the case of an S_N(ANRORC)-mechanism ^{15}N becomes a part of the exocyclic nitrogen atom. The introduction of a ^{15}N-label at N-3 in 9 could be achieved as outlined in scheme 1.



Acid hydrolysis of 4 yielded as main product 2-amino-3-benzoyl-5,6-diphenylpyrazine (6) and only a small amount of 4,6,7-triphenylpteridin-2-one[8]. Formation of 7, being labelled at N-3, was performed by reaction of 6 with 1,3-^{15}N-labelled urea. In this reaction no trace of a [^{15}N-1, ^{15}N-3]pteridin-2-one was formed as proved by mass spectrometry[9]. By the reaction of 7 with a mixture of $POCl_3$ and PCl_5 8 was formed which then was converted into 9 by treatment with hydrogen sulphide in basic medium and a subsequent methylation of the thio compound formed with methyl-iodide[10]. This laborious way to prepare 9 led us to develop techniques for small scale operations with KNH_2, containing ^{15}N, in liquid $^{15}NH_3$. So we could study besides the amino-de(methylthio)lation of the ^{15}N-labelled 9 with unlabelled KNH_2 (experiment 1) that of unlabelled 3 with $K^{15}NH_2$ (experiment 2).

In experiment 1 compound 9 (10% of excess of ^{15}N) was reacted with 4 equivalents

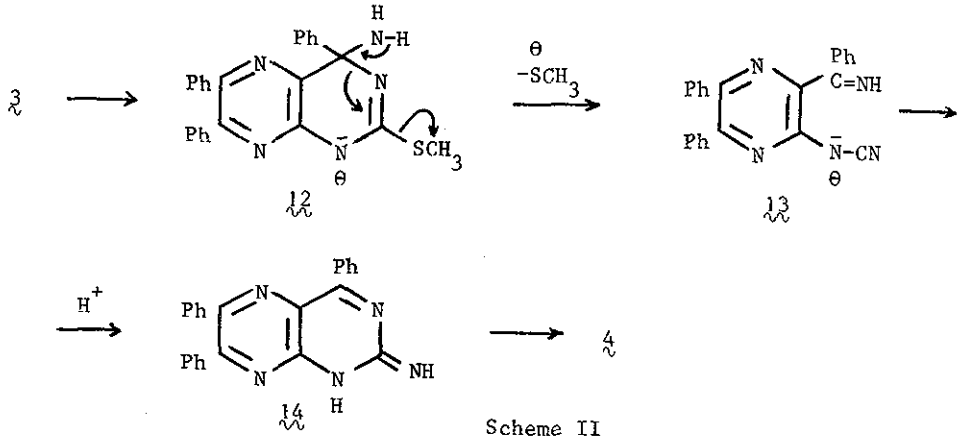
of KNH_2 in liquid NH_3 and the 2-amino derivative 10 was isolated by column chromatography. Attempts to establish by acid hydrolysis into 4,6,7-triphenylpteridin-2-one whether ^{15}N is present in the exocyclic nitrogen atom in 10 failed due to the formation of 6, leading thus to a complete loss of ^{15}N. Diazotization with sodium nitrite in an aqueous acid was also not successful[11]. We found however that the conversion of 10 into the corresponding pteridin-2-one could nicely be achieved when the diazotization was carried out at room temperature using glacial acetic acid as solvent and adding the sodium nitrite as a solid[12]. The crude pteridin-2-one was converted into 11 by a mixture of $POCl_3$ and PCl_5. Measurement of the ^{15}N excess in 11 by mass spectrometry showed that 11 contained 5.0% of excess of ^{15}N. This means that 50% of compound 9 reacts in the amino-de(methylthio)lation according to an S_N(ANRORC) mechanism (see table 1)[13]. We assume that the remaining 50% reacts via an S_N(AE) pathway[13]. When compound 3 was reacted with 10 equivalents of $K^{15}NH_2$ (6.2% of excess of ^{15}N) in liquid $^{15}NH_3$, it was found from the results of the ^{15}N-measurements that 3 under these conditions reacts into 10 according to the S_N(ANRORC)-mechanism for 85% (exp.2). Apparently the percentage according to which this ring opening-ring closure mechanism occurs, is strongly dependent on the concentration of KNH_2[14,15].

