On the Amination of Pteridines by Liquid Ammonia-Potassium Permanganate

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7-Phenyl-, 7-(*p*-methoxyphenyl)-, 7-methyl-, 7-*t*-butyl-, 6,7-diphenyl-, 6,7-dimethyl- and 2-phenylpteridine are converted in good yields into their respective 4-amino compounds, when they are dissolved in liquid ammonia (−40°) and potassium permanganate is added to the solution. Increase of the temperature of the amino-oxidation did not change the position of substitution, the yields are however lower. The intermediary of 4-aminodihydropteridines in these reactions has been proved by ^{1}H nmr spectroscopy.

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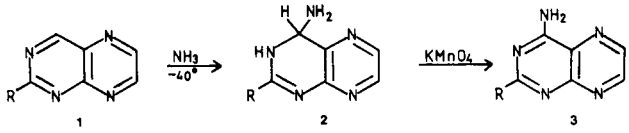
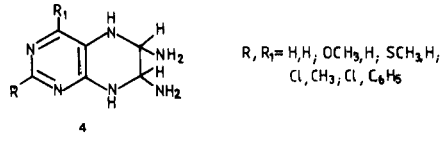
It has previously been reported [1] that treatment of pteridine (**1a**) with potassium permanganate in liquid ammonia at −40° gave 4-aminopteridine (**3a**). This amination-oxidation procedure, when applied to 2-chloropteridine (**1b**) leads to an exclusive amination at C-4, yielding 4-amino-2-chloropteridine (**3b**). No amino-dechlorination at C-2 takes place. In both cases the intermediate species are the C-4 1:1 covalent σ-adducts 4-amino-3,4-dihydro-2-R-pteridines **2a,b** [2,3].

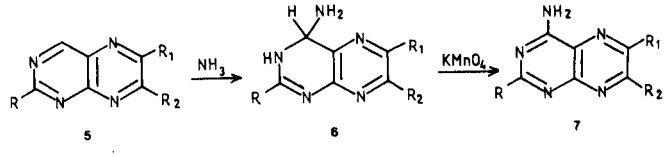




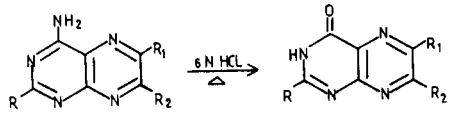
It was observed by means of ^{1}H and ^{13}C nmr spectroscopy that the regiospecificity of the addition is dependent on the temperature. At temperatures up to 25°, the addition of ammonia takes place to both C-6 and C-7, causing the formation of the 2:1 σ-adducts 6,7-diamino-5,6,7,8-tetrahydropteridines **4** [2,3].

In an extension of this work we became interested in the behaviour of 7-, 6,7- and 2-substituted pteridines **5a-5g** towards potassium permanganate in liquid ammonia at −40° and at room temperature. Amination-oxidation of all these compounds at −40° according to the procedure reported [1] leads to introduction of one amino group. These reactions proceed with good yield.

The amino compounds obtained from the 7-aryl- and 7-alkylpteridines are all featuring the presence of two distinct low-field singlets in their respective ^{1}H nmr spectra. Since these data do not allow an unequivocal assignment of the position of the amino group *i.e.* position 2,4 or



a) R = R1 = H, R2 = C6H5
b) R = R1 = H, R2 = p-C6H4 OCH3
c) R = R1 = H, R2 = CH3
d) R = R1 = H, R2 = t-C4H9
e) R = H, R1 = R2 = C6H5
f) R = H, R1 = R2 = CH3
g) R = C6H5, R1 = R2 = H



6, we converted the amino compounds **7a, 7d** into their respective pteridones. By heating with 6*N* hydrochloric acid for 15 minutes the pteridones **8a** and **8d** were obtained and found to be identical with the corresponding pteridin-4-ones, synthesized independently [4,5]. It indicated that in the amination-oxidation reaction the amino group is substituted at position 4 of the pyrimidine ring. The structure of compound **7a** was confirmed by comparing its physical and chemical properties with those of the compound obtained by the condensation of 4,5,6-triaminopyrimidine sulfate with phenylglyoxal [6].

