ELECTRONIC STRUCTURE AND PROPERTIES OF PTERIDINES AND N-ALKYLPTERIDINIUM SALTS

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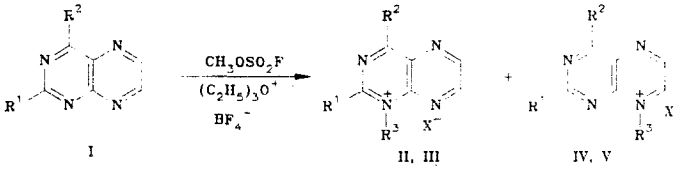
The electronic structure of pteridines and N-methylpteridinium cations was calculated in terms of the CNDO/2 approximation. The obtained data on the electron density distribution in the molecules of pteridines and also the energy characteristics of the pteridinium cations make it possible to predict the outcome of quaternization. The results from the calculations are compared with the experimental data. It is shown that the direction of nucleophilic attack in N-alkylpteridinium cations correlates with the total charge of the fragment of the covalently bonded atoms.

The pteridine structure enters the composition of many compounds of plant and animal origin and also a whole series of biologically active substances, and this explains the increased interest of chemists in compounds of this type [1]. An enormous number of papers have been devoted to uncharged pteridine substrates, whereas the data on pteridinium quaternary salts have until recently been fragmentary. It is sufficient to say that in reviews on the quaternization of nitrogen heterocycles there are hardly any data on N-alkylpteridinium salts [2, 3], while the first communication on the production of a 1-methyl-4-dimethylaminopteridinium salt only appeared in 1960 [4]. Quite recently we showed that 4-morpholinopteridine and also 2,4-substituted pteridines (I) under the influence of powerful alkylating agents (triethyloxonium fluoroborate or methyl fluorosulfonate) form two series of derivatives, i.e., the quaternary $N_{(1)}$-alkylpteridinium (II, III) and $N_{(8)}$-alkylpteridinium (IV, V) salts [5-7].



I II, III IV, V

II, IV $R^3=CH_3$, $X=FSO_3$; III, V $R^3=C_2H_5$, $X=BF_4$

In the present work we give new data on the quaternization of pteridines, and we also discuss the results from quantum-chemical calculations for a series of pteridines and the pteridinium cations which they form. These make it possible to predict the direction of the quaternization of pteridines and also the behavior of pteridinium substrates in reactions with nucleophiles.

The quantum-chemical calculations were conducted by the CNDO/2 method [8], which even with "averaged" geometry gives a quite satisfactory picture of the electron density distribution in the molecules [9, 10]. The geometric parameters of pteridine were selected on the basis of the data from x-ray crystallographic analysis [11], and the mean values of the bond lengths and bond angles were used as parameters of the substituents; the charges in the pteridines (Ia-i) are given in Table 1.

The quaternization of pteridines can, in principle, take place at any of the four nitrogen atoms of the pteridine system, while for the dialkylamino derivatives it can also take place at the exocyclic nitrogen atom. In each specific case the direction of attack

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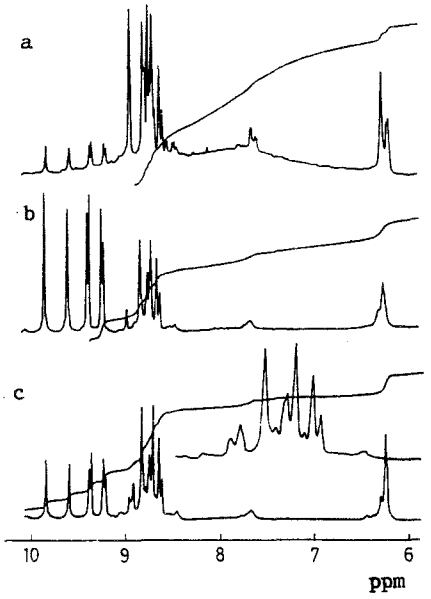


Fig. 1. The PMR spectra of mixtures of unsubstituted pteridine (Ia) with methyl fluorosulfonate: a) The spectrum of the precipitate produced preparatively during the reaction in methylene chloride; b) the spectrum of the reaction solutions in DMSO-d_6, recorded immediately after mixing; c) the spectrum of the reaction solutions in DMSO-d_6, recorded 1 h after mixing.

will be determined both by the basicity of the atoms and by the steric hindrances. Analysis of the calculated data (Table 1) shows that the basicity of the nitrogen atoms in the pyrimidine ring is higher in all cases than in the pyrazine ring. This relationship is preserved even with the introduction of such a strong electron acceptor as the ethoxycarbonyl group at position 4.