Table 1

Exp.	Substrate (1 mmole in 25 ml of NH_3)	Reagent	% of excess of ^{15}N in			% S_N(ANRORC)
			substrate	(10)	(11)	
1	9	4 eq KNH_2	10.0	10.0	5.0	50
2	3	10 eq KNH_2	0	6.2	5.7	85

From the results obtained it is evident that C-4 in 3 is, in despite of the presence of the phenyl group, vulnerable to a nucleophilic addition of an amide ion. Similar observations have been made with 4,6-diphenyl-2-halogenopyrimidines[14,15]. The adduct 12 undergoes the ring opening leading to the open chain

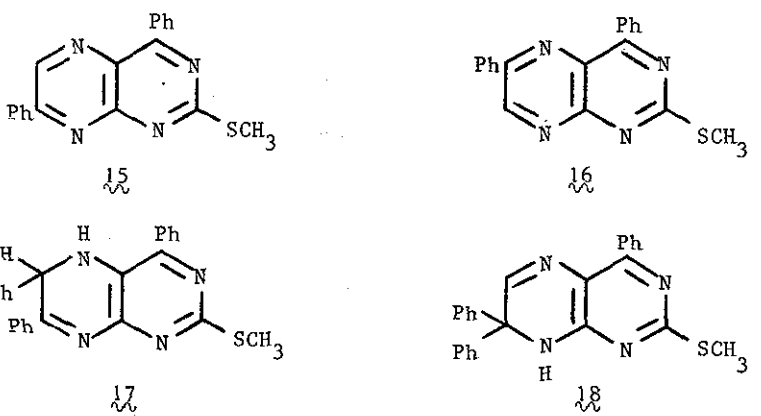
intermediate 13 which recyclizes via 14 into 4 (scheme 2).



Scheme II

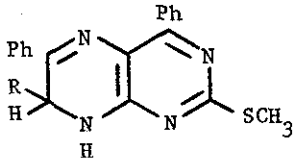
b) On the ring contraction of 3 into 5a

In order to discern whether C-6 and/or C-7 is expelled during the above mentioned ring contraction, we tried to synthesize a compound in which one of the phenyl groups either at position 6 or at position 7 is deuterated. The obvious method to synthesize this compound was the phenylation of the relatively easily available 4,7-diphenyl-2-(methylthio)pteridine (15) or of its structural isomer 4,6-diphenyl-2-(methylthio)pteridine (16) with deuterated phenyllithium and subsequent oxidation of the intermediary dihydro compound obtained. Phenylation of pteridines have never been published[16], but this method is successfully used for the preparation of phenyldiazines[17].



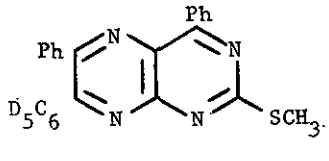
From introductory experiments we learned that treatment of 15 with phenyllithium and work-up of the reaction mixture with water gave us a compound with m/e 408; it indicates the formation of a 2-(methylthio)triphenyldihydropteridine. Since this compound was found to be very resistant to oxidation with O_2, $KMnO_4$ in acetone and Fe^{3+}, it was evident that this compound cannot have structure 17. Furthermore heating of this compound with hydrochloric acid gave, surprisingly, benzophenone, indicating that the addition of phenyllithium had taken place to a carbon atom already carrying a phenyl group (either C-4 or C-7). This phenomenon is not unprecedented and has been observed in related reactions[18]. A conclusive structure assignment was based on its ^{13}C-nmr spectrum and shows that the phenylation product of 15 is 7,8-dihydro-2-(methylthio)-4,7,7-triphenylpteridine (18) (See Experimental).

