# Heterocyclic Studies. Part VI.[1] Some 2-Substituted Derivatives of Ethyl Pteridine-4-carboxylate

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Syntheses of seven 2-substituted derivatives of ethyl pteridine-4-carboxylate (III; X = Cl, OH, OEt, $NH_2$, $NMe_2$, SH, or SMe) are described. The 2-hydroxy- and 2-mercapto-derivatives were obtained as 3,4-covalently hydrated species and the latter could not be dehydrated. The other compounds were prepared both as anhydrous and 5,6:7,8-dihydrated species, which were interconvertible. The influence of the 2-substituent on the position and extent of hydration is discussed. $^1$H N.m.r. spectra are recorded.

In a recent paper in this series it was shown that ethyl pteridine-4-carboxylate (III; X = H) forms a stable dihydrated species (IV; X = H) in aqueous solution.[2] This contrasts markedly with the behaviour of pteridine which exists in aqueous solution as a mixture of the anhydrous compound and an unstable 3,4-hydrated species (VI).[3] Examination of cations of methyl derivatives of ethyl pteridine-4-carboxylate suggests that there is a delicate balance between the factors which influence the position and ease of hydration in this system.[2] It was decided therefore to explore the effects of introducing various 2-substituents into ethyl pteridine-4-carboxylate, since such substituents might well have different effects on hydration at different sites in the molecule.

All the diamino-pyrimidines (II) required for synthesis of the pteridines (III) were already known[4] except the methylthio-derivative (II; X = SMe) which was obtained by methylation and reduction of the mercapto-nitropyrimidine (I). Five of the diamines (II; X = Cl, SMe, OEt, $NH_2$, or $NMe_2$) were condensed with polyglyoxal in suitable solvents to yield corresponding pteridines (III). It was desirable to use individual solvents and reaction conditions for each case to overcome various difficulties associated with adduct formation and decomposition. None of the reaction conditions tried yielded the 2-hydroxy- or 2-mercapto-derivative (III; X = OH or SH) directly as the anhydrous compound but in each case a 3,4-covalent hydrate (V; X = O or S) was obtained by condensing the relevant diamine with glyoxal in aqueous solution. The com-

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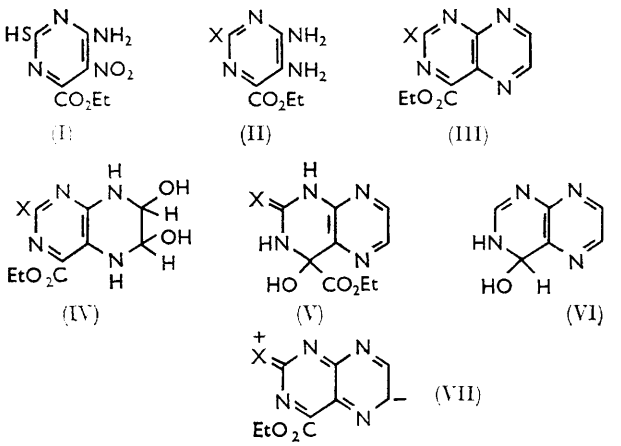
[2] J. Clark, *J. Chem. Soc.* (*C*), 1967, 1543.
[3] D. D. Perrin, *J. Chem. Soc.*, 1962, 645.
[4] J. Clark, W. Kernick, and A. J. Layton, *J. Chem. Soc.*, 1964, 3221.

pounds could not be dehydrated by refluxing in high boiling solvents such as diglyme.

A number of the pteridines (III) were converted to covalently dihydrated species (IV) by methods which

