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# Ring Transformations in Reactions of Heterocyclic Compounds with Nucleophiles. XI.*,1) On the Conversion of Pteridines into Purines[2]

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2-Methylthio-4,6,7-triphenylpteridine (**1**) is slowly converted by potassium amide in liquid ammonia at −33° into 2-amino-4,6,7-triphenylpteridine (**2**) as the main product and into a ring contraction product which is proved to be 6,8-diphenyl-2-methylthiopurine (**3**). The latter is found to be the major product when 4,6-diphenyl-2-methylthiopteridine (**4**) and 4,7-diphenyl-2-methylthiopteridine (**5**) are treated likewise. The mechanism of the ring contraction is discussed.

## Introduction

In a previous paper we reported[2] on the covalent amination of pteridine and some of its derivatives by liquid ammonia. By $^1$H-NMR (nuclear magnetic resonance) spectroscopy good evidence was obtained for addition of the nucleophile across the C4-N3 bond or both the C6-N5 and the C7-N8 bonds. The addition across the C4-N3 bond is a kinetically favoured process. In connection with those studies on $\sigma$-adduct formation and as a continuation of our investigations on the mechanism of displacement reactions with strong nucleophiles[4] (potassium amide, lithium piperidide) in diazaaromatics, containing a group with considerable leaving character, we became interested in the behaviour of substituted pteridines towards potassium amide in liquid ammonia.

For that purpose we studied initially 2-methylthio-4,6,7-triphenylpteridine (**1**). This compound features the presence of the relatively large phenyl group on positions which are known to be easily attacked in the parent compound *i.e.* pteridine, by the nucleophile. The bulky phenyl group will retard or prevent addition to the positions 4, 6, and 7, making the amino-dethiomethylation at C2 a process, which is highly competitive with the addition reaction.

## Results and Discussion

Treatment of 2-methylthio-4,6,7-triphenylpteridine (**1**) in liquid ammonia with 4 equivalents of potassium amide at −33° for 3 hr results in the formation of 2-amino-4,6,7-triphenylpteridine (**2**) in moderate yield (25%). The structure of **2** was proved by identity with the product obtained by amination of 2-chloro-4,6,7-triphenylpteridine with ethanolic ammonia.

Thin-layer chromatography (TLC) analysis of the reaction product of **1** with potassium amide indicates that besides **2** and unreacted **1** (50%) another species, having a characteristic blue fluorescence, is present. After isolation and purification by column chromatography we were able to identify this compound as 6,8-diphenyl-2-methylthiopurine (**3**). The yield of the

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* Dedicated to the memory of Prof. Eiji Ochiai.

1) Part X, see H.C. van der Plas and M.C. Vollering, *Rec. Trav. Chim.*, (Pays Bas), **93**, 300 (1974).

2) Pteridine Studies Part II: Part I, A. Nagel, H.C. van der Plas and A. van Veldhuizen, *Rec. Trav. Chim.* (Pays Bas), **94**, 45 (1975).

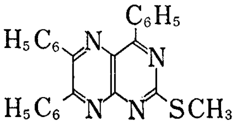
3) Location: *Wageningen, The Netherland.*

4) A.P. Kroon, H.C. van der Plas and G. van Garderen, *Rec. Trav. Chim.* (Pays Bas), **93**, 325 (1974).

purine **3** amounted to 8%. The structure assignment of **3** was based on its spectroscopic properties ($^1$H-NMR (DMSO-$d_6$) $\delta$ 2.67 ppm 3H, $\delta$ 7.6 ppm 10H; accurate mass measurement indicates the molecular formula $C_{18}H_{14}N_4S$, first fragmentation to $C_{17}H_{11}N_4$, (M-$SCH_3$); UV spectrum $\lambda_{max}$ 264 nm, $\varepsilon=7.7\cdot10^3$; $\lambda_{max}$ 358 nm, $\varepsilon=4.4\cdot10^3$), and was confirmed by infrared (IR)-identity and undepressed melting point with an authentic specimen obtained by condensation of 4,5-diamino-2-methylthio-6-phenylpyrimidine (**6**) with benzaldehyde.

This ring contraction of a pteridine into a purine system is unprecedented, in contrast to the ring expansion of purines into pteridines, which has already been described.[5] However the reported ring contraction bears close relationship to the known conversions of 2,3-diphenylquinoxaline into 2-phenylbenzimidazole[6] and of 2-chloro-3-phenylquinoxaline into benzimidazole[7] by potassium amide in liquid ammonia.