Now it has been established that position 7 in the pteridine ring is the preferred position of attack by phenyllithium, it is evident that 16 is a more appropriate compound to serve our purpose. Reaction of 16 with phenyllithium yields indeed 7,8-dihydro-2-(methylthio)-4,6,7-triphenylpteridine (19a). This compound could not be isolated, since it very easily undergoes oxidation by air. Treatment with $KMnO_4$ in acetone gives 3 in quantitative yield. Analogously, by the action of pentadeuterophenyllithium on 16 and oxidation of 19b we were able to obtain 20.



19a R = C_6H_5

19b R = C_6D_5



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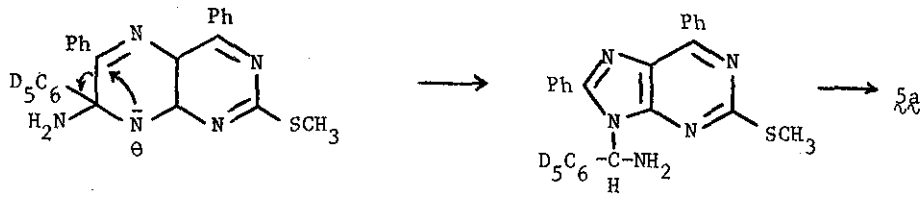
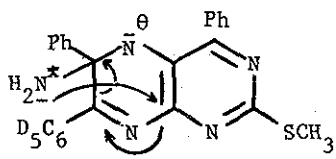
After reaction of 20 (99.8% d_5) with KNH_2 in liquid NH_3 the purine was isolated and its deuterium content was established by mass spectrometry. From the data it appeared to consist of a mixture of compound 5a (m/e 318) and 5b (m/e 323) in the ratio 5a/5b=87/13. From this result the conclusion seems justified that mainly C-7

is expelled confirming our earlier proposal, that the ring contraction starts with initial attack at C-7 i.e. 21. Ring opening as indicated gives purine 22 which by a base-catalyzed elimination of pentadeuterobenzylideneimine yields 5a. However to exclude the alternative mechanism in which amide anion attacks C-6 in 3 yielding the adduct 23 which then undergoes a ring closure to the purine with a concomitant elimination of pentadeuterobenzonitrile, we reacted 3 with $K^{15}NH_2$ in liquid $^{15}NH_3$. By mass spectrometry it was shown that the purine formed did not contain any ^{15}N enrichement thus excluding the intermediacy of 23 as reactive species in the ring contraction.



21 22

Both the phenylation reactions as well as the results of the deuterium and ^{15}N-labelling experiments fully confirm that C-7 is more vulnerable for a nucleophilic attack than C-6. Attempts to prove the existence of this adduct by ^{1}H- and ^{13}C-NMR measurements failed, probably due to the low solubility of 16 in liquid NH_3.



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Combining the results discussed in sections a and b it is evident that the pteridine 3 is multireactive towards the amide ion. It undergoes addition at position 2 (yielding 4 according to an S_N(AE)-process), at position 4 (yielding 4 via an S_N(ANRORC)-mechanism), at position 7, (yielding the purine 5a) and at position 6 (also yielding the purine 5a). The order of reactivity is approximately C-4 ≥ C-2 >

C-7 > C-6, based on quantitative product studies and on the distribution of the ^{15}N and the D in the amino compounds as well as in the purine derivatives.

Experimental

Melting points are uncorrected. ^{1}H-nmr spectra were recorded with a JEOL JNM C-60H spectrometer. ^{13}C-nmr spectra were measured on a Varian XL-100-15 spectrometer operating at 25.2 MHz, equipped with a pulse unit and a 620 L-16K on line computer system.

1. 2-Amino-3-benzoyl-5,6-diphenylpyrazine (6)

2-Amino-4,6,7-triphenylpteridine[5] (375 mg, 1.0 mmole) and 5 ml 6N HCl were heated for 10 hours at 150° in a sealed tube. After cooling the contents of the tube were extracted with $CHCl_3$. The extracts were dried over $MgSO_4$ and evaporated. The solid obtained was recrystallized from methanol yielding 252 mg (72%) of 6 as tiny yellow needles, m.p. 193°C. Analysis calcd. for $C_{23}H_{17}N_3O$ (351.39): C: 78.61, H: 4.88; found C: 78.42, H: 5.00.