There are no steric hindrances in the molecule of unsubstituted pteridine. The direction of electrophilic attack by the alkylating agent will therefore be determined only by the charges at the nitrogen atoms. According to the data on the distribution of charges in the molecule of pteridine (Ia) (Table 1) it is seen that the most likely centers of quaternization are the $N_{(1)}$ and $N_{(3)}$ atoms, which have approximately identical negative charge. The $N_{(5)}$ and $N_{(8)}$ atoms can also undergo quaternization although with smaller probability. Thus, the formation of a mixture of isomeric cations must be expected as a result of the quaternization of unsubstituted pteridine. This suggestion is confirmed by experiment. The quaternization of unsubstituted pteridine (Ia) actually takes place ambiguously and gives a complex mixture of products. If methyl fluorosulfonate is added to a solution of pteridine (Ia) in methylene chloride, a crystalline precipitate is formed. However, the PMR spectrum of this precipitate in DMSO-d_6 does not reveal any signs of the formation of N-alkylpteridinium cations (Fig. 1). In addition to the absorption of the unreacted pteridine (Ia) in the region of 9-10 ppm, the spectrum contains signals which can be assigned to the resonance of the $C_{(4)}$-hydrated forms of the $N_{(1)}$- and $N_{(3)}$-methylpteridinium cations, i.e., the signals of 4-H at 6.2-6.3 ppm, the singlets of 2-H at 8.8-9.0 ppm, and two sets of doublets for the 6-H and 7-H protons at 8.5-8.8 ppm (Fig. 1). Such an assignment of the signals for the protons agrees well with the published data [12, 13] on the PMR spectra of the hydrates of protonated pteridines. The variation of the PMR spectra of the reaction solutions of pteridine and methyl fluorosulfonate with time in DMSO-d_6 (Fig. 1b, c) also indicates gradual conversion of the pteridine into compounds for which the structure of the hydroxyl adducts of the $N_{(1)}$- and $N_{(3)}$-methyl cations with respect to the C_4 atom is most probable.

According to [12, 13], the introduction of donating substituents into the pyrimidine ring hinders the hydration of pteridines. However, the direction of quaternization in 2- and 4-substituted pteridines in this case will no longer be determined only by the charges at the nitrogen atoms but also by the steric effect of the substituents. According to the data from the calculations and also in view of the blocking of the neighboring nitrogen atom by the bulky substituent the $N_{(1)}$-alkylpteridinium salts must be formed preferentially as a result of the quaternization of 4-substituted pteridines (Ib-d), since the charge at the $N_{(1)}$ atom is higher in absolute value than at the $N_{(5)}$ and $N_{(8)}$ atoms (Table 1), while the formation of the $N_{(8)}$-alkyl salts must predominate in the case of the 2- and 2,4-substituted pteridines (Ie-i). These data agree well with experiment on the quaternization of pteridines (Ii-o) (Table 2) if account is taken of the fact that the dimethylamino group

TABLE 1. The Charges at the Atoms and the Energy Characteristics of $N_{(1)}$- and $N_{(8)}$-methylpteridinium Cations