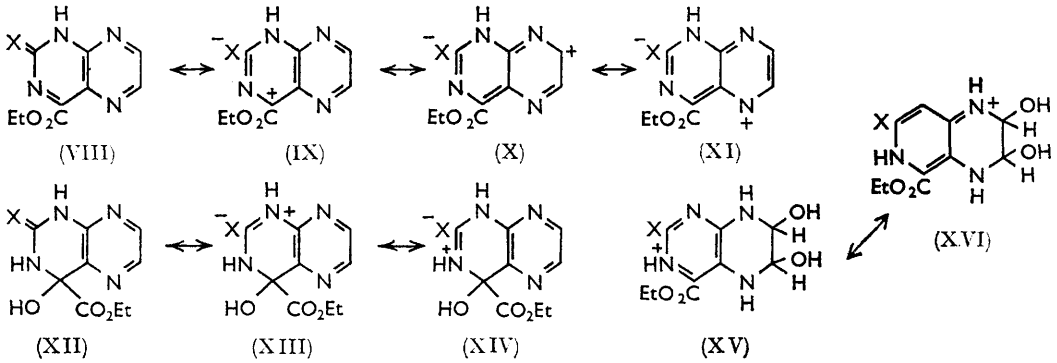


have been described previously.[5] Aqueous acidic solutions of the pteridines (III; X = $NH_2$, $NMe_2$, OEt, Cl, or SMe) were rapidly neutralised and buffered to yield the corresponding 5,6:7,8-dihydrated compounds (IV). Some of the dihydrates (IV; X = Cl, MeS, or OEt) were also made directly from the relevant diamine (II; X = Cl, MeS, or OEt) and glyoxal in aqueous solution. The dimethylamino- and amino-derivatives (IV; X = $NMe_2$ or $NH_2$) dehydrated very readily and anhydrous pteridines (III) resulted from the application of this method.

The dihydrates (IV) were converted to corresponding anhydrous compounds (III) by heating in suitable solvents (*e.g.* t-butanol, diglyme, or toluene) or by vacuum sublimation. In some cases (*e.g.* X = Cl) condensation of the diamine with glyoxal to yield the dihydrate (IV) followed by sublimation of the latter was the best preparative route to the pteridine (III).

Interesting differences in the positions and degree of hydration of the pteridines (III) at equilibrium in aqueous solution were observed. The chloro- and methylthio-compounds were almost completely dihydrated, the amino- and dimethylamino-compounds were almost entirely anhydrous, and the ethoxy-compound was partly hydrated. In the cases of the hydroxy- and mercapto-derivatives only 3,4-monohydrated species (V) appeared to be present at equilibrium. These variations are explicable in terms of the electronic effects of the 2-substituents. Those compounds in which the 2-substituent exerted a relatively weak electron-donating (+*E*) effect (Cl and SMe) were largely dihydrated like the parent (III; X = H),[2,5] while the compounds with the more powerful electron-donating (+*E*) groups ($NH_2$ and $NMe_2$) were mainly anhydrous. Canonical forms such as (VII), which increase the electron density in the pyrazine ring and discourage the nucleophilic [6] hydration reaction, are progressively more important along the series (X = Cl, SMe, OEt, and $NMe_2$).[7] The inductive (−*I*) effects of these groups should discourage 3,4-hydration by reducing the polarity of the 3,4-bond [8] but should have little effect on hydration of the distant pyrazine ring.

The 2-hydroxy- and 2-mercapto-compounds are special cases since they almost certainly exist largely as



amide and thioamide tautomers respectively (VIII; X = O or S).[9] The 2-substituent should, in these cases, exert a −*E* effect (IX)—(XI) which would aid nucleophilic attack at the 4- or 7-position. Attack at position 4 to yield a 3,4-hydrate appeared to be favoured, perhaps because there is very effective resonance stabilisation (XII)—(XIV) of the product.[10] Furthermore this resonance leaves an undisturbed heteroaromatic pyrazine ring. 2-Hydroxypteridine is also 3,4-dihydrated for the same reason.[11]

The structures of the pteridines (III) or (VIII) and their hydrates (IV) or (V) follow from $^1H$ n.m.r. spectra (Table 1). The chemical shifts of the pyrazine and pyrimidine protons in the aromatic pteridines, the

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[6] A. Albert and W. L. F. Armarego, *Adv. Heterocyclic Chem.*, 1965, **4**, 1; D. D. Perrin, *ibid.*, p. 43.
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[8] W. L. F. Armarego and J. I. C. Smith, *J. Chem. Soc.* (*C*), 1966, 234.
[9] D. J. Brown and S. F. Mason, *J. Chem. Soc.*, 1956, 3443; A. R. Katritzky and J. M. Lagowski, *Adv. Heterocyclic Chem.*, 1963, **1**, 341 *et seq.* and 396 *et seq.*
[10] A. Albert and W. L. F. Armarego, *Adv. Heterocyclic Chem.*, 1965, **4**, 34.
[11] A. Albert and C. F. Howell, *J. Chem. Soc.*, 1962, 1591.