2. 2-chloro-4,6,7-triphenyl[^{15}N-3]pteridine (8)

700 mg of 6 (2.0 mmoles) were stirred with 480 mg (8.0 mmoles) of ^{15}N,^{15}N-urea containing 30.3% ^{15}N at 200°C for 1 hour. Recrystallization of the product from aqueous DMF yielded the pteridin-2-one (7) as yellow needles m.p. 299-300°C (490 mg, 65%) (See for the formation of the unlabelled compound from 2-amino-4,6,7-triphenylpteridine, section 5).

Treatment of 7 with $POCl_3$ and PCl_5 for 1 hour at 100°C,was followed by thorough decomposition of the reagents with water. Extraction of the aqueous layer with $CHCl_3$ yields 8 (m.p. 209-210°C) in 35%. It proved to be identical with an authentic specimen[5].

3. 2-(methylthio)-4,6,7-triphenyl[^{15}N-3]pteridine (9)

400 mg (1.0 mmole) of 8 were suspended in a mixture of 10 ml of ethanol and 10 ml of water containing 100 mg (2.5 eq.) NaOH. The solvent was saturated at 0°C with

H_2S. The mixture was heated slowly and finally boiled for 10 min. with vigorous stirring. To the filtered red-coloured solution was added 20 ml of glacial acetic acid. After cooling overnight the filtered product was dissolved in 2 ml N KOH and the solution was shaken vigorously with methyliodide (0.2 ml; 3.5 mmoles). The resulting suspension was extracted with $CHCl_3$ and the extract purified by column chromatography. Pure 9 was obtained, m.p. 233-234°C in a yield of 30% (130 mg). (lit.[5] 232-234°C).

4. Phenylation reactions

a) phenylation of 4,6-diphenyl-2-(methylthio)pteridine (16)

When a solution of 66 mg (0,2 mmoles) of 16 in 10 ml of sodium-dried benzene is treated with 0,2 ml of phenyllithium (1,3 N) at room temperature a green solution is obtained. After treatment with water (10 ml), the benzene layer is separated, dried over $MgSO_4$ and concentrated in vacuo. The residual oil is dissolved in acetone, and $KMnO_4$ is added until the permanganate colour remains. The acetone is removed in vacuo and the residue is dissolved in $CHCl_3$, filtered and chromatographed on silicagel using $CHCl_3$ as the eluent. A yellow product was obtained as tiny crystals (62 mg, 75%) which proved to be identical with an authentic specimen of 2-(methylthio)-4,6,7-triphenylpteridine (3)[4].

Following the same procedure and using pentadeuterophenyllithium as the reagent, compound 20 was obtained.

b) phenylation of 4,7-diphenyl-2-(methylthio)pteridine (15)

The phenylation of this compound was performed in the same way as described in a). After isolation an orange-coloured syrup was obtained, which was characterized by ^{13}C-nmr spectroscopy as 18 (C-2 170.3; C-4 158.3; C-6 154.2; C-7 65.1; C-9 152.6; C-10 116.7)[19].

5. Diazotization of 2-amino-4,6,7-triphenylpteridine (4)

To a solution of 30 mg of 4 in 5 ml of glacial acetic acid, in small portions 200

mg of solid $NaNO_2$ were added in a period of 15 minutes. The solution was stirred well. After the addition 5 ml of water were added and the precipitate was collected by suction, washed with water, alcohol and ether to yield the corresponding pteridin-2-one (21 mg, 70%), m.p. 299-300°C).

Analysis: calcd. for $C_{24}H_{16}N_4O$ (376.40): C: 76.58, H: 4.28; found: C: 76.39; H: 4.58.

6. Amination procedure

The reactions in liquid ammonia with potassium amide were carried out as described before[5]. The all glass apparatus used for the experiments in liquid $^{15}NH_3$ was essentially the same. $^{15}NH_3$ was prepared by treating $^{15}NH_4NO_3$ with a concentrated solution of KOH in H_2O at 100° for 2 hours. After the experiment it was reconverted into $^{15}NH_4NO_3$ in an average yield of 85%.

Acknowledgements

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