The structure of the amino compounds obtained from the 6,7-disubstituted pteridines was also based on ^{1}H nmr data (see Table 1) and on the conversion of one of the amino compounds *i.e.* **7e** into the known pteridin-4-one **8e** [7,8].

The 4-amino structure of the product obtained from **5g** was proved by its ^{1}H nmr spectrum showing the two *doublets* (J = 3 Hz) of the hydrogens at C-6 and C-7.

Also ^{13}C nmr data were in accordance with the assigned

Table 1

^{1}H NMR Spectral Data (δ-Values)

Pteridine	H2	H4	H6	H7	Solvent [c]
unsubstituted	9.66 (s)	9.82 (s)	9.13 (d) [a]	9.32 (d) [a]	A
7-phenyl-(**5a**)	9.62 (s) [a]	9.74 (s)	9.60 (s) [a]	–	A
4-amino-3,4-dihydro-7-phenyl-(**6a**)	7.68 (s)	5.58 (s)	8.88 (s)	–	B
4-amino-7-phenyl-(**7a**)	8.60 (s)	–	9.48 (s)	–	C
7-*p*-methoxyphenyl-(**5b**)	9.60 (s)	9.70 (s)	9.52 (s)	–	A
4-amino-3,4-dihydro-7-*p*-methoxyphenyl (**6b**)	7.64 (s)	5.50 (s)	8.82 (s)	–	B
4-amino-7-*p*-methoxyphenyl-(**7b**)	8.51 (s)	–	9.37 (s)	–	C
7-methyl- (**5c**)	9.60 (s)	9.71 (s)	8.97 (s)	–	A
4-amino-3,4-dihydro-7-methyl- (**6c**)	7.58 (s)	5.49 (s)	8.18 (s)	–	B
4-amino-7-methyl-(**7c**)	8.57 (s)	–	8.80 (s)	–	C
7-*t*-butyl-(**5d**)	9.49 (s)	9.59 (s)	9.12 (s)	–	A
4-amino-3,4-dihydro-7-*t*-butyl- (**6d**)	7.57 (s)	5.52 (s)	8.42 (s)	–	B
4-amino-7-*t*-butyl- (**7d**)	8.54 (s)	–	9.00 (s)	–	C
6,7-diphenyl-(**5e**) [b]	9.60 (s)	9.78 (s)	–	–	A
4-amino-6,7-diphenyl-(**7e**)	8.60 (s)	–	–	–	C
6,7-dimethyl- (**5f**)	9.54 (s)	9.63 (s)	–	–	A
4-amino-3,4-dihydro-6,7-dimethyl (**6f**)	7.48 (s)	5.43 (s)	–	–	B
4-amino-6,7-dimethyl (**7f**)	8.44 (s)	–	–	–	C
2-phenyl-(**5g**)	–	9.82 (s)	9.00 (d) [a]	9.23 (d) [a]	A
1:1 σ-adduct(**6g**)		5.60 (br)	8.05 (d) [a]	8.12 (d) [a]	B
2:1 σ-adduct		7.78 (s)	4.12 (d) [a]	4.25 (d) [a]	B
4-amino-2-phenyl-(**7g**)	–	–	8.81 (d)	9.11 (d)	C

[a] Resonance signals may be interchanged. [b] Due to its high insolubility in liquid ammonia no resonance signals have been recorded at −40° as well as when the solution is allowed to be at room temperature. [c] A Deuteriochloroform; B Liquid ammonia; C d6-dimethylsulfoxide.

structures. Compound **7d** (in d6-dimethylsulfoxide) gives among others two ^{13}C-resonance signals at 159.2 (C-2) and 141.8 (C-6) ppm. They are associated with bond ^{13}C-^{1}H coupling constants of 196 and 185 Hz, respectively. In the case of compound **7e** the signal at 159.4 (C-2) ppm has the coupling constant ^{1}J (CH) = 198 Hz. In ^{13}C nmr spectra of both compounds **7d** and **7e** an upfield shift (about 9 ppm) for C-10 is observed, being also found in the ^{13}C nmr spectrum of 4-aminopyrimidine [9].