Compound*	R^1	R^2	Charges, ecu**										ΣE_R^b, au
			$N_{(1)}$	$C_{(2)}$	$N_{(3)}$	$C_{(4)}$	$N_{(5)}$	$C_{(6)}$	$C_{(7)}$	$N_{(8)}$	$C_{(9)}$	$C_{(10)}$	
Ia	H	H	−0,1742	0,1672	−0,1728	0,1120	−0,1170	0,0551	0,0822	−0,1415	0,1652	0,0415	
Ib	H	$COOC_2H_5$	−0,1611	0,1589	−0,1504	0,0714	−0,1055	0,0603	0,0807	−0,1418	0,1623	0,0443	
Ic	H	SCH_3	−0,1823	0,1758	−0,1911	0,1791	−0,1121	0,0582	0,0829	−0,1444	0,1713	0,0216	
Id	H	$N(CH_3)_2$	−0,1901	0,1818	−0,2232	0,2238	−0,1239	0,0542	0,0836	−0,1365	0,1793	0,0021	
Ie	$N(CH_3)_2$	H	−0,2151	0,2724	−0,2069	0,1315	−0,1258	0,0511	0,0832	−0,1382	0,1848	0,0109	
If	SCH_3	$N(CH_3)_2$	−0,2355	0,2407	−0,2357	0,2408	−0,0930	0,0422	0,0894	−0,1647	0,1792	−0,0003	
Ig	CH_3	CH_3	−0,2075	0,2104	−0,2195	0,1579	−0,1300	0,0551	0,0822	−0,1393	0,1767	0,0058	
Ih	SCH_3	CH_3	−0,1996	0,2285	−0,2138	0,1604	−0,1295	0,0590	0,0820	−0,1370	0,1789	0,0069	
Ii	$N(CH_3)_2$	CH_3	−0,2426	0,2813	−0,2312	0,1717	−0,1176	0,0500	0,0856	−0,1528	0,1819	−0,0010	
IIIb***	H	$COOC_2H_5$	0,0374	0,2277	−0,1334	0,1342	−0,0690	0,0770	0,1172	−0,1284	0,1792	0,0492	−33,651
Vb***	H	$COOC_2H_5$	−0,1805	0,2189	−0,1217	0,1142	0,0377	0,0377	0,1433	−0,0018	0,1848	0,0565	−33,639
IIc	H	SCH_3	0,0630	0,2424	−0,1799	0,1955	−0,0999	0,0779	0,1158	−0,1104	0,2002	0,0209	−24,652
IVc	H	SCH_3	−0,1817	0,2266	−0,1611	0,1815	−0,0064	0,0351	0,1531	0,0620	0,2124	0,0187	−24,641
IId	H	$N(CH_3)_2$	−0,0881	0,2581	−0,1561	0,3068	−0,0262	0,0734	0,1259	−0,1626	0,1449	0,0385	−28,652
IVd	H	$N(CH_3)_2$	−0,2205	0,2440	−0,1928	0,2708	0,0649	0,0308	0,1445	−0,0237	0,1910	0,0268	−28,623
IIe	$N(CH_3)_2$	H	−0,0637	0,3465	−0,1702	0,1989	−0,0445	0,0700	0,1217	−0,1534	0,1743	0,0387	−28,604
IVe	$N(CH_3)_2$	H	−0,2542	0,3360	−0,1646	0,1680	0,0544	0,0333	0,1441	−0,0217	0,1965	0,0355	−28,610
IIf	SCH_3	$N(CH_3)_2$	−0,0598	0,2726	−0,2105	0,2962	−0,0449	0,0664	0,1193	−0,1580	0,1697	0,0211	−31,460
IVf	SCH_3	$N(CH_3)_2$	−0,2485	0,2776	−0,2140	0,2732	0,0611	0,0269	0,1452	−0,0273	0,1962	0,0154	−31,436
IIg	CH_3	CH_3	0,0055	0,2908	−0,2079	0,2229	−0,0930	0,0728	0,1161	−0,1236	0,1956	0,0130	−27,010
IVg	CH_3	CH_3	−0,2455	0,2814	−0,1901	0,2098	0,0506	0,0341	0,1444	−0,0223	0,1915	0,0276	—
IIh	SCH_3	CH_3	−0,0485	0,2677	−0,1836	0,2379	−0,0489	0,0719	0,1195	−0,1571	0,1670	0,0334	−27,217
IVh	SCH_3	CH_3	−0,2394	0,2711	−0,1820	0,2085	0,0524	0,0354	0,1442	−0,0247	0,1901	0,0300	−27,202
IIi	$N(CH_3)_2$	CH_3	−0,0726	0,3456	−0,2063	0,2400	−0,0522	0,0684	0,1195	−0,1539	0,1761	0,0234	−31,190
IVi	$N(CH_3)_2$	CH_3	−0,2670	0,3369	−0,2024	0,2130	0,0493	0,0299	0,1458	−0,0238	0,2011	0,0163	−31,208

*The charge at the nitrogen atom of the exocyclic amino group is 0.1548 for (Id), 0.1577 for (Ie), 0.1508 for (If), and 0.1569 ecu for (Ii).

