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

By ADRIEN ALBERT* and KYUJI OHTA

(*Department of Medical Chemistry, John Curtin School of Medical Research, Australian National University, Canberra*)

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.

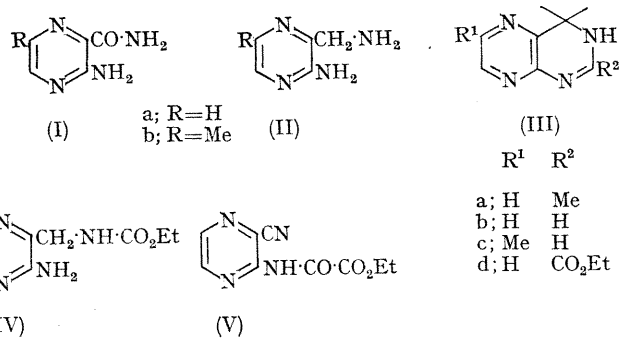
HITHERTO all reactions for converting pyrazines into pteridines have inserted a substituent in the 4-position. This limitation is avoided in a new synthesis, which uses 2-aminopyrazine-3-carboxamide (Ia), readily prepared[1] from aminomalonamidamidine[2] and glyoxal. This amide (Ia) was converted (in 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 Me_2SO + 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) (CH_2), and another at 7·66 (3H) (2-CH_3), 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-methylpyrazine[3] 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 (Et_3N–$CHCl_3$ 20—25°) gave 90% of 2-amino-3-ethoxycarbonylaminomethylpyrazine (IV), m.p. 131·5—132·5°. This urethane was cyclized, by refluxing with ethanolic sodium ethoxide, to the known[5] 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) a; R=H b; R=Me (II) (III)

	R^1	R^2
a;	H	Me
b;	H	H
c;	Me	H
d;	H	CO_2Et

(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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