A New Synthesis of 4-(Alkyl)aminopteridines (1,2)

Hiroshi Hara (3) and Henk C. van der Plas*

Laboratory of Organic Chemistry, Agricultural University Wageningen, The Netherlands

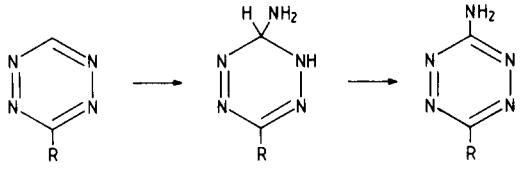
Received February 3, 1982

On treatment of pteridine with potassium permanganate in liquid ammonia, 4-aminopteridine is obtained in good yield. The C_4 σ adduct 4-amino-3,4-dihydropteridine is the intermediate species. Similarly, 2-chloropteridine undergoes amination at C_4, yielding 4-amino-2-chloropteridine; thus no replacement of the chloro atom occurs. By this amination-oxidation procedure 4-ethylaminopteridine and its 2-chloro derivatives are also easily obtained.

J. Heterocyclic Chem., **19**, 1527 (1982).

Very recently it has been reported (4) that treatment of a solution of 3-R-1,2,4,5-tetrazines (**1**, R = alkyl, aryl) in liquid ammonia with potassium permanganate gave 6-amino-3-R-1,2,4,5-tetrazines (**3**) in reasonable-to-good yields. The ^1H nmr evidence was obtained (4) suggesting that in the Chichibabin amination of **1** into **3**, 6-amino-3-R-1,6-dihydro-1,2,4,5-tetrazine (**2**) is the actual species that undergoes the oxidation.

Figure 1

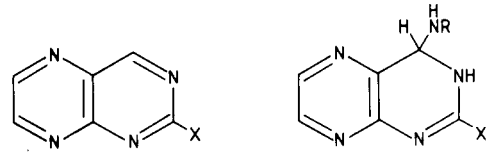


1 **2** **3**

Some years ago we presented sound ^1H nmr evidence (5,6) that pteridine (**4a**) when dissolved in liquid ammonia at -40°, forms 4-amino-3,4-dihydropteridine (**5a**). The successful mild oxidation of **2** into **3** induced us to investigate whether this method could also be applied to synthesize 4-aminopteridines and some of their derivatives. In short communication was want to report the first successful attempts of this new version of the Chichibabin amination in pteridine chemistry. When pteridine (**4a**) was added to a solution of potassium permanganate in liquid ammonia at -40° and the mixture was reacted for 10 minutes, 4-aminopteridine (**6a**) could be isolated in 49% yield. Under the same reaction conditions, 2-chloropteridine (**4b**) was converted into 4-amino-2-chloropteridine (**6b**). No replacement of the chloro atom took place. It is likely that the formation of **6a** and **6b** occurs *via* intermediacy of the 4-amino-3,4-dihydropteridines **5a** and **5b** respectively, of which the existence has been proved earlier by ^{13}C and ^1H nmr spectroscopy (5,6).

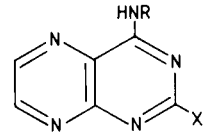
A similar procedure was applied to the introduction of an (ethylamino) group at position 4 of the pteridine ring. On allowing **4a** to react with a solution of potassium permanganate in ethylamine for 20 minutes at -75°, besides starting material (21%) a compound (35%) was isolated of

Figure 2



4a: X = H
b: X = Cl
c: X = NHC$_2$H$_5$

5a: X = H, R = H
b: X = Cl, R = H
c: X = H, R = C$_2$H$_5$
d: X = Cl, R = C$_2$H$_5$