With regard to the mechanism of the conversion of **1** into **3** we assume that it proceeds *via* an initial addition of the amide ion to the C=N bond of the pyrazine ring. Whether this attack will take place at C6 or C7 of the pteridine **1** is, as yet, unknown. It is evident that the presence of the phenyl groups on both positions certainly has a considerable blocking effect on the addition. The low yield of **3** probably reflects this hindered attack. The $\sigma$-adduct formed is believed to undergo a rearrangement leading to **3** under elimination of benzylideneimine (see in the scheme below). Although in this scheme the expulsion of C7 is depictured, it is clear that there is no real evidence for it; the possible expulsion of C6 cannot be excluded. In order to obtain more information about the possibility of a C6 and/or C7 expulsion during the ring contraction we synthesized the isomeric 4,6- and 4,7-diphenyl-2-methylthiopteridines (**4** and **5** respectively) and treated both compounds with potassium amide



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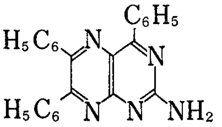

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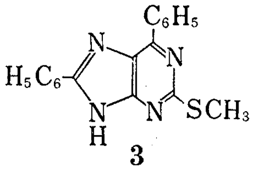

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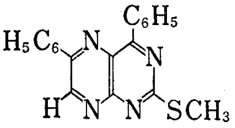

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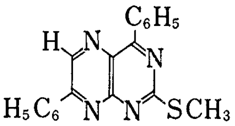

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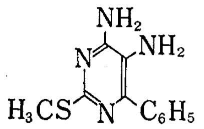

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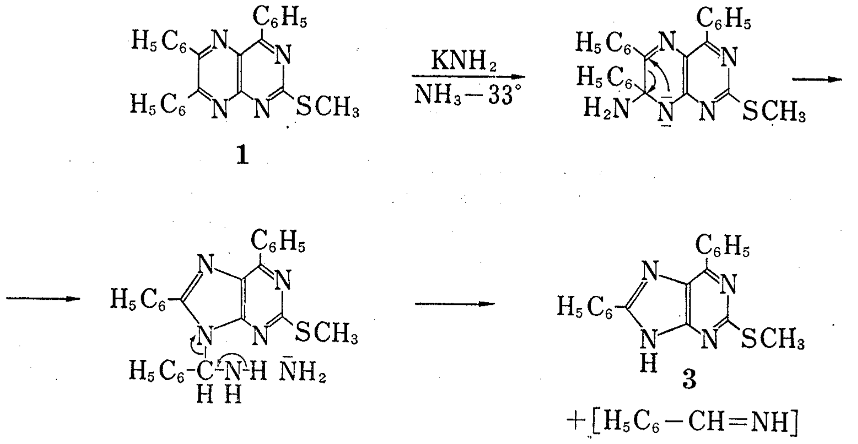

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[7] P.J. Lont and H.C. van der Plas, *Rec. Trav. Chim.* (Pays Bas), **91**, 850 (1972).

in liquid ammonia at −33° for 1 hr. It appears that both isomers are converted into the same purine derivative *i.e.* **3** in a yield (20%) being thus considerably higher than that obtained from **1**. Besides the recovery of 60% of unreacted **4** and **5** no indication for the expulsion of the carbon atom, carrying the phenyl group, yielding 2-methylthio-6-phenylpurine was obtained. Thus it is evident that both pteridine derivatives **4** and **5** undergo a reaction in which the carbon atom, carrying the hydrogen atom, is expelled during the ring contraction. Attempts to measure by $^1$H-NMR spectroscopy the adduct of **4** (or **5**) with the amide ion by the method described previously,[8] failed, probably due to the low solubility of the compounds.

