

Synthesis of Pteridines, unsubstituted in the 4-Position, from Pyrazines via 3,4-Dihydropteridines

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Summary Pteridines unsubstituted in the 4-position have been prepared from pyrazine intermediates by a new, general method that permits synthesis of several pteridines which could not be made from pyrimidine intermediates.

HITHERTO all reactions for converting pyrazines into pteridines have inserted a substituent in the 4-position. This limitation is avoided in a new synthesis, which uses 2-aminopyrazine-3-carboxamide (Ia), readily prepared¹ from aminomalonamidamide² and glyoxal. This amide (Ia) was converted (in 75% yield) into the known 2-amino-3-cyanopyrazine (m.p. 189°) by phosphoryl chloride in *NN*-dimethylformamide, a new example of a recently discovered reaction.³ Hydrogenation of this nitrile over Raney-nickel gave 87% of 2-amino-3-aminomethylpyrazine (IIa), m.p. 84—85° after purification through the phosphate, liberation at pH 10.5, and final sublimation.

The diamine (IIa), heated under reflux with triethyl

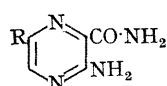
orthoacetate, furnished 70% of 3,4-dihydro-2-methylpteridine (IIIa), decomp. 177°. The n.m.r. spectrum of the cation (in Me₂SO + DCl) showed an AB quartet (2H) with principal peaks at τ 1.64 and 1.72 (protons on C-6 and C-7), a sharp peak at 5.12 (2H) (CH₂), and another at 7.66 (3H) (2-CH₃), thus establishing that C-4 is hydrogenated. The diamine (IIa) and triethyl orthoformate similarly gave 74% of 3,4-dihydropteridine (IIIb), which decomposed at 181° and had u.v. spectra (neutral species and cation) almost identical with those of the 2-methyl derivative. Similarly, hydrogenation of 2-amino-3-cyano-5-methylpyrazine³ gave 73% of 2-amino-3-aminomethyl-5-methylpyrazine (IIb), m.p. 81.5—82.5°, which was converted by triethyl orthoformate into 3,4-dihydro-6-methylpteridine (IIIc) (decomp. 181°). All of these dihydropteridines are new and probably could not be made by the reduction of the corresponding pteridines, because pteridine itself gave only 5,6,7,8-tetrahydropteridine on reduction.⁴ These dihydropteridines were oxidized by manganese dioxide in tetrahydrofuran at

20—25° to the corresponding pteridines of which 6-methylpteridine (m.p. 95°, decomp.) was unknown although its preparation from 4,5-diaminopyrimidine had often been attempted.

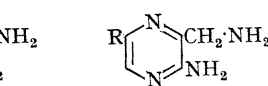
The diamine (IIa) and ethyl chloroformate ($\text{Et}_3\text{N}-\text{CHCl}_3$, 20—25°) gave 90% of 2-amino-3-ethoxycarbonylamino-methylpyrazine (IV), m.p. 131.5—132.5°. This urethane was cyclized, by refluxing with ethanolic sodium ethoxide, to the known⁵ 2-hydroxy-3,4-dihydropteridine (68%) which was then oxidized by alkaline potassium ferricyanide at room temperature to 2-hydroxypteridine (78%). Hitherto attempts to oxidize 3,4-dihydropteridines have led to over-oxidation to 4-pteridones which arise by dehydrogenation of the covalent hydrates of the pteridines first formed. The two oxidizing reagents used above avoid this difficulty.

2-Ethoxalylamido-3-cyanopyrazine (V), m.p. 160—161°, prepared (88%) from 2-amino-3-cyanopyrazine and ethoxalyl chloride (in pyridine at 1°), gave 2-ethoxycarbonyl-3,4-dihydropteridine (IIId) (decomp. 161°) when hydrogenated over Raney nickel at 20° [n.m.r. in Me_2SO : singlets at τ 1.81 (2H) (protons on C-6 and C-7) and 5.16 (2H) (4-methylene), also a triplet and a quartet at 8.70 (3H) and 5.70 (2H) (ethyl group)]. Hydrogenation at 70° gave also 2-ethoxycarbonyl-1,2,3,4-tetrahydropteridine, m.p. 97—98° [n.m.r.

in Me_2SO : singlets at τ 2.09 (2H) (protons on C-6 and C-7), 5.01 (1H) and 5.81 (2H) (protons on C-2 and C-4 respectively)]. Dehydrogenation of 2-ethoxycarbonyl-3,4-dihydropteridine (MnO_2) gave 2-ethoxycarbonylpteridine (68%; m.p. 129°).

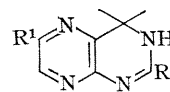


(I)



(II)

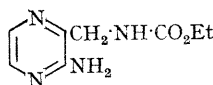
a; R=H
b; R=Me



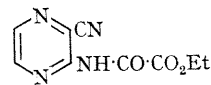
(III)

R¹ R²

a; H Me
b; H H
c; Me H
d; H CO₂Et



(IV)



(V)

These are the first pteridines with a strongly electron-attracting group in the 2-position, and the first recorded 1,2,3,4-tetrahydropteridine.

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