**ecu – Electron charge unit.

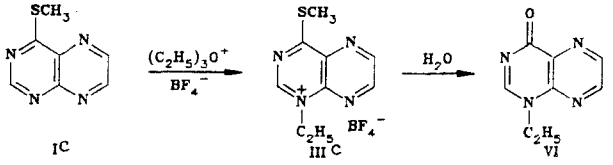
***The N-ethylpteridinium cation.

TABLE 2. The Quaternization of Pteridines in Methylene Chloride

Compound	R^1	R^2	Alkylating agent*	T_{react}, °C	Reaction time, h	Reaction product (yield, %)	
						PMR	preparative
Ia	H	H	A	20	0,3	Complex mixture	—
Ia	H	H	B	20	0,3	Complex mixture	Complex mixture
Ic	H	SCH_3	A	20	0,3	—	IIIc(86)
Ii	$N(CH_3)_2$	CH_3	B	20	0,3	—	IVi (86)
Ij	Piperidino	CH_3	A	20	0,3	—	Vj (81)
Ik	$N(CH_3)_2$	$COOC_2H_5$	A	35	0,3	Vk (100)	—
Il	Morpholino	H	A	35	0,3	V l (100)	—
Il	Morpholino	H	B	20	0,3	IV l (100)	—
Im	H	Morpholino	A	40	3	—	IIIm (77) + +V m(8)
In	SCH_3	Morpholino	A	40	1	IIIn(33) + +Vn (67)	IIIn (28) + +Vn (51)
In	SCH_3	Morpholino	B	20	1	—	IIn (63)
Io	Morpholino	CH_3	B	20	0,3	—	IVo (94)
Io	Morpholino	CH_3	A	20	0,3	—	Vo (67)

*A = Triethyloxonium fluoroborate, B = methyl fluorosulfonate.

in the calculations replaces the morpholine and piperidine residues in the real molecules. In the absence of a substituent at position 4 [the 2-morpholinopteridine (Il)] and also in the case of 2-methylamino-4-ethoxycarbonylpteridine (Ik) the obtained pteridinium salts (Vk, l, IVl) are unstable and cannot be isolated from the solution. However, they are recorded in the PMR spectra (see the experimental section), and their structure was established reliably on the basis of familiar relationships for pteridinium salts [5, 13].



Ic IIIc VI

As test for the relative thermodynamic stability of the isomeric pteridinium cations it is possible to use the calculated values of the total resonance energy of the covalently bonded atoms (ΣE_R^b). The $N_{(1)}$-alkyl salts of the 4-substituted pteridines (IIIb, IIc, d) are more stable than the isomeric $N_{(8)}$-alkylpteridinium cations (Vb, IVc, d) (Table 1), while in the case of the 2- and 2,4-substituted pteridines the 8-methylpteridinium salts (IVe, i) are more stable with the exception of the 2-methylthio derivatives (Table 2). The difference in energy between the 1- and 8-alkylpteridinium salts amounts to 4-15 kcal/mole.* The stability of the isomeric pteridinium cations is also one of the factors which determines the yield of the respective salts. In fact, the 1-ethyl-4-methylthiopteridinium salt (IIIc) was isolated as a result of the reaction of 4-methylthiopteridine (Ic) with triethyloxonium fluoroborate (Table 2). The PMR spectrum of (IIIc) in trifluoroacetic acid corresponds to the proposed structure (see the experimental section). In other solvents, however, the salt (IIIc) is unstable on account of the high mobility of the methylthio group at the $C_{(4)}$ atom and is extremely sensitive to moisture, forming 1-ethylpteridin-4-one (VI) under the influence of water.