## Synthesis of the Starting Substances 1, 4, and 5

The hitherto undescribed 2-methylthio-4,6,7-triphenylpteridine (**1**) is conveniently prepared by condensation of 4,5-diamino-2-methylthio-6-phenylpyrimidine (**6**) with benzil. The required pyrimidine derivative **6** was prepared by methylation of the corresponding mercapto compound. Condensation of **6** with phenylglyoxal yielded a mixture of diphenyl-2-methylthiopteridines. The $^1$H-NMR spectrum of this mixture dissolved in $CDCl_3$, showed, besides the phenyl multiplets, a high field resonance at $\delta$ 2.78 ppm and two singlets at $\delta$ 9.25 and $\delta$ 9.44 ppm. Based on the facts that i H7 in pteridine shows a lower field absorption resonance[9–11] than H6 and ii the phenyl group substituted in the pyrazine ring influences the chemical shifts of both adjacent hydrogen atoms in an identical manner (see table), we ascribed the low field adsorption at 9.44 ppm to H7 of **4** and the absorption at $\delta$ 9.25 ppm to H6 of **5**. Based on the ratio of the integrals of the absorptions of both hydrogen atoms at $\delta$ 9.25 ppm and $\delta$ 9.44 ppm the ratio **4**: **5** is about 1: 10. After separation of the mixture the ultraviolet (UV) spectra of **4** ($\lambda_{max}$ 293 nm, $\varepsilon=30.2\cdot10^3$; $\lambda_{max}$ 397 nm, $\varepsilon=11.6\cdot10^3$) and **5** ($\lambda_{max}$ 280 nm, $\varepsilon=24.2\cdot10^3$; $\lambda_{max}$ 389 nm, $\varepsilon=14.2\cdot10^3$) were measured and found to be in good agreement with data published in the literature on 6- and 7-substituted pteridines.[12,13]

TABLE I

| | H6[a] | H7[a] | |
|---|---|---|---|
| 2-Methylthio-4-phenyl-pteridine[b] | 8.84 | 9.03 | — |
| Compound 4[b] | — | 9.44 | −0.41 |
| Compound 5[b] | 9.25 | — | −0.41 |

*a*) $\delta$-values in ppm
*b*) Spectrum measured in $CDCl_3$ using TMS as an internal standard ($\delta$=0.00 ppm)

### Experimental

**4,5-Diamino-2-methylthio-6-phenylpyrimidine** (6)——4,5-Diamino-6-phenyl-2-thiopyrimidine[14] (2.8 g; 12.8 mmoles) dissolved in 25 ml 1 N KOH was shaken vigorously with methyliodide (0.88 ml; 14.1 mmoles) for 15 min. After refrigeration the filtered crude product was recrystallized from 25 ml of ethanol to yield 2.0 g (67%) of pure 1, mp 188—190°. *Anal.* Calcd. for $C_{11}H_{12}N_4S$ (232.30): C, 56.87; H, 5.21. Found: C, 56.46; H, 5.17.

**2-Methylthio-4,6,7-triphenylpteridine** (1)——To the above described diamine (see section 1) (2.0 g; 8.6 mmoles) in 25 ml of ethanol were added 2.2 g of benzil (10.4 mmoles). After refluxing for 16 hr the contents of the flask were cooled in an ice-bath and filtered. The solid material was purified by chromato-

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9) S. Matsuura and T. Goto, *J. Chem. Soc.*, **1963**, 1773.
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12) A. Albert, D.J. Brown and H.C.S. Wood, *J. Chem. Soc.*, **1954**, 3832.
13) A. Albert, D.J. Brown and G.W.H. Cheeseman, *J. Chem. Soc.*, **1952**, 1620.
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graphy (silica gel, activity I) using chloroform as eluent. After evaporation of the solvent the solid material was recrystallized from a mixture of benzene and methanol (40 ml, 1/1 v/v). The yield amounted to 1.5 g (43%) of pure 2-methylthio-4,6,7-triphenylpteridine, mp 232—234°. *Anal.* Calcd. for $C_{25}H_{18}N_4S$ (406.19): C, 73.86; H, 4.46. Found: C, 74.06; H, 4.48.

**2-Chloro-4,6,7-triphenylpteridine**——2-Chloro-4,5-diamino-6-phenylpyrimidine[2] (440 mg; 2.0 mmoles) and benzil (505 mg; 2.4 mmoles) were dissolved in warm 2-ethoxyethanol (5 ml) and the solution was kept at 120° for 5 hr. To the hot solution were added 5 ml of methanol and 5 ml of water, after which the pteridine crystallized. The crude material was purified by the same procedure as described above for the methylthio derivative (**1**) (see section 2) mp 209—210°, yield 458 mg (58%). *Anal.* Calcd. for $C_{24}H_{15}ClN_4$ (394.85): C, 73.00; H, 3.83. Found: C, 72.82; H, 4.12.