TABLE 1

$^1$H n.m.r. spectroscopy [a] (τ values)

| X | Solvent | Ester group $CH_3$ [c] | Ester group $CH_2$ [d] | 6-H | 7-H | Exchangeable hydrogen [e] | 2-Substituent [f] | |
|---|---|---|---|---|---|---|---|---|
| | | | | Pteridines (III) | | | | |
| $NH_2$ | $CDCl_3$ | 8·52 | 5·38 | 1·32 [g] | 1·02 [g] | 4·02 | | |
| $NMe_2$ | $CDCl_3$ | 8·55 | 5·42 | 1·47 | 1·14 | | 6·61 | |
| OEt | $CDCl_3$ | 8·52 | 5·37 | 1·08 | 0·86 | | 8·45 [c] | 5·27 [d] |
| Cl | $CDCl_3$ | 8·51 | 5·35 | 0·86 | 0·70 | | | |
| SMe | $CDCl_3$ | 8·55 | 5·38 | 1·08 | 0·86 | | 7·23 | |
| | | | | 3,4-Hydrated pteridines (V) | | | | |
| S | DMSO | 8·83 | 5·81 | 1·68 | 1·57 | 2·62(1), −0·25(1), −1·90(1) | | |
| O | DMSO | 8·85 | 5·81 | 1·77 | 1·68 | 2·95(1), 1·43(1), −0·58(1) | | |
| | | | | 5,6:7,8-Dihydrated pteridines (IV) | | | | |
| $NH_2$ | N-DCl–$D_2O$ | 8·67 | 5·57 | 4·93 [h] | 4·82 [h] | | | |
| $NMe_2$ | N-DCl–$D_2O$ | 8·65 | 5·53 | 4·90 | 4·78 | | 6·86 | |
| OEt | DMSO | 8·68 | 5·68 | 5·22 [j] | | 4·23(2), 2·62(1), 1·53(1) | 8·73 [c] | 5·82 [d] |
| OEt | N-DCl–$D_2O$ | 8·68 | 5·55 | 4·88 | 4·75 | | 8·68 [c] | 5·49 [d] |
| Cl | DMSO | 8·68 | 5·68 | 5·20 [j] | | 4·07(2), 2·11(1), 0·95(1) | | |
| Cl | N-DCl–$D_2O$ | 8·66 | 5·53 | 4·83 | 4·71 | | | |
| SMe | DMSO | 8·68 | 5·70 | 5·18 [j] | | 4·27(1), 4·17(1), 2·40(1), 1·50(1) | 7·57 | |
| SMe | N-DCl–$D_2O$ | 8·67 | 5·54 | 4·85 | 4·73 | | 7·43 | |
| | | | | Pyrimidines (II) | | | | |
| H | DMSO | 8·68 | 5·70 | | | 3·58(2), 3·05(2) | 2·16 | |
| $NH_2$ | DMSO | 8·68 | 5·67 | | | 6·1, [k] 2·42 | | |
| $NMe_2$ | DMSO | 8·70 | 5·73 | | | 4·50(2), 3·37(2) | 7·02 | |
| OH | DMSO | 8·68 | 5·70 | | | 4·00, 1·5 to 3·0, [l] 5·5 to 6·5 [l] | | |
| OEt | DMSO | 8·68 | 5·69 | | | 4·00(2), 2·93(2) | 8·73 [c] | 5·81 [d] |
| SH | DMSO | 8·67 | 5·67 | | | 3·60, 1·7 to 0·8 [l] | | |
| SMe | DMSO | 8·68 | 5·69 | | | 3·75(2), 2·89(2) | 7·58 | |
| Cl | DMSO | 8·69 | 5·70 | | | 3·46(2), 2·47(2) | | |

[a] Measured on Varian A 60A spectrometer at normal probe temperature (~30°). [b] DMSO = deuteriated dimethyl sulphoxide with tetramethyl silane as internal standard; $CDCl_3$ = deuteriated chloroform with tetramethyl silane as internal standard. Spectra in $D_2O$ measured with dioxan (τ = 6·32) as internal standard. [c] Triplet; $J$ 7·2 c./sec. [d] Quartet; $J$ 7·2 c./sec. [e] Signals removed on shaking with $D_2O$. Where signals were sufficiently sharp to integrate accurately, the number of protons involved is given in parentheses. [f] Except 2-$NH_2$; signal for this group given under exchangeable hydrogen. [g] 6- and 7-Protons of all pteridines (III) and (V) give AB quartets; $J$ ~ 2·0 c./sec. [h] 6- and 7-Protons of all hydrates (IV) and (XV) give AB quartets; $J$ ~ 2·5 c./sec. [i] Spectra in N-DCl in $D_2O$ are of dihydrated cations (XV) whether the anhydrous pteridine (III) or the hydrate (IV) is used. [j] Part of incompletely resolved AB quartet. [k] Broad absorption including 'water peak' due to equilibration of exchangeable hydrogens and solvent water. [l] Broad weak absorption in this region.