6a: X = H, R = H
b: X = Cl, R = H
c: X = H, R = C$_2$H$_5$
d: X = Cl, R = C$_2$H$_5$
e: X = NHC$_2$H$_5$, R = C$_2$H$_5$

which the ^1H nmr spectrum unequivocally indicates that we have obtained either 4-(ethylamino)pteridine (**6c**) or the isomeric compound 2-(ethylamino)pteridine (**4c**). The latter was synthesized by reaction of 2-chloropteridine (**4b**) with ethylamine and found to be different (mp, ir, ^1H nmr) from the product obtained in the amination-oxidation procedure. Thus, in the amination-oxidation reaction, **6c** has been obtained. 4-Ethylamino-3,4-dihydropteridine (**5c**) is involved as intermediate as was proved by ^1H nmr spectroscopy. It was observed that the hydrogen at position 4, being found at 9.82 ppm in a solution of **4a** in deuteriochloroform, had shifted to 5.30 ppm, when **4a** was dissolved in liquid ethylamine at -65°. The upfield shift of 4.52 ppm being attributed to the change of hybridization of C_4 from sp^2 (in **4a**) to sp^3 (in **5c**) is of the same magnitude as observed in the adduct formed with liquid ammonia ($\Delta\delta$ = 4.30 ppm) (5). In contrast to **5a**, adduct **5c** decomposes rapidly even at -75°C and therefore the ^1H nmr spectrum was measured as quickly as possible.

Compound **4b** could be converted into 2-chloro-4-

(ethylamino)pteridine (**6d**), when subjected to treatment with a solution of potassium permanganate in ethylamine at -75° for about 20 minutes. Attempts to detect the proposed intermediate **5d** by ^{1}H nmr spectroscopy at -70° failed. The adduct formation is very fast, but **5d** is unstable and decomposes. On keeping **4b** with ethylamine and potassium permaganate at -75° overnight, besides the introduction of the ethylamino group at C_4, the chlorine atom is replaced and 2,4-di(ethylamino)pteridine (**6e**) is obtained. Compound **6e** is also formed on reaction of 2-chloro-4-(ethylamino)pteridine (**6d**) with ethylamine at room temperature.

In summary the method described in this paper proves to be useful for introducing an amino or alkylamino group at position 4 of the pteridine ring, even in compounds in which a labile chloro atom is present.

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H nmr spectra were obtained with an Hitachi Perkin-Elmer R-24B (60 MHz) using TMS as internal standard. The data of ^{1}H nmr spectra are shown in Table 1.

4-Aminopteridine (**6a**).

Potassium permanganate (105 mg, 1 redox equivalent was dissolved in liquid ammonia (ca 20 ml) and pteridine (132 mg, 1 mmole) was added to this solution in one portion with stirring. After 10 minutes methanol (20 ml) was slowly added through the condenser, cooled by dry-ice/acetone and the solution was allowed to stand overnight. Brown precipitate (manganese dioxide) was filtered by suction and washed with methanol (10 ml). Silica gel (1 g) was added to the methanolic solution and the solvent was evaporated under reduced pressure. Purification by column chromatography on silica gel using chloroform as eluent gave crystals (72 mg, 49%), mp 309-311° (in closed tube), which were recrystallized from water to afford colorless fine prisms, mp 309-311° (in closed tube), lit (7) mp 309-312°.

4-amino-2-chloropteridine (**6b**).

This compound was prepared according to the procedure described above for the preparation of **6a**. 2-Chloropteridine (84 mg, 0.5 mmole) was converted into **6b** (86 mg, 94%), mp 245-249° (from ethanol).

Anal. Calcd. for $C_6H_4ClN_5$: C, 39.68; H, 2.22. Found: C, 39.70; H, 2.15.

4-(Ethylamino)pteridine (**6c**).

Pteridine (66 mg, 0.5 mmole) was added to a cooled solution of potassium permanganate (53 mg) in ethylamine (10 ml) bath temperature -75°). After 20 minutes (20 ml) was poured into the reaction mixture, which was allowed to stand overnight. Separation of the products by column chromatography, using chloroform as the eluent, gave starting material (14 mg, 21.2%), mp 134-136°, and 4-(ethylamino)pteridine (31 mg, 35.4%), mp 141-142°.

Anal. Calcd. for $C_8H_9N_5$: C, 54.84; H, 5.18. Found: C, 54.91; H, 5.03.

2-(Ethylamino)pteridine (**4c**).

A mixture of 2-chloropteridine (42 mg, 0.25 mmole) and ethylamine (5 ml) was refluxed for 3 hours. After evaporation of the excess of ethylamine, the product was purified by preparative tlc [eluent chloroform-methanol (100:7)], yellow needles, mp 137-138°.