**2-Amino-4,6,7-triphenylpteridine**——2-Chloro-4,6,7-triphenylpteridine (400 mg, 1.0 mmoles) was heated at 100° for 1/2 hr together with 5 ml of ethanolic ammonia (saturated at room temperature) in a sealed tube. Upon cooling the pure product crystallized in quantitative yield, mp 271—272°. *Anal.* Calcd. for $C_{24}H_{17}N_5$ (375.42): C, 76.78; H, 4.56. Found: C, 76.38; H, 4.84.

**4,6- and 4,7-Diphenyl-2-methylthiopteridine (4, resp. 5)**——4,5-Diamino-2-methylthio-6-phenylpyrimidine (464 mg, 2.0 mmoles) and phenylglyoxal monohydrate (320 mg, 2.1 mmoles) were dissolved in 5 ml of hot 2-ethoxyethanol. The solution was boiled for 5 min. Upon addition of water (5 ml) and methanol (10 ml) a yellow crystalline material deposited (565 mg, 85%). It could be separated into its components by column chromatography (silica gel activity I, eluent chloroform) to yield 424 mg of 4,7-diphenyl-2-methylthiopteridine (**5**), mp 165—166° and 42 mg of 4,6-diphenyl-2-methylthiopteridine (**4**), mp 218—220°. *Anal.* Calcd. for **5**: $C_{19}H_{14}N_4S$ (330.40): C, 69.06; H, 4.27. Found: C, 69.01; H, 4.27. *Anal.* Calcd. for **6**, $C_{19}H_{14}N_4S$ (330.40): C, 69.06; H, 4.27. Found: C, 69.04, H, 4.31.

**6,8-Diphenyl-2-methylthiopurine (3)**——To 464 mg (2.0 mmoles) of 4,5-diamino-2-methylthio-6-phenylpyrimidine (**6**) and 80 mg copper (II) acetate in 10 ml of 50% aqueous methanol a solution of 212 mg (2.0 mmoles) of benzaldehyde in 2.5 ml of methanol was added. The solution was gently refluxed for 15 min. A precipitate was obtained, which was filtered and freed from copper(II) ions by treatment of an aqueous ethanolic suspension of this precipitate by hydrogen sulphide. After filtration and evaporation to dryness *in vacuo,* the remaining solid was extracted with hot chloroform. The filtered chloroform solution slowly deposited the purine derivative upon cooling, mp 305° (decomp.), yield 398 mg (61%). *Anal.* Calcd. for $C_{18}H_{14}N_4S$ (318.39): C, 67.90; H, 4.43. Found: C, 67.80; H, 4.51.

**2-Methylthio-4-phenylpteridine**——4,5-Diamino-2-methylthio-6-phenylpyrimidine (**6**) (70 mg, 0.3 mmoles) and glyoxal trimer monohydrate (75 mg, 1.0 mmoles) were dissolved in 2 ml of ethanol. The solution was refluxed for 30 min. The solvent was removed *in vacuo* and the crude product was purified by chromatography on silica gel activity I, using chloroform as the eluent. Yield, 62 mg (81%), mp 177—179° (from ethanol). *Anal.* Calcd. for $C_{13}H_{10}N_4S$ (254.31): C, 61.39; H, 3.96. Found: C, 61.50; H, 3.89.

**General Procedure for the Reactions of the Compounds 1, 4 and 3 with Potassium Amide in Liquid Ammonia**——To 10 ml of dry liquid $NH_3$ (distilled from $KNH_2$), in a 50 ml three-neck round-bottomed flask, equipped with a dry-ice/acetone condenser, were added a few crystals of $Fe(NO_3)_3 \cdot 9H_2O$ catalyst and 160 mg (4 mmoles) of potassium. After stirring for 30 min at $-33°$ the pteridine derivative (1 mmole) was added under the exclusion of moisture. The reaction was terminated after 3 hr by the addition of 220 mg (4 mmoles) of ammonium chloride. After the ammonia was evaporated, the residue was thoroughly extracted with warm chloroform (5 × 20 ml). The filtered chloroform extracts were concentrated *in vacuo* and the residual gum (or solid) separated into its components by column or preparative thin layer chromatography. The eluentia used were chloroform or a mixture of chloroform/methanol in the ratio 95: 5.

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