The quaternization of 4-morpholinopteridine (Io) by the same alkylating agent leads to a mixture of the isomeric $N_{(1)}$- and $N_{(8)}$-ethylpteridinium salts (IIIm) and (Vm), while the introduction of a methylthio group at position 2 hinders the alkylation of the $N_{(1)}$ atom, and this naturally affects the yields of the 1- and 8-ethylpteridinium salts (IIIn) and (Vn) (Table 2). If there are bulky dialkylamino groups, which block the $N_{(1)}$ and $N_{(8)}$ atoms of the pyrimidine ring, at position 2, quaternization takes place exclusively at the $N_{(8)}$ atom with the formation of the salts (IVi, l, o) and (Vj-l, o) (Table 2). The

*1 au = 627.52 kcal/mole.

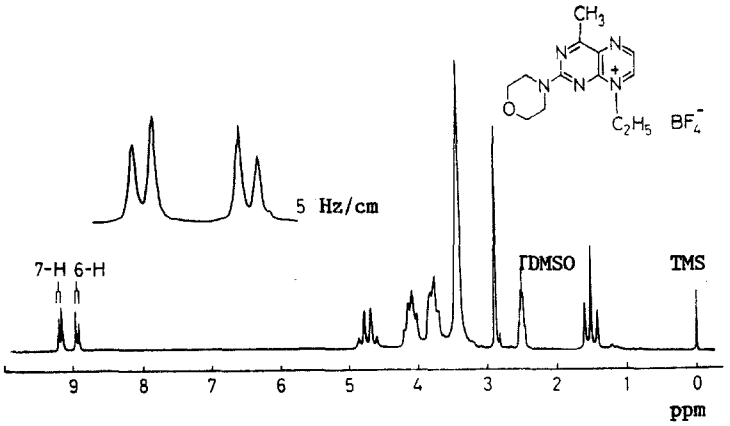


Fig. 2. The PMR spectrum of 4-methyl-2-morpholino-8-ethylpteridinium fluoroborate (Vo) in DMSO-d_6.

structure of the obtained pteridinium cations was established on the basis of the PMR data (see the experimental section, Fig. 2), which were analyzed in detail in [5, 13].

The electron density distribution in the N-methylpteridinium cations (II-V) (Table 1) makes it possible to predict the direction of nucleophilic attack in the reactions of pteridinium salts with various nucleophiles. Comparison of the data in Tables 1 and 3 shows that in the transition from the pteridines to the cations (II-V) there is a significant increase in the positive charge at the α-carbon atom in relation to the N-alkyl group. In the 1-alkylpteridinium salts (II, III) the positive charge is also increased at the remaining carbon atoms of the pteridine system, while for compounds (IV, V), on the other hand, a decrease in charge is observed at the $C_{(6)}$ atom [$C_{(\beta)}$] compared with the uncharged pteridines (Ib-i). The maximum positive charge both in the pyrimidinium cations (II, III) and in the pyrazinium cations (IV, V) is at the $C_{(2)}$ atom [with the exception of the cations (IId, f) and (IVd, f), in which the maximum charge is at the $C_{(4)}$ atom on account of the inductive effect of the nitrogen atom of the amino group] (Table 1).