To investigate whether the reactions described above proceed by the intermediary of 4-amino-7R(6,7-R or 2R)-3,4-dihydropteridines, ^{1}H nmr spectra of compounds **5a-5g** were measured in liquid ammonia at −40° (in the case of **5g** also at −60°). It was observed (Table 1) that in this solvent the absorption of hydrogen atom in position 4 of compounds **5a-5d**, and **5f** was found to be highly upfield shifted ($\Delta\delta \sim 4$ ppm) compared to the one found for H-4 in solutions of **5a-5d** and **5f** in deuteriochloroform. This upfield shift was attributed to the formation of the σ-adducts **6a-6d, 6f** involving the change of hybridization of C-4 from sp^2 (in **5a-5d, 5f**) to sp^3 (in **6a-6d, 6f**).

These results strongly indicate the involvement of these σ-adducts in the amination-oxidation reaction.

Under above mentioned conditions the ^{1}H nmr spectrum of compound **5e** only showed a low noise base line probably because of its sparing solubility in liquid ammonia. Since in our amination-oxidation experiment a large excess of ammonia was used, we were still able to obtain the 4-aminoderivative **7e** in good yield.

The ^{1}H nmr spectrum of the compound **5g**, dissolved in liquid ammonia (−60°) showed besides the signals characteristic of the 1:1 σ-adduct **6g** also those of the 2:1 σ-adduct **4** (R = C_6H_5, R_1 = H). At −40° only traces of 1:1 σ-adduct were observed. As the amination-oxidation reaction was carried out in the presence of potassium permanganate, which oxidizes the 1:1 adduct faster than the 2:1 adduct the equilibrium probably shifts in favour of 1:1 adduct yielding mainly 4-aminoderivative **7g**. Only traces of the 6,7-diamino compound were detected by mass spectrometry in the reaction product (The same effect was observed with pteridine itself).

As was already indicated before in pteridine the regiospecificity of the addition is dependent of the temperature. Therefore we also measured the ^{1}H nmr spectra of solutions of the pteridine derivatives **5** in liquid ammonia after these solutions have been allowed to come to room temperature. We observed nearly no change in the ^{1}H nmr spectra of compounds **5a-5d, 5f**, proving that the addition at C-4 is also occuring at higher temperature. Apparently due to the presence of an aryl or alkyl substituent at 7, addition at C-6 is prevented; this means that in the pteridines **5** the kinetic and thermodynamically controlled

addition favours the same position 4. A solution of **5e** at +20° did not show any signals; in the spectrum of **5g** only the presence of 2:1 σ-adduct was recorded (see Table 1).

To determine the stability of the σ-adducts ^{1}H nmr spectra of compounds **5a-5g** were measured after 5, 45, 60 minutes or even after standing overnight at room temperature. Under these conditions only the σ-adducts of 7-phenyl- and 7-*t*-butylpteridines were found to be fully stable. The adduct of 7-*p*-methoxyphenylpteridine slowly decomposed and gave a yellow precipitate. The solution of 7-methylpteridine turned to dark blue and black after 5 and 60 minutes, respectively. Similarly, the solution of 6,7-dimethylpteridine coloured dark blue after 15 minutes. Even after standing overnight no ^{1}H nmr resonance signals of **5e** were observed. The 2:1 σ-adduct of 2-phenylpteridine is stable after standing 30 minutes at room temperature but decomposes during staying overnight.