TABLE 2

Pteridines (III)

| X | Solvent | Time (hr.) | Yield (%) | M.p. | Formula | Found (%) C | Found (%) H | Found (%) N | Required (%) C | Required (%) H | Required (%) N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| OEt | t-Butanol (20 ml.) | 1¼ | 28 | 91° | $C_{11}H_{12}N_4O_3$ | 53·1 | 4·8 | 22·3 | 53·2 | 4·9 | 22·5 |
| $NMe_2$ | Ethanol (20 ml.) | ½ | 49 | 112 | $C_{11}H_{13}N_5O_2$ | 53·7 | 5·4 | 28·8 | 53·4 | 5·3 | 28·4 |
| SMe | Diglyme (10 ml.) | ¼ | 38 | 89 | $C_{10}H_{10}N_4O_2S$ | 47·8 | 4·0 | 22·8 | 48·0 | 4·0 | 22·4 |
| Cl | Toluene (50 ml.) | 16 | 17 | 79 | $C_9H_7ClN_4O_2$ | 45·0 | 3·1 | 23·7 | 45·3 | 3·0 | 23·5 |
| $NH_2$ | Toluene (50 ml.) | 48 | 37 | 189 | $C_9H_9N_5O_2$ | 49·3 | 4·1 | 31·8 | 49·3 | 4·1 | 32·0 |

See also preparations by dehydration of 5,6:7,8-dihydrates.

TABLE 3

Pteridine dihydrates (IV)

| X | Yield (%) | M.p. | Formula | Found (%) C | Found (%) H | Found (%) N | Required (%) C | Required (%) H | Required (%) N |
|---|---|---|---|---|---|---|---|---|---|
| OEt ..... | 51 | 125° | $C_{11}H_{16}N_4O_5$ | 46·6 | 5·9 | | 46·45 | 5·7 | |
| $NMe_2$ ..... | 79 | 67 | $C_{11}H_{17}N_5O_4$ | Too unstable to characterise | | | | | |
| SMe ..... | 70 | 131 | $C_{10}H_{14}N_4O_4S$ | 42·3 | 4·7 | 19·3 | 42·0 | 4·9 | 19·5 |
| Cl ..... | 53 | 119 | $C_9H_{11}ClN_4O_4$ | 39·5 | 4·1 | | 39·9 | 4·1 | |
| $NH_2$ ..... | 64 | 162 | $C_9H_{13}N_5O_4$ | 42·1 | 5·2 | 27·4 | 42·35 | 5·1 | 27·4 |

monohydrates, and the dihydrates agree with those previously published for corresponding protons in closely related compounds.[2,5,12] Spectra of the pteridines (III) and (VIII) were also measured in N-deuterium chloride. All except the 2-hydroxy- and 2-mercapto-derivatives formed predominantly 5,6:7,8-dihydrated cations (Table 1) as expected in view of the resonance stabilisation possible in such structures, (XV) ⟷ (XVI).[12,13] The hydroxy- and mercapto-compounds were unstable in acid conditions.

## EXPERIMENTAL

*Ethyl 6-Amino-2-methylthio-5-nitropyrimidine-4-carboxylate.*—Ethyl 6-amino-2-chloro-5-nitropyrimidine-4-carboxylate [4] (2·46 g.) in chloroform (15 ml.) and sodium hydrogen carbonate (2·5 g.) in water (40 ml.) were stirred at 15° during the addition, over 5 min., of sodium sulphide nonahydrate (5 g.) in the minimum of water, and for a further 3 hr. The deep red aqueous layer was separated and shaken with methyl iodide (0·34 ml.) for 2 hr. The *methylthio-ester* (1·5 g.) was filtered off and the filtrate shaken with more methyl iodide (0·4 ml.) to yield more product (0·25 g.). The material had m.p. 130° (from aqueous ethanol) (Found: C, 37·4; H, 4·1; N, 21·9. $C_8H_{10}N_4O_4S$ requires C, 37·2; H, 3·9; N, 21·7%).