Anal. Calcd. for $C_8H_9N_5$: C, 54.84; N, 5.18. Found: C, 54.88; N, 5.11.

2-Chloro-4-(ethylamino)pteridine (**6d**).

2-Chloropteridine (84 mg, 0.5 mmole) was added to a cooled solution (10 ml, -75°) of potassium permanganate (53 mg) in ethylamine. After 20 minutes, ethylamine was rapidly evaporated under reduced pressure at room temperature. The residue was purified by column chromatography and preparative tlc using ethyl acetate as the eluent to give colorless fine needles (61 mg, 58.2%), mp 141-142°.

Anal. Calcd. for $C_8H_8ClN_5$: C, 45.83; H, 3.85. Found: C, 45.80; H, 4.03.

2,4-Di(ethylamino)pteridine (**6e**),

A. 2-Chloropteridine (84 mg, 0.5 mmole) was added to a solution of potassium permanganate (53 mg) in 10 ml of ethylamine at -75° and the solution was kept at this temperature overnight. After work-up (see the preparation of **6d**), 2,4-di(ethylamino)pteridine (61 mg, 55.9%) was obtained, mp 123.5-124.5° (from benzene).

Anal. Calcd. for $C_{10}H_{14}N_6$: C, 55.02; H, 6.47. Found: C, 54.94; H, 6.47.

B. A mixture of 2-chloro-4-(ethylamino)pteridine (30 mg) and ethylamine (3 ml) was stirred at room temperature for 3 hours. After the excess of ethylamine was evaporated, the residue was recrystallized from benzene to afford yellow prisms (16 mg, 51.3%), mp 122-124°; ^{1}H nmr data completely coincided with those of the product prepared by procedure A. Measurement of mixed melting point gave no depression.

Acknowledgment.

We wish to express our gratitude to Mr. H. Jongejan for carrying out the microanalysis and to Mr. A. van Veldhuizen for measuring some of the ^{1}H nmr spectra.

Table 1

^{1}H NMR Data of Some 4-Aminopteridies (**6a-e**) and 2-(Ethylamino)pteridine (**4c**)

Pteridine	Solvent	H-2 (s)	H-4 (s)	H-6 and H-7 (a) (each d, J = 2 Hz)	CH_3 (t, J = 7 Hz)	CH_2 (q, J = 7 Hz)
4-Amino- (**6a**)	A	8.93	—	9.18, 9.24	—	—
4-Amino-2-chloro- (**6b**)	B	—	—	8.95, 8.74	—	—
4-(Ethylamino)- (**6c**)	C	8.71	—	8.57, 8.94	1.39	3.73
2-(Ethylamino)- (**4c**)	C	—	9.12	8.43, 8.77	1.32	3.67
2-Chloro-4-(ethylamino)- (**6d**)	C	—	—	8.50, 8.85	1.37	3.72
2,4-Di(ethylamino)- (**6e**)	C	—	—	8.03, 8.55	1.24, 1.30	3.57 (4H)

A. Deuteriumoxide-trifluoroacetic acid. B. Deuteriochloroform-perdueteriomethanol. C. Deuteriochloroform.
(a) These signals may be interchanged.

REFERENCES

(1) Part VII on pteridine chemistry. For part VI see J. Tramper, A. Nagel and H. C. van der Plas, *Rec. Trav. Chim.*, **98**, 224 (1979).

(2) Part **88** of pyrimidines. For part **87** see Z. Swistun and H. C. van der Plas, *J. Heterocyclic Chem.*, **18**, 1639 (1981).

(3) Postdoctoral fellow, Science University of Tokyo, Japan.

(4) A. D. Counotte-Potman and H. C. van der Plas, *J. Heterocyclic Chem.*, **18**, 123 (1981).

(5) A. Nagel, H. C. van der Plas and A. van Veldhuizen, *Rec. Trav. Chim.*, **94**, 95 (1975).

(6) J. P. Geerts, A. Nagel and H. C. van der Plas, *Org. Magn. Reson.*, **8**, 607 (1976).

(7) M. Kocevar, B. Stanovnik and M. Tisler, *Heterocycles*, **15**, 293 (1981).