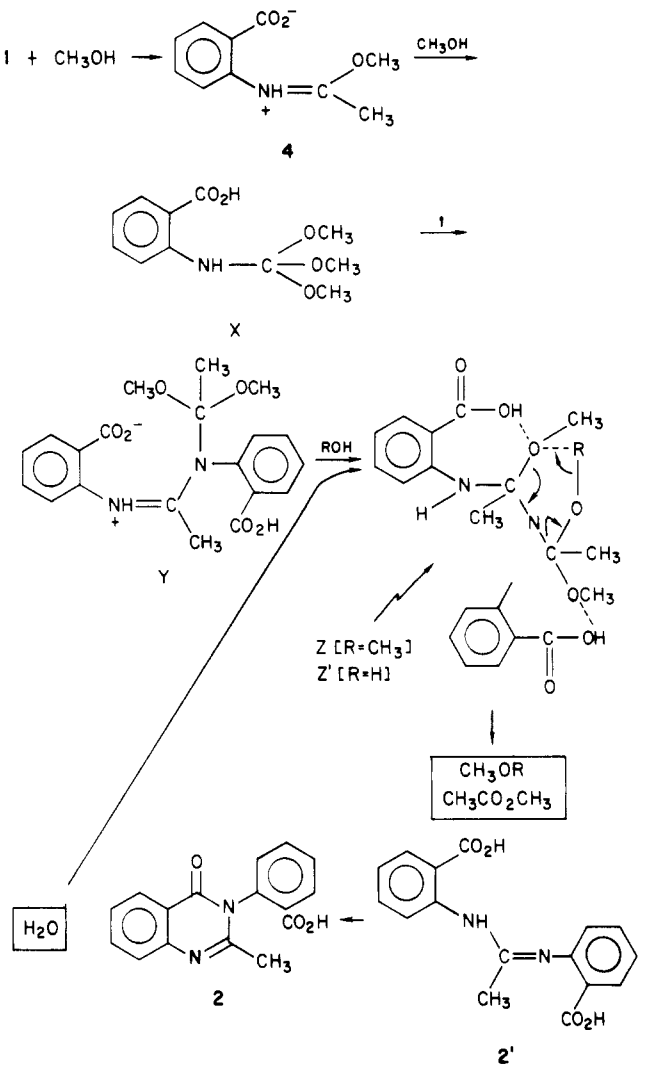
Scheme I[a]



[a] R is CH_3 in the initial cycle, but R is H in all subsequent cycles.

of 1 to *o*-acetamidobenzoic acid by adsorbed water vapor, the reaction was assisted by H-bonding arrays in the crystals, such that nucleophilic attack by adsorbed water molecules occurred exclusively at the C-2 position, i.e., adjacent to the heterocyclic nitrogen atom of 1. It is reasonable to assume, therefore, that similar H-bonding of 1 with $HOCH_3$ may give sequentially intermediates that lead to product 2 perhaps as outlined in Scheme I.

Quite clearly, the high specificity and the enhanced reactivity of the reaction of acetylanthranyl and methanol are directly related to the heterogenous conditions. A similar crystal-orienting influence on rate of reaction was reported by others for the solid-state transformation of methyl *p*-(dimethylamino)benzenesulfonate.[16]

Our future work will be directed toward a better understanding of how enhanced reactivity and improved selectivity is affected by crystal packing. From a more general point of view, such efforts to understand enhancement of chemical reaction rates and improvement of selectivity due to orientation and proximity properties are in relation with mechanisms of enzymatic catalysis.

Registry No. 1, 525-76-8; 2, 4005-06-5; methyl acetate, 79-20-9; methanol, 67-56-1.

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Stable Derivatives of 5,6,7,8-Tetrahydropteridines

William Pendergast* and William R. Hall

Department of Organic Chemistry, Wellcome Research Laboratories, Research Triangle Park, North Carolina 27709

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Folic acid (**1a**) and other 6- and 7-substituted derivatives of pterin (**1b**) undergo chemical or enzymatic reduction in the pyrazine ring to yield the corresponding tetrahydro derivatives **2** (Chart I) which are of central importance in biology and medicine;[1] however, the instability of the hydrogenated derivatives[2] has limited the chemotherapeutic utility of pterins and diaminopteridines to the fully aromatic species.[3] Taylor[4] demonstrated that removal of the electron-donating hydroxy and amino substituents to give the parent pteridine (**3a**) greatly enhanced the stability of the reduced pteridine nucleus (**4a**) compared with that of the reduced pterins **2** and lumazines (**4b**); Clark[5] showed that the presence of the electron-withdrawing group in 4-(ethoxycarbonyl)pteridine (**3b**) greatly increased the stability of the covalently dihydrated species **4d** compared with that of the parent pteridine (**4c**).[6] Thus we predicted that electron-attracting substituents would stabilize 5,6,7,8-tetrahydropteridines even in the presence of those polar, electron-donating groups which are essential for effective binding of pteridines to enzymes.[1] In the present study the synthetic targets were 2-substituted 6,7-dimethyl-5,6,7,8-tetrahydropteridines, a system which is at once simple and of biological relevance because of its relationship to tetrahydro-6,7-dimethylpterin (**2**, $R^1 = R^2 = CH_3$; $R^3 = H$), an experimental substrate for the monooxygenase enzymes which hydroxylate phenylalanine and tryosine.[1a,7]

Discussion and Results

The aromatic pteridines were obtained by condensation of the appropriate 4,5-diaminopyrimidine **5**[8] with diacetyl at the reflux in *tert*-butyl alcohol (Table I). Reductions of the (ethoxycarbonyl)pteridines to the 5,6,7,8-tetrahydro derivatives were carried out with sodium borohydride in methanol at room temperature (Table II).