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were obtained as potassium bromide pellets using spectrometer A-100 (Jasco). The ^{1}H nmr spectra were recorded on Hitachi Perkin-Elmer R-24B (60 MHz) and Varian EM-390 (90 MHz) spectrometers with TMS as internal standard. The mass spectra were obtained on AEJ MS-902, equipped with a VG-ZAB console. For the column chromatography silica gel 60 (70-230 mesh ASTM) Merck was used. The data of ^{1}H nmr spectra are shown in Table 1.

General Procedure for the Amination of Pteridines **5**.

a) At Low Temperature (−40°).

To a stirred solution of liquid ammonia (20-25 ml) containing 316 mg (2 mmoles) of potassium permanganate the corresponding pteridine (2 mmoles) was added in one portion. The stirring was continued for 4 hours (compounds **5a-5d, 5g**) or 6 hours (compounds **5e, 5f**), at the temperature of about −40°. Then the ammonia was evaporated at room temperature and to the residue methanol (50 ml) was added. The mixture was allowed to stand overnight. Brown precipitate (manganese dioxide) and separated substances (in the case of the compounds **7a, 7b, 7e, 7f**) were filtered by suction and washed with methanol. The residue on the filter was exhaustively extracted with boiling methanol (compounds **7a, 7b**) or boiling chloroform (compounds **7e, 7f**). To the combined methanol (or methanol-chloroform) solutions silica gel (1-2 g) was added and the solvent was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel for purification (eluent:methanol/chloroform 1:9 (compounds **7c, 7d**), or methanol/chloroform 0.5:9.5 (compounds **7a, 7g**) or chloroform and methanol/chloroform 0.5:9.5 (compounds **7b, 7e, 7f**).

b) At Room Temperature (20°).

A mixture of 0.5 mmole of the pteridine **5a-5d** and about 5 ml of liquid ammonia was sealed in a glass tube filled with nitrogen and maintained at room temperature for 1 hour (compounds **5a, 5c, 5d**) or 2 hours (compound **5b**). Under these conditions 7-methylpteridine gave a blue and then a black solution, 7-*t*-butylpteridine turned into a pale yellow solution and 7-phenylpteridine after dissolving first yielded a slight yellow precipitate. In the case of 7-*p*-methoxyphenylpteridine a yellow precipitate was observed from the beginning of the reaction. Thereupon 79 mg (0.5 mmole) of potassium permanganate was introduced to the reaction mixture after having been cooled to −40°. and stirred. After 10 minutes ammonia was allowed to evaporate and to a dark residue methanol (20 ml) was added; the mixture was left overnight. Then the brown precipitate was filtered by suction and the solvent was evaporated under reduced pressure. In the case of the compounds **7a, 7b**, the residue on the filter was exhaustively extracted with boiling methanol. The obtained products were purified by column chromatography using the same eluents as described in section a. In all cases the same substances were obtained as by the procedure mentioned in section a.

4-Amino-7-phenylpteridine (**7a**).

This compound was obtained in a yield of 90% (method a), 60%, besides 30% of the starting material (method b), cream-coloured crystals, mp 284-286° (from dimethylsulfoxide/water), lit [6] mp, 265-267°, ms: m/e 223.0861 (M^+) (Calcd. 223.0858); ir: 3360, 3300 cm^{-1} (NH_2).

The ir and ^{1}H nmr spectra of this compound were identical with those of an authentic sample prepared by the condensation of 4,5,6-triaminopyrimidine sulfate with phenylglyoxal according to the prescription given in [6]. After several crystallizations from aqueous dimethylsulfoxide the obtained substance melted at 284-285°.

4-Amino-7-*p*-methoxyphenylpteridine (**7b**).

This compound was obtained in a yield of 61%, besides 24% of the starting material (method a), and 10%, besides 80% of the starting pteridine (method b), yellow crystals, mp 297-300° dec (from dimethylsulfoxide); ms: m/e 253 (M^+).

Anal. Calcd. for $C_{13}H_{11}N_5O$ (253.26): C, 61.65; H, 4.38. Found: C, 61.85; H, 4.10.

