# Alkylation of 4-Pteridones in Dimethylformamide

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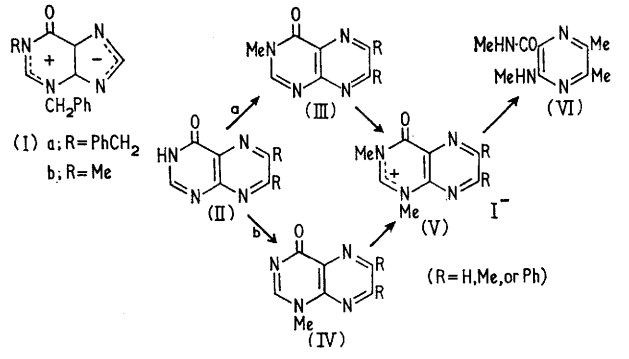
4-Pteridone (II) and its 6,7-dimethyl or -diphenyl derivatives are alkylated by methyl iodide in dimethylformamide to give the corresponding 1,3-dimethyl-4-oxopteridinium salts (V). Both 1-methyl and 3-methyl-4-pteridone give the same dimethyl derivative (V). The preferential attack in the pyrimidine ring is related to the charge distribution in (V). Calculations by the HMO and SCF-PPP method show that the negative charge at N-1 or N-3 in (II) is much larger than the charge at N-5 or N-8.



ALKYLATION of hypoxanthine with methyl iodide or methyl toluene-*p*-sulphonate, takes place in the imidazole ring. Thus in dimethylacetamide at 125°, salts of 7,9-dimethylhypoxanthine betaine are formed.[1] The pyrimidine nitrogen atoms are, however, alkylated, if a substituent is already present at either N-1 or N-3. Thus Montgomery *et al.*[2] isolated 1,3-dibenzylhypoxanthine betaine (Ia) or its bromide salt in 8 and 67% yield respectively, when 1- or 3-benzylhypoxanthine was heated in acetonitrile with benzyl bromide. The corresponding 3-benzyl-1-methylhypoxanthine derivative (Ib) was obtained when 3-benzylhypoxanthine was treated with methyl iodide in dimethylformamide.

The alkylation of the analogous 4-pteridone (II; R = H) has been studied by Albert *et al.*[3] Diazomethane converted this compound into a mixture of 4-methoxypteridine and 3-methyl-4-pteridone (III; R = H), the latter being the predominant product. With dimethyl sulphate at pH 8, a mixture of 3-methyl- (III; R = H) and 1-methyl-4-pteridone (IV; R = H) was obtained. It is thus apparent that under a variety of conditions methylation of 4-pteridone took place exclusively in the pyrimidine moiety.




SCHEME

In view of the results of Montgomery *et al.*,[2] it appeared of interest to establish whether the monomethylpteridones (III) and (IV) could be further substituted in the pyrimidine ring. Reaction of these compounds (R = H, Me, or Ph) with methyl iodide in dimethylformamide proceeded smoothly, each pair yielding the same 1,3-dimethyl-4-oxopteridinium salt (V).

In the light of these results it appeared probable that 4-pteridone (II; R = H) itself would undergo a two-step reaction to yield (V; R = H). This proved to be the case, although the product was obtained as an intractable tar, and the final yield was only 10% or less. The 6,7-dimethyl and 6,7-diphenyl derivatives of (V) were more stable and could be isolated in 50% yields. In all three cases, paper chromatography of the products showed that methylation of (II) yielded only (V).

The structure of (V; R = Me) was established both by alkaline degradation to the known pyrazine (VI),[4] and by comparison of its i.r. spectrum with that of an authentic sample.*

The conversion of (II) into (V) (Scheme 1) was studied with the 6,7-dimethyl derivative (II; R = Me). At various stages of the reaction between (II) and methyl iodide, samples were removed for paper chromatography. The strips corresponding to either of the possible intermediates (III) and (IV) were extracted with methanol, and the u.v. spectra of the extracts were measured. The 1-methyl derivative (IV; R = Me) was readily identified, but the quantity of the 3-methyl derivative present was too small for unequivocal identification. It appears therefore that the main route of the alkylation is (II) ⟶ (IV) ⟶ (V). Attempts to measure the contributions of the two possible simultaneous reactions (II) ⟶ (III) and (II) ⟶ (IV) spectroscopically were unsuccessful.

The ease of methylation of the pyrimidine ring in (II) can be related to the polarity of the various nitrogen atoms. The charge distribution of two possible tautomers of (II) was calculated by the HMO [5] and SCF-PPP method.[6] Figures 1 and 2 show that, irrespective of tautomerism, the greatest electron density is always found at one of the nitrogen atoms of the pyrimidine ring. Figure 2 also shows that the total energy of the tautomers (A) and (B) of 4-pteridone is only slightly different. Although the charge at N-3 in tautomer (B) is larger than the charge at N-1 in tautomer (A), the reaction involves mainly form (A). This is the form predominant

* Provided by Dr. R. B. Angier.

