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THE UNIQUE TRANSANNULAR METHYLATION OF 2-AMINO-4-HYDROXYPTERIDINE

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AMINO- and hydroxy-pteridines have invariably methylated on a nuclear-nitrogen atom of the ring bearing the substituents. Thus 4-amino-[1], 4-methylamino-[1], 2,4-diamino-[2], 4-amino-2-hydroxy-[2], 2-hydroxy-[3], and 4-hydroxy-[3], pteridines all methylate entirely on $N_{(1)}$ with the exception of the last example which also gives an O- and $N_{(3)}$-methyl derivative. Moreover, 6-hydroxy-, 7-hydroxy-, and 6,7-dihydroxy-, pteridines give respectively 5-, 8-, and 5,8-di-, methylated derivatives[3].

On the other hand, 2-amino-4-hydroxypteridine (I), which is the fundamental nucleus of most known natural

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[1] D.J. Brown and N.W. Jacobsen, J. chem. Soc. 1978 (1960).

[2] D.J. Brown and N.W. Jacobsen, unpublished work.

[3] A. Albert, D.J. Brown, and H.C.S. Wood, J. chem. Soc. 2066 (1956).

pteridines, is now shown to undergo transannular methylation yielding 2-amino-4,8-dihydro-8-methyl-4-oxopteridine (VI). This phenomenon may be of particular interest if suggestions of $N_{(8)}$-substitution in natural pteridines (as in riboflavine) prove well founded[4].

2-Amino-4-hydroxypteridine (I) and methanolic methyl iodide at 100° for 12 hours yield a single ruby-coloured hydroiodide, $C_7H_8IN_5O$. Since methylation on $N_{(5)}$ is precluded by valency, the base must have one of the five structures (II-VI). These have now all been unambiguously prepared.

4-Hydroxy-2-methylaminopteridine (II), dec. 374-378°, resulted from condensing glyoxal with 4,5-diamino-6-hydroxy-2-methylaminopyrimidine, made from 4-amino-6-hydroxy-2-methylaminopyrimidine[5] via its 5-nitro derivative. Compound (II) was also made from (V) in alkali by a now familiar type of rearrangement[6,7]. 2-Amino-4-methoxypteridine (III),

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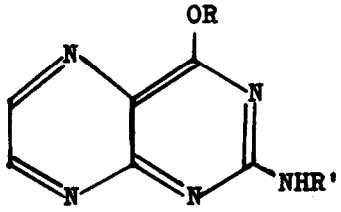
[4] Inter alia., H.S. Forrest and H.K. Mitchel, J. Amer. chem. Soc. 76, 5658 (1954); T. Masuda, T. Kishi, M. Asai, and S. Kuwada, Chem. pharm. Bull. 7, 366 (1959); R. Tschesche, F. Korte, and L. Reichle, Z. Naturforsch. 10B, 346 (1955); E.C. Taylor and H.M. Loux, J. Amer. chem. Soc. 81, 2474 (1959).

[5] B. Roth, J.M. Smith, and M.E. Hultquist, J. Amer. chem. Soc. 73, 2864 and 2869 (1951).

[6] D.J. Brown, E. Hoerger, and S.F. Mason, J. chem. Soc. 4035 (1955); D.J. Brown, Nature, in press.

[7] W.V. Curran and R.B. Angier, J. Amer. chem. Soc. 80, 6095 (1958).

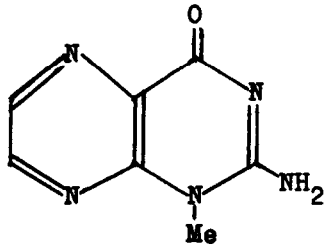
m.p. 204-205° (dec.), 2-amino-1,4-dihydro-1-methyl-4-oxopteridine (IV), m.p. 336° (dec.), and its 3,4-dihydro-3-methyl-isomer (V), dec. 319-320°, were made by similar condensations from respectively 2,4,5-triamino-6-methoxypyrimidine[5], 2,4,5-triamino-3,6-dihydro-3-methyl-6-oxopyrimidine[5,7], and its 1,6-dihydro-1-methyl-isomer[7].



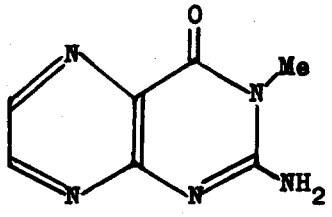
(I) R = R' = H

(II) R=H; R' = Me

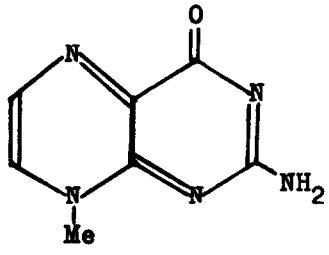
(III) R=Me; R' = H



(IV)



(V)



(VI)

In addition, mild alkaline hydrolysis of 2(4)-amino-1,4(1,2)-dihydro-4(2)-imino-1-methylpteridine[2] yielded (IV), and the position of methylation was confirmed by further degradation to 2-carboxy-3-methylaminopyrazine[2]. The remaining isomer (VI) was made from 2,5-diamino-4-hydroxy-6-methylaminopyrimidine[8] and glyoxal. The hydrochloride of

[8] W.E. Fidler and H.C.S. Wood, J. chem. Soc. 4157 (1957).

(VI) was identified with that of methylated-(I) by its decomposition point (280-285°; unchanged by admixture), by paper chroratography in six solvent systems, and by infrared spectrum.

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