In order to determine the direction of nucleophilic attack we will consider the 4-substituted pteridinium salts (IIIb, Vb, IIc, d, IVc, d). In these compounds there are only two alternative centers for the addition of the nucleophile, i.e., the $C_{(2)}$ and $C_{(7)}$ atoms. The $C_{(6)}$ atom is not considered on account of the small charge (smaller than in the uncharged pteridines). We will treat the molecule as a system of point charges. It seemed quite reasonable to suppose that at distances significantly exceeding the covalent radii the nucleophiles will be directed not at an individual point charge but at a group of charges of some fragment of the molecule, and only at distances commensurable with the covalent radii of the atoms will the nucleophile interact with a specific atom of this fragment, carrying the largest positive charge. Such an approach formed the basis of the electrostatic potential method [14]. In the present situation, however, there is no need to construct an electrostatic potential map; it is sufficient to consider the values of the total charges of the covalently bonded atoms for each reaction center. As such fragments it is logical to select the centers of possible addition of the nucleophile with their closest environment. Thus, the fragment Φ_1 with center $C_{(2)}$ includes $C_{(2)}$ and the atoms covalently bonded to it $H_{(2)}$, $N_{(1)}$, and $N_{(3)}$, while the Φ_2 fragment with center at $C_{(7)}$ includes the atoms $C_{(7)}$, $H_{(7)}$, $C_{(6)}$, and $N_{(8)}$. On Φ_1 and Φ_2 in the 1-alkylpteridinium cations (II) and (III) we have charges of 0.191 and 0.105, respectively, for (IIIb), 0.183 and 0.122 for (IIc), and 0.076 and 0.78 ecu for (IId). In the 1-alkyl cations (IIIb) and (IIc) the charge at Φ_1 is larger than at Φ_2 and the nucleophile will consequently be directed toward the Φ_1 fragment in reactions with these pteridinium salts and will react with the $C_{(2)}$ atom. For compound (IId) the total charges at Φ_1 and Φ_2 have similar values, but the positive charge at the $C_{(2)}$ atom is larger than at $C_{(7)}$. Addition of the nucleophile at the $C_{(2)}$ atom will therefore be preferred. For the 8-alkylpteridinium cations (IV) and (V) we have the following distribution of charges at Φ_1 and Φ_2: −0.039 and 0.245 for (Vb); −0.075 and 0.310 for (IVc); −0.129 and 0.217 ecu for (IVd). As we see, in spite of the fact that the $C_{(2)}$ atom in the 8-alkyl cations (IV) and (V) carries the largest positive charge, the overall charge of Φ_1 is negative. Thus, the nucleophile will be directed

TABLE 3. The PMR Spectra (the aromatic region)*

Compound**	Chemical shifts ppm (QE)***			$^3J_{6,7}$, Hz (QE)	Compound	Chemical shifts, ppm (QE)***			$^3J_{6,7}$, Hz (QE)
	6-H	7-H	4-H			6-H	7-H	4-H	
Ik	8,48	8,83	—	1,9	Iℓ	8,52	8,81	9,24	1,9
IVk	8,85 (0,37)	9,08 (0,25)	—	3,5 (1,6)	IVℓ	8,81 (0,29)	8,97 (0,16)	9,38 (0,14)	3,5 (1,6)
Vk	8,89 (0,41)	8,99 (0,16)		3,5 (1,6)	Vℓ	8,91 (0,39)	8,91 (0,10)	9,44 (0,20)	—

*The spectra of the pteridines (Ik, ℓ) and the salts (IVk, ℓ) and (Vk, ℓ) formed by them were obtained with the addition of 1 eq of methyl fluorosulfonate and triethyloxonium fluoroborate in a solution in methylene-D_2 chloride at 20°C.
**(Ik, IVk, Vk) $R^1 = N(CH_3)_2$, $R^2 = COOC_2H_5$, (IVk) $R^3 = CH_3$, (Vk) $R^3 = C_2H_5$; (Iℓ, IVℓ, Vℓ) R^1 = morpholino, R^2 = H, (IVℓ) $R^3 = CH_3$, (Vℓ) $R^3 = C_2H_5$.
***QE = Quaternization effect.

toward Φ_2, and the addition of the nucleophile will take place at the $C_{(7)}$ atom, which has the largest positive charge in Φ_2.

The results from the analysis can be extended to the 4-morpholinopteridinium cations (IIIo) and (Vo), for which compounds (IId) and (IVd) are models, since the replacement of the dimethylamino group by the morpholine residue will not lead to appreciable changes in the electron density distribution in the pteridine system. The experimental data on the addition of O-, N-, and C-nucleophiles to the isomeric 1- and 8-ethyl-4-morpholinopteridinium cations (IIIo, Vo) [5] correspond fully to the results from the quantum-chemical analysis.

For the 2,4-disubstituted pteridinium cations addition at position 2 becomes sterically hindered. The most likely center for nucleophilic attack therefore remains position $C_{(7)}$, and this is observed in the experiments with the 2-dialkylamino-4-methyl-substituted 8-ethylpteridinium salts (IVi, o, Vj, o) [6].

EXPERIMENTAL

The calculated data were obtained on an EC-1022 computer by the CNINDO program [15], modified by the authors, with a minimal basis set of 140 AOs and a memory of not more than 250 K. The total energy was divided among the components according to Fisher and Kollmar, [16].