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TABLE 1

N.m.r. and i.r. spectra of 4-oxopteridines

| Derivative of 4-oxopteridine | Solvent | N.m.r. spectra [a] 1-Methyl | 3-Methyl | 6- and 7-Substituent | 2-H | C=O stretching vibration (cm.$^{-1}$) |
|---|---|---|---|---|---|---|
| 1-Me, 6,7-$Ph_2$ (IV; R = Ph) ..... | TFA | 262 | | 464 | 573 | 1650; 1655 |
| 3-Me, 6,7-$Ph_2$ (III; R = Ph) ..... | TFA | | 242 | 441 | 578 | 1680 |
| 1,3-$Me_2$, 6,7-$Ph_2$ (V; R = Ph) [b] ..... | DMSO | (248?) [c] | (227?) [c] | 448 | 616 | 1670; 1720 |
| 1,3-$Me_2$ (V; R = H) [b] ..... | $D_2O$ | (252?) | (232?) | 550 (two hydrogens) | 594 [d] | 1655; 1710 |
| 1,3,6,7-$Me_4$ (V; R = Me) [b] ..... | $D_2O$ | (255?) | (235?) | 172, 175 | 595 [d] | 1670; 1720 |

[a] All values in c./sec. [b] These compounds exist only as salts, *i.e.*, as pteridinium iodides. [c] The assignment of these values has not been definitely proved. In accordance with the relative position of the *N*-methyl bands in (III) and (IV) (R = Ph), the band at lower field has been tentatively assigned to the 1-methyl substituent. [d] This band disappeared when the solution was heated for about 10 min.

in solution, as indicated by the similarity of the absorption spectrum of (II) and (III) (Table 2).

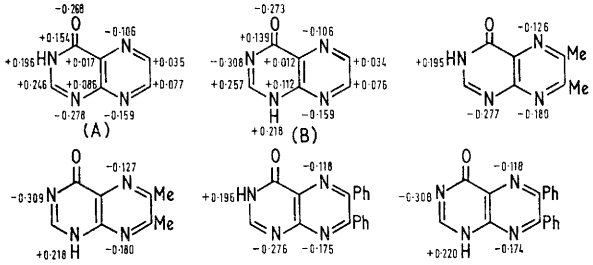
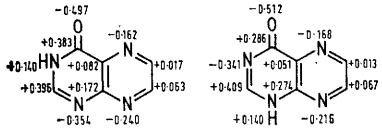


FIGURE 1 Charge distribution of two tautomers of 4-pteridones by the HMO method



| (ev) | | (ev) |
|---|---|---|
| −396·9 | Total energy | −395·8 |
| −6·0 | HOMO energy | −6·3 |
| +1·3 | LEMO energy | +1·1 |
| 6·0 | Ionisation potential | 6·3 |

FIGURE 2 Charge distribution of two tautomers of 4-pteridone by the SCF–PPP method

In the monomethyl derivatives (III) and (IV), the unsubstituted nitrogen of the pyrimidine ring bears a much higher negative charge than positions 5 and 8 in the pyrazine moiety (Figure 3). Therefore after

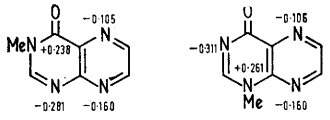


FIGURE 3 Charge distribution of 1-methyl and 3-methyl-4-pteridone by HMO method

substitution of a methyl group at N-1 or N-3, further attack of the alkylating agent is directed towards the alternative position in the pyrimidine ring.

It is also noteworthy that introduction of methyl or phenyl groups at positions 6 and 7 has only a negligible influence on the charge distribution in the pyrimidine ring. Indeed, alkylation of the 4-pteridones (II; R = Me or Ph) takes the same course as the reaction of the unsubstituted compound.

The n.m.r. spectra of some of the pteridines studied are shown in Table 1. In order to obtain comparable values, all derivatives were measured as cations, compounds (III) and (IV) being dissolved in trifluoroacetic acid. The quaternary pteridinium ions (V; R = H or

