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NOVEL ADDUCTS IN THE PTERIDINE FIELD

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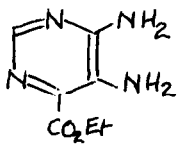
No monosubstituted pteridine derivative with a true negative group has been reported previously. 4-Ethoxycarbonylpteridine (II) (m.p. 76°) has now been prepared and shown to undergo an unusual and remarkably facile addition of two molecules of water or ethanol to the pyrazine ring. The adducts V (m.p. 125-127°) and VI (m.p. 162-164°) are reasonably stable, isolable compounds formed by dissolving the pteridine in the appropriate solvent.

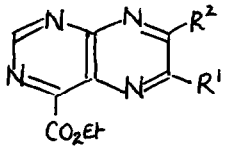
4-Ethoxycarbonyl-7-methylpteridine (III) is incompletely dihydrated at equilibrium in aqueous solution at 20° and the 6,7-dimethyl derivative (IV) is only slightly hydrated. However, the cations of III and IV as well as that of II are largely dihydrated in aqueous solution and this made it possible to isolate pure hydrates of all the compounds. In each case rapid neutralisation and buffering of an acidic solution of the pteridine was followed by crystallisation of the dihydrated neutral species. Production of the hydrates in cold, near neutral solution ensured that, even when the hydrated species was unstable, reversion to the stable anhydrous species would be slow.

The same dihydrates of 4-ethoxycarbonylpteridine, its 7-methyl and its 6,7-dimethyl derivative were also prepared directly from glyoxal, methylglyoxal or diacetyl and 4,5-diamino-6-ethoxycarbonylpyrimidine (I) in aqueous solution at room temperature. The hydrates could not, under these conditions, have been formed

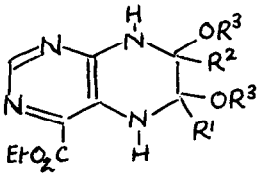
by hydration of the corresponding anhydrous pteridines. In the case of compounds II and III hydration would be too slow to account for the products and in the case of compound IV would



I



II; R^1=R^2=H
III; R^1=H, R^2=Me
IV; R^1=R^2=Me



V; R^1=R^2=R^3=H
VI; R^1=R^2=H, R^3=Et
VII; R^1=H, R^2=Me
VIII; R^1=R^2=Me

not have occurred at all. Furthermore, the adduct V obtained in this way or by neutralisation of the cation had m.p. 181° and was apparently stereoisomeric with that obtained by simply dissolving the pteridine (II) in water.

The structures of the adducts were deduced from spectroscopic evidence, pKa values and elementary analyses. For example: comparison of the N.M.R. spectrum of II in $CDCl_3$ or D_2O with the spectrum in D_2O after 24 hours standing (Table) shows a marked upfield shift of the 6- and 7-protons and a much smaller shift of the 2-proton. This is consistent with formation of the adduct (V) but not with ring-opening, or hydration of the pyrimidine ring. The ultraviolet spectrum of the adduct V closely resembles that of the diaminopyrimidine (I), which has the same conjugated system, but is quite different to that of the pteridine (II). The pKa value (3.62 ± 0.04 at 20°) obtained by titrating the pteridine (II) after equilibration with water is much too high

TABLE

Ultraviolet Spectroscopy[a]

Compound	Solvent	λ max(mμ)	log E_{max}
II	Cyclohexane	240,295,301,304,310,	3.43,3.82,3.88,3.89,3.79
II	H_2O[b]	245 304,311	3.49 3.90,3.88
V[c]	H_2O(pH 6)	235,257,347	3.84,3.57,3.98
V(cation)	H_2O(pH 1.6)	240,284,347	3.74,3.59,4.08[d]
I	H_2O(pH 7.0)	228,253,337	3.89,3.64,3.93
I(cation)	H_2O(pH 2.0)	232,279,338	3.70,3.66.4.03

a shoulders and inflexions underlined

b immediately after dissolution

c sample m.p. 181°

d solution of II at same pH has same spectrum

N.M.R. Spectroscopy[e]

Compound	Solvent	Spectrum(Chemical Shift in τ units and multiplicity)		
		2-H	6-H	7-H
II	$CDCl_3$	0.38, 1	0.87,2(J≃1.5c/s)	0.68,2(J≃1.5c/s)
II	D_2O	0.48, 1	0.80,2(J≃1.5c/s)	0.62,2(J≃1.5c/s)
II(V)	D_2O/24hrs.	2.05, 1	4.87, m	
VI	$CDCl_3$	1.67, 1	5.11, 1 (broad)	

e selected peaks only; measured on Varian A60A spectrometer

for the pteridine (II) but is about right for the adduct (V) (1) Similar evidence confirms the structure of the ethanol adduct (VI) and hydrates of the other pteridines.

Some form of covalent hydration is common in polyazanaphthalenes but hydration of unsubstituted rings is normally observed only

in solution (2) For example, pteridine, as a neutral molecule, is reversibly hydrated at the 3,4-bond in solution (3). Certain tri- and tetra-azanaphthalene derivatives form dihydrated cations with structures analogous to these described in this paper (4) but no neutral molecule hydrated in this way has been described.

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