The unsubstituted pteridine (Ia) was obtained by the method in [17].

4-Methylthiopteridine (Ic) was synthesized by the condensation of the respective 4,5-diaminopyrimidine with an aqueous solution of glyoxal or dioxane-2,3-diol with heat in ethanol according to the procedure in [18]; 2-dimethylamino- and 2-piperidino-4-methylpteridines (Ii) and (Ij) were obtained according to the method in [7]; 2-dimethylamino-4-ethoxycarbonylpteridine (Ik) was obtained according to [19]; 4-morpholinopteridine was obtained according to [5]; 2-methylthio-4-morpholinopteridine and 2-morpholino-4-methylpteridine were obtained according to [6].

The 4-methyl-2-piperidino-8-ethylpteridinium fluoroborate (Vj) was obtained according to [7], and 4-morpholino-8-ethylpteridinium (Vm) and 4-morpholino-1-ethylpteridinium (IIIm) fluoroborates were obtained according to [5]; 2-methylthio-4-morpholino-1-ethylpteridinium (IIIn), 2-methylthio-4-morpholino-8-ethylpteridinium (Vn), and 4-methyl-2-morpholino-8-ethylpteridinium (Vo) fluoroborates were obtained according to [6]; 2-dimethylamino-4,8-dimethylpteridinium fluorosulfonate (IVi) was obtained according to [7].

The elemental analysis for C, H, and N agreed with the calculated compositions.

4-Amino-2-morpholino-5-nitropyrimidine ($C_8H_{11}N_5O_3$). A mixture of 3.5 g (20 mmole) of 4-amino-5-nitro-2-chloropyrimidine [17] in 30 ml of ethanol and 5.0 ml of morpholine was

boiled for 7 h. The mixture was then cooled, and the precipitate was filtered off. The yield was 4.1 g (92%). The product formed yellow crystals from ethanol; mp 202-203°C. PMR spectrum (DMSO-d_6): 3.5-4.0 (8H, m, protons of morpholine ring); 8.08 (2H, bs, NH_2); 8.92 ppm (1H, s, 6-H).

4,5-Diamino-2-morpholinopyrimidine ($C_8H_{13}N_5O$). A mixture of 2 g (8.9 mmole) of 4-amino-2-morpholino-5-nitropyrimidine, 7 g of (59 mmole) of granulated tin, and 20 ml of concentrated hydrochloric acid was boiled for 1 h. The reaction mass was made alkaline to pH 10, and the precipitated tin hydroxide was filtered off. The mother solution was extracted with ether (3 × 100 ml), and the ether extracts were dried with potassium hydroxide and evaporated to dryness. We obtained 0.6 g (32%) of 4,5-diamino-2-morpholinopyrimidine; mp 189-190°C (from ethanol). PMR spectrum (DMSO-d_6): 2.85 (2H, bs, NH_2); 3.7-4.1 (8H, m, protons of morpholine ring); 4.63 (2H, bs, NH_2); 8.67 ppm (1H, s, 6-H).

2-Morpholinopteridine (Iℓ) ($C_{10}H_{11}N_5O$). A solution of 1.4 g (7.2 mmole) of 4,5-diamino-2-morpholinopyrimidine and 4 ml of 40% aqueous glyoxal in 35 ml of water was heated on a water bath for 30 min. The reaction mass was then extracted continuously with chloroform for 3 h. The chloroform extracts were dried with calcined sodium sulfate and evaporated to dryness. The residue was recrystallized from petroleum ether; bp 80-100°C. The yield was 1.3 g (84%); mp 138-139°C. PMR spectrum (deuterochloroform): 3.6-4.3 (8H, m, protons of morpholine ring); 8.54 (1H, d, 6-H $^3J_{6,7}$ = 2.0 Hz); 8.86 ppm (1H, d, 7-H).

The quaternization of the pteridines was conducted in methylene chloride at 20-40°C with a 1.3-1.5 excess of triethyloxonium fluoroborate or methyl fluorosulfonate.