TABLE 2

Physical properties of 4-oxopteridines

| Derivative of 4-oxopteridine | $\lambda_{max.}$ [a] (nm.) | log $\varepsilon_{max.}$ | $R_F$ [b] | Fluorescence [c] | Ref. |
|---|---|---|---|---|---|
| II, R = H | 233 | 3·93 | 0·3 | Violet | 8 |
| | 273sh | 3·51 | | | |
| | 314 | 3·75 | | | |
| 6,7-$Me_2$ | 232 | 4·42 | 0·6 | Violet | 8 |
| (II; R = Me) | 273 | 4·11 | | | |
| | 315 | 4·28 | | | |
| 6,7-$Ph_2$ | 224 | 4·30 | 1·3 | Blue | 11 |
| (II; R = Ph) | 261 | 4·26 | | | |
| | 353 | 3·90 | | | |
| 3-Me | 237 | 4·03 | 0·6 | Violet | 9 |
| (III; R = H) | 277sh | 3·57 | | | |
| | 315 | 3·73 | | | |
| 3,6,7-$Me_3$ | 239 | 4·10 | 1·0 | Violet | 9 |
| (III; R = Me) | 280sh | 3·72 | | | |
| | 315 | 3·86 | | | |
| 3-Me, 6,7-$Ph_2$ | 224 | 4·58 | 1·6 | Blue | New |
| (III; R = Ph) | 264 | 4·21 | | | |
| | 353 | 4·05 | | | |
| 1-Me | 232 | 4·05 | 0·3 | Blue | 3 |
| (IV; R = H) | 328 | 3·88 | | | |
| 1,6,7-$Me_3$ | 235 | 4·11 | 1·2 | White | 10 |
| (IV; R = Me) | 330 | 3·96 | | | |
| 1-Me-6,7-$Ph_2$ | 227 | 4·48 | 1·4 | Blue | New |
| (IV; R = Me) | 258sh | 4·15 | | | |
| | 281 | 4·13 | | | |
| | 361 | 4·16 | | | |
| 1,3-$Me_2$ | 222 | 4·23 | 1·3 | Sky blue | New |
| (V; R = H) | 249 | 4·15 | | | |
| | 310sh | 3·28 | | | |
| | 355 | 3·76 | | | |
| 1,3,6,7-$Me_4$ | 223 | 4·34 | 1·2 | Sky blue | New |
| (V; R = Me) | 250sh | 3·92 | | | |
| | 310 | 3·79 | | | |
| | 325sh | 3·67 | | | |
| | 356sh | 3·18 | | | |
| 1,3-$Me_2$-6,7-$Ph_2$ | 224 | 4·52 | 1·7 | Green | New |
| (V; R = Ph) | 286 | 4·25 | | | |
| | 393 | 4·12 | | | |

[a] For u.v. spectra, all pteridines were dissolved in absolute ethanol, with the exception of 4-oxopteridine and its 1- and 3-methyl derivatives, which were measured in methanol. [b] For the solvent used, see Experimental section. All $R_F$ values refer to theophylline ($R_F$ = 1) as reference. [c] Under a Mineralight lamp (λ *ca.* 255 nm.).

Me) were dissolved in $D_2O$, but the phenylated derivative of (V) was only sparingly soluble in water and required the use of deuteriated dimethyl sulphoxide. The assignment of signals to the 1- and 3-methyl groups in the pteridines (V) remains uncertain. The 2-H signal of the compounds (V; R = H and Me) disappeared after a few hours at room temperature and within about 10 min., when the solution in $D_2O$ was boiled.

Table 1 reveals a marked influence of the phenyl groups in (V) on the position of the 2-H signal. Similarly, in Table 2, the absorption maxima of pteridines (II)—(V) (R = Ph) show a bathochromic displacement of 30—40 nm. relative to the compounds with R = H or Me. FMM Models * indicate strong interference of the *ortho*-hydrogens in the diphenylated derivatives, similar to *o*-terphenyl.[7] However, the charge distribution in (II; R = Ph), calculated on the assumption of an angle of 45° between the plane of the pyrazine ring and the phenyl groups, was practically identical with that given in Figure 1.

In the i.r. spectrum of the 1,3-dimethyl derivatives (V), two sharply separated bands were found in the region 1650—1720 $cm.^{-1}$, characteristic for carbonyl stretching, while the pteridines (II), (III), and (IV) showed either a single band, or a band with a small shoulder or a narrow double peak in this range (see Table 1). At present there is no evidence to show whether the two carbonyl bands in the spectrum of (V) may represent two forms bearing the positive charge either at N-1 or N-3.

## EXPERIMENTAL

All m.p.s are uncorrected. Elemental analyses by Dr. F. Strauss, Oxford.

For chromatography on Whatman paper No. 1 (descending method), the following solvent was used: n-butanol–acetic acid–water, 12 : 3 : 5 (v/v). All $R_F$ values in Table 2 are expressed relative to theophylline as standard ($R_F$ = 1). For analysis of the mixtures obtained during methylation of (II; R = Me), n-butanol, saturated with water, was used, solid ammonium carbonate serving as source of ammonia vapour. This solvent provided excellent separation of all components of the system [$R_F$ values relative to theophylline: (II) 0·43, (III) 1·15, (IV) 0·95, and (V) 2·0].

N.m.r. spectra were measured on a Jeol instrument at 60 MHz, and i.r. spectra on a Perkin-Elmer Model 337 spectrophotometer (KBr disc).