*Ethyl 5,6-Diamino-2-methylthiopyrimidine-4-carboxylate* (II; X = SMe).—A suspension of sodium hydrogen carbonate (5 g.) in water (20 ml.) was added to a well stirred solution of ethyl 6-amino-2-methylthio-5-nitropyrimidine-4-carboxylate (1 g.) in acetone (20 ml.). Sodium dithionite (5 g.) was added during 5 min. and, 1 min. later, water (100 ml.) was added. The acetone was removed under reduced pressure to give the *diamino-ester* (0·61 g.), m.p. 227° (from ethanol) (Found: C, 41·8; H, 5·1. $C_8H_{12}N_4O_2S$ requires C, 42·1; H, 5·3%).

*Ethyl 2-Substituted Pteridine-4-carboxylates* (III; X = OEt, $NMe_2$, $NH_2$, SMe, or Cl).—The relevant diamine (0·001 mole), polyglyoxal (0·07 g.), and solvent were heated under reflux for the specified time (see Table 2). Except for (III; X = $NH_2$) the products were isolated by removal of the solvent under reduced pressure followed by thorough extraction of the residue with boiling light petroleum (b.p. 60—80°). Filtration of the hot extracts from charcoal and dried magnesium sulphate and concentration of the filtrates gave the pteridines. The amino-compound was isolated by filtering the hot reaction mixture to remove insoluble matter and concentrating the filtrate to small bulk. The product was finally sublimed at $10^{-4}$ mm.

*Ethyl 4-Hydroxy-2-oxo-(or thioxo)-1,2,3,4-tetrahydropteridine-4-carboxylate* (V; X = O or S).—The relevant diamine (II; X = SH or OH) (0·2 g.), glyoxal (2·1 ml. of 3% aqueous solution), and water (50 ml.) were heated under reflux for 10 min. (3 hr. when X = SH) before the volume was reduced to 5 ml. The hydrated pteridines crystallised from water. The *oxo-compound* (V; X = O) had m.p. 161° (Found: C, 45·4; H, 4·3; N, 24·3. $C_9H_{10}N_4O_4$ requires C, 45·4; H, 4·2; N, 23·7%) and the *thioxo-compound* (V; X = S) decomposed above 180° (Found: C, 42·75; H, 4·2; N, 22·7. $C_9H_{10}N_4O_3S$ requires C, 42·5; H, 4·0; N, 22·1%).

*Ethyl 2-Substituted 6,7-Dihydroxy-5,6,7,8-tetrahydropteridine-4-carboxylates* (IV).—The relevant anhydrous pteridine (III) (0·1 g.) was dissolved in N-hydrochloric acid (0·1 ml.) and kept for 2 min. A mixture of N-sodium hydroxide (0·1 ml.), 0·1M-potassium dihydrogen orthophosphate (0·1 ml.), and 0·1M-disodium hydrogen orthophosphate (0·1 ml.) was added all at once to rapidly bring the pH value of the solution to approximately 6. The hydrated pteridine (Table 3) separated on cooling the solution in ice.

5,6:7,8-Dihydrates were also obtained in some cases by condensation of a 4,5-diamino-pyrimidine with polyglyoxal in aqueous solution. The relevant diamine (0·0005 mole) was shaken or heated with polyglyoxal (0·04 g.) and water (3 ml.) at the stated temperature for the stated time. The mixtures were cooled as necessary to yield the products indicated below. Structures were confirmed by comparison of $^1$H n.m.r. or i.r. spectra with those of authentic specimens.

| Pyrimidine (II) | Reaction temp. | Time (hr.) | Yield (%) (III) | Yield (%) (IV) |
|---|---|---|---|---|
| X = OEt ..... | 20° | 72 | | 17 |
| | 100 | ¼ | 28 | |
| $NMe_2$ ..... | 20 | 72 | 48 | |
| SMe ..... | 100 | ¼ | | 47 |
| Cl ..... | 100 | ½ | | 31 |
| $NH_2$ ..... | 20 | ½ | 30 | |

5,6:7,8-Dihdrated pteridines prepared by either method could be sublimed at 150°/$10^{-4}$ mm. with accompanying dehydration to yield only the corresponding anhydrous pteridines.

We thank Mrs. R. Maynard who measured some of the $^1$H n.m.r. spectra.

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