Quaternization of 4-methylthiopteridine (Ic) ($C_9H_{11}N_4BF_4S$). To a solution of 0.75 g (5.1 mmole) of (Ic) in 15 ml of dry methylene chloride we added a solution of 1.2 g (6.1 mmole) of triethyloxonium fluoroborate in 3 ml of dry methylene chloride. The precipitate of the salt (IIIc) which formed after a few minutes as fine yellow needles was filtered off and washed with methylene chloride and absolute ether. After drying under vacuum we obtained 0.9 g (60%) of (IIIc); mp 137-139°C. PMR spectrum (trifluoroacetic acid): 1.54 (3H, t, CH_3); 2.78 (3H, s, SCH_3); 4.80 (2H, q, N–CH_2); 9.06 (1H, d, 6-H, $^3J_{67}$ = 2.0 Hz); 9.15 (1H, s, 2-H); 9.19 ppm (1H, d, 7-H). The compound was unstable; during recrystallization of the salt from ethanol the fluoroborate of 1-ethylpteridin-4-one was formed; its treatment with an aqueous solution of sodium acetate gave 1-ethylpteridin-4-one (VI) ($C_8H_8N_4O$); mp 230-231°C. PMR spectrum (DMSO-d_6): 1.37 (3H, t, CH_3); 4.35 (2H, q, N–CH_2); 8.84 (1H, s, 2-H); 8.92 ppm (2H, s, 6-H and 7-H). Mass spectrum, m/z (I > 10%): 40 (25), 41 (12), 52 (18), 57 (11), 66 (21), 67 (14), 68 (11), 69 (13), 79 (32), 80 (22), 83 (13), 93 (28), 120 (100), 121 (31), 148 (27), 176 (76, M^+).

4,8-Dimethyl-2-morpholinopteridinium Fluorosulfonate (IVo) ($C_{12}H_{16}FN_5O_4S$). To a suspension of 3 g (13 mmole) of 4-methyl-2-morpholinopteridine in 2.5 ml of dry methylene chloride we added 1.95 g (17 mmole) of methyl fluorosulfonate in 1 ml of methylene chloride. When the initial pteridine had dissolved, the mixture was cooled to 0°C and kept for 15 min. The precipitate was filtered off and washed well with methylene chloride and with ether. The yield was 4.2 g (94%); mp 137-139°C. PMR spectrum (DMSO-d_6): 2.88 (3H, s, CH_3); 3.72 and 4.07 (8H, m, protons of morpholine ring); 4.20 (3H, s, N–CH_3); 8.86 (1H, d, 6-H) and 9.10 ppm (1H, d, 7-H, $^3J_{67}$ = 3.6 Hz).

Quaternization of 2-Methylthio-4-morpholinopteridine (In) by Methyl Fluorosulfonate. To a solution of 1 g (3.8 mmole) of 2-methylthio-4-morpholinopteridine (In) in 4 ml of absolute methylene chloride we added dropwise a solution of 0.48 g (4.2 mmole, 0.35 ml) of methyl fluorosulfonate in 2 ml of absolute methylene chloride while heating the mixture to boiling. The mixture was kept for 1 h, and the precipitate was then filtered off, washed with methylene chloride and with ether, and recrystallized from ethanol. We obtained 0.9 g (63%) of 1-methyl-2-methylthio-4-morpholinopteridinium fluorosulfonate (IIn) ($C_{12}H_{16}FN_5O_4S_2$); mp 203-204°C. PMR spectrum (DMSO-d_6): 2.76 (3H, s, SCH_3); 3.97 (3H, s, N–CH_3); 3.84-4.32 and 4.93 (8H, m, protons of morpholine ring); 8.98 (1H, d, 6-H); and 9.09 ppm (1H, d, 7-H, $^3J_{67}$ = 2.1 Hz).

The formation of the 8-methyl-2-morpholinopteridinium (IVℓ), 2-morpholino-8-ethylpteridinium (Vℓ), 2-dimethylamino-8-methyl-4-ethoxycarbonylpteridinium (IVk), and 2-dimethylamino-4-ethoxycarbonyl-8-ethylpteridinium (Vk) cations was detected in the PMR spectra of the reaction mixtures (Table 3). Their structures were established on the basis of the changes in the chemical shifts of the ring protons and the spin-spin coupling constants as a result of quaternization [13].

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