The following pteridines were synthesised by known methods: 4-pteridone [3,8] and its 1- [3] and 3-methyl derivatives; [3,9] 6,7-dimethyl-4-pteridone [8] and its 1-methyl [10] and 3-methyl derivatives; [9] and 6,7-diphenyl-4-pteridone.[11]

1-*Methyl*-6,7-*diphenyl*-4-*pteridone* (IV; R = Ph).—A solution of 4,5-diamino-3-methyl-6-oxopyrimidine (2 g.) [12] and benzil (6 g.) in dimethylformamide (100 ml.) was heated under reflux for 2 hr. and was then evaporated to dryness under reduced pressure. Unchanged benzil was extracted from the residue with ether. The remaining product crystallised from methanol as plates (1 g., 22%), decomp. >295° (Found: C, 72·8; H, 4·5; N, 17·5. $C_{19}H_{14}N_4O$ requires C, 72·6; H, 4·5; N, 17·8%).

3-*Methyl*-6,7-*diphenyl*-4-*pteridone* (III; R = Ph).—Condensation of 4,5-diamino-1-methyl-6-oxopyrimidine [9] with benzil was carried out as in the previous example. The product crystallised from ethanol as prisms (40%), m.p. 278—279° (Found: C, 72·6; H, 4·6; N, 17·5%).

Both compounds (III) and (IV) (R = Ph) reacted at room temperature with methyl iodide in dimethylformamide to yield (V; R = Ph), identical with the product obtained by methylation of (II; R = Ph).

*Methylation of* 4-*Pteridones* (II).—A solution of these pteridines (1 g.) in dimethylformamide (50 ml.) and methyl iodide (10 ml.) was stirred overnight at room temperature and was then evaporated to dryness under reduced pressure. The residue was washed several times with acetone to remove free iodine. The properties of the products (V; R = H, Me, or Ph) are described in Table 3.

TABLE 3

1,3-Dimethyl-4-oxopteridinium iodides (V)

| Compound | Crystal form and colour [a] | Yield (%) | M.p. (decomp.) (°C) |
|---|---|---|---|
| (V; R = H) | Brown microprisms | 10 [b] | 213—215 (decomp.) [c] |
| (V; R = Me) | Yellow plates [d] | 52 | 243—245 |
| (V; R = Ph) | Yellow micro-crystals | 50 | 278—280 (decomp.) |

| Compound | Formula | Found (%) C | H | N | Calc. (%) C | H | N |
|---|---|---|---|---|---|---|---|
| (V; R = H) | $C_8H_9IN_4O$ | 32·3 | 3·0 | 17·7 | 31·6 | 3·0 | 18·4 |
| (V; R = Me) | $C_{10}H_{13}IN_4O$ | 36·3 | 4·0 | 16·8 | 36·1 | 3·9 | 16·9 |
| (V; R = Ph) | $C_{20}H_{17}IN_4O$ | 51·9 | 3·9 | 11·7 | 52·6 | 3·7 | 12·3 |

[a] All compounds were recrystallised from 95% ethanol. They were unstable and tended to decompose with time. [b] The crude product was a black tar and was crystallised repeatedly. [c] The compound darkened when heated above 200°. [d] Solutions in polar solvents showed strong blue fluorescence.

*Alkaline Degradation of* 1,3,6,7-*Tetramethyl*-4-*oxopteridinium Iodide* (V; R = Me).—The pteridine (V; R = Me) (1 g.) was boiled for 2 min. in 2N-sodium hydroxide. The solution was neutralised with acetic acid and the precipitate was recrystallised from light petroleum (b.p. 40—50°) to yield 5,6-dimethyl-2-methylamino-3-(*N*-methylcarboxamido)pyrazine (VI) (0·4 g.), m.p. 97—98°.[4]

*Calculation of Charge Distribution by the SCF-PPP Method.*—For the LCAO-SCF calculations, the Pople-Pi program, written by T. Janiszewski,[6] was kindly supplied by the Quantum Chemistry Program Exchange through Deutsches Rechenzentrum, Darmstadt. In this program, an initial Hückel computation provides trial coefficients for a Pople-type Hartree-Fock matrix,[13,14] which is iterated to self-consistence (tolerance in coefficients $10^{-4}$). Thereafter, π-charge densities, bond orders, and total energy are computed. For parameterisation, we have followed closely the proposal of Berthod *et al.*,[15] except for the bielectronic bicentric integrals, for which the Mataga-Nishimoto

* Framework Molecular Models, Prentice-Hall, Inc., Englewood Cliffs, N.J.

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scheme,[16] rather than the Roothaan expressions,[17] were used. In Figure 2, ionisation potentials have been equated to the HOMO eigenvalue,[18] but electronic transitions were taken as the energy difference between the configurations of the ground and the appropriate singly-excited states.[19]

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