4-Amino-7-methylpteridine (**7c**).

This compound was obtained in a yield of 88% (method a), 10% (method b). Colourless crystals mp 246-248° (from chloroform/ether); ms: m/e 161 (M^+).

Anal. Calcd. for $C_7H_7N_5$ (161.17): C, 52.16; H, 4.38. Found: C, 51.87; H, 4.09.

4-Amino-7-*t*-butylpteridine (**7d**).

This compound was obtained in a yield of 92% (method a), 90% (method b), colourless crystals, mp 265-266° (from chloroform/light petroleum, bp 80-100°); ms: m/e 203 (M^+).

Anal. Calcd. for $C_{10}H_{13}N_5$ (203.24): C, 59.09; H, 6.45. Found: C, 58.90; H, 6.05.

4-Amino-6,7-diphenylpteridine (**7e**).

This compound was obtained in a yield of 70% (method a), light yellow needles, mp 173-175° after solidifying mp 205-207° (from aqueous acetone), lit [10] mp 175°; ms: m/e 299 (M^+).

4-Amino-6,7-dimethylpteridine (**7f**).

This compound was obtained in a yield of 47% (method a), colourless crystals, mp 295° dec (from water), lit [11,12], mp 295° dec; ms: m/e 175 (M^+).

4-Amino-2-phenylpteridine (**7g**).

This compound was obtained in a yield of 50% (method a), colourless crystals, mp 250-251° (from ethanol), lit [13] mp 239-240°; ms: m/e 223 (M^+).

7-Phenylpteridin-4-one (**8a**).

A solution of 100 mg (0.448 mmole) of the compound **7a** in 5 ml of 6*N* hydrochloric acid was heated under reflux for 15 minutes. After cooling the separated crystals were filtered off, washed with water until acidic reaction disappeared and dried, 72 mg (72% yield) of colourless crystals were obtained, mp > 300° dec (from aqueous dimethylformamide), lit [4] mp 295° dec; ms: m/e 224 (M^+); ir: 1720 cm^{-1} (CO); ^{1}H nmr (in d6-dimethylsulfoxide): δ 9.5 (1H, s, H-6), 8.4 (1H, s, H-2), 7.8-7.5 (3H, m, arom H), 8.5-8.2 (2H, m, arom H).

The ir and ^{1}H nmr spectra of this compound were identical with those of an authentic sample prepared by the oxidation of 7-phenylpteridine with *m*-chloroperbenzoic acid [4].

7-*t*-Butylpteridin-4-one (**8d**).

This compound was obtained in the same way as described above for 7-phenylpteridin-4-one, 100 mg (0.49 mmole) of 4-amino-7-*t*-butylpteridine yielded 62 mg (62%) of **8d** as colourless crystals, mp > 300° dec (after reprecipitation from a dilute sodium hydroxide solution by acetic acid), lit [5] mp was not given; ms: m/e 204 (M^+); ir: 1715 (CO).

The ir spectrum of this substance was identical with that of 7-*t*-butylpteridin-4-one obtained by the condensation of 4,5-diamino-6-hydroxypyrimidine with *t*-butylglyoxal at *p*H 7 [5].

6,7--Diphenylpteridin-4-one (**8e**).

This compound was obtained in the same way as 4-oxo derivatives **8a** and **8d** presented above. Compound **7e** (60 mg, 0.2 mmole) gave after reprecipitation from a dilute solution of sodium hydroxide by acetic acid 31 mg (52%) of colourless crystals, mp 308-310° dec, lit [7,8] mp 297-298°, 295°, respectively; ms: m/e 300 (M^+); ir: 1698 cm^{-1} (CO); ^1H nmr (d6-dimethylsulfoxide): δ 8.45 (1H, s, H-2), 7.45 (10H, m, aromat H).

The ir and ^1H nmr spectra of this compound were identical with those of the substance obtained by the condensation of 4,5-diamino-6-hydroxypyrimidine with benzil [7].

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