The latter reactions were followed by thin-layer chromatography in 5% $MeOH/CH_2Cl_2$ on silica gel or were allowed to proceed until a qualitative UV spectrum of a

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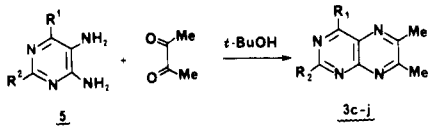
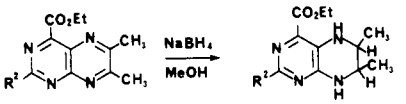
Table I. 6,7-Dimethyl-4-(ethoxycarbonyl)- and 6,7-Dimethyl-4-(trifluoromethyl)pteridines



	R^1	R^2	5,[a] g	diacetyl (mL)	reactn time, h	*t*-BuOH, mL	yield of 3, %	mp, °c
3c	CO_2Et	NH_2	0.25	1.0	1.75	12.5[c]	61	150–153
d	CO_2Et	Cl	0.40	2.0	5.0	70	42	77–78
e	CO_2Et	Me_2N	1.00	2.5	0.17	60	98	140–141
f	CO_2Et	MeS	0.50	2.0	4.0	50	80	111–112
g	CO_2Et	EtO	0.92	4.0	2.5	100	77	105
h	CF_3	EtO	0.20	4.0	2.5	32	72	132–134
i	CF_3	NH_2	1.31	25.0	1.5	125	99	235–236
j	CF_3	Me_2N	0.50	10.0	1.25	50	40	126–127

[a] For preparation of diamine precursors, see ref. 8. [b] Yields based on diamine; products crystallized from pentane except **3c** (benzene/pentane) and **3i** (CH_2Cl_2/pentane). [c] Reaction in ethanol.

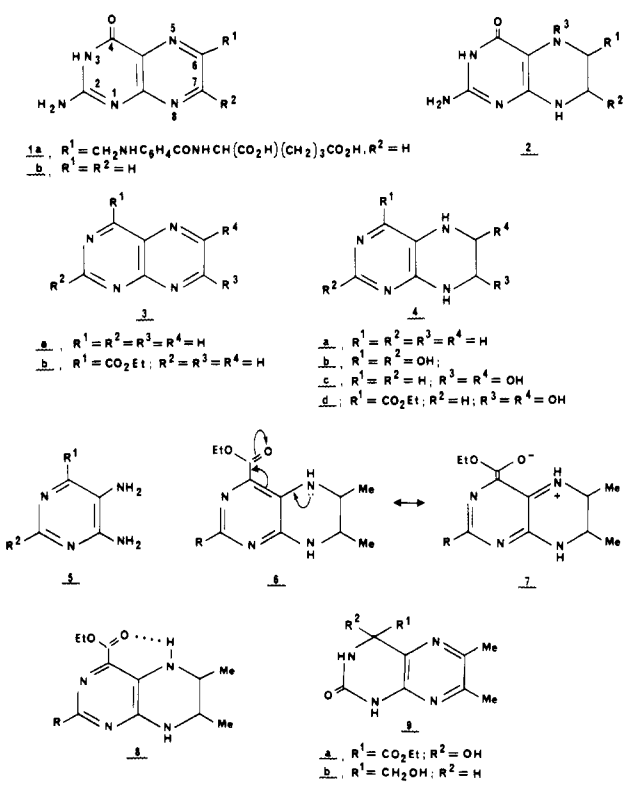
Table II. 6,7-Dimethyl-4-(ethoxycarbonyl)-5,6,7,8-tetrahydropteridines



	amount of 3			MeOH,	$NaBH_4$		reactn		yield	
R^2		g	mol	mL	g	mmol	time, min	recryst solvent	of 4, %	mp, °C
NMe_2	**3e**	0.5	1.82	25	0.45	11.90	7	pentane	**4e**, 38	87–88
MeS	**3f**	0.3	1.08	20	0.25	6.61	6	*a*	**4f**, 30	206–207
NH_2	**3c**	0.12	0.49	15	0.15	3.97	14	CH_2Cl_2	**4g**, 37	206–208
Cl	**3d**	0.30	1.12	20	0.20	5.30	6	EtOAc[b]	**4h**, 26	260–261
EtO	**3g**	1.40	5.07	140	3.0	79.3	7	EtOAc[c]	**4i**, 40	145–146

[a] Crystallized directly from reaction mixture. Some solid filtered off before CH_2Cl_2 extraction; combined with extraction residue and crystallized from EtOAc. [c] Reaction quenched with water, methanol removed by evaporation, and crude precipitate crystallized from EtOAc.

Chart I



sample of the reaction mixture resembled that of the corresponding 4,5-diaminopyrimidine starting material, which had a similar conjugated π-system. Structures of both the aromatic and reduced pteridines were confirmed by elemental analyses, ^1H NMR spectroscopy, and where indicated by high-resolution mass spectrometry. Hydrogenation of the pyrazine ring resulted in an upfield shift of the 6- and 7-methyl signals by 1.3–1.6 ppm, with the coupling due to the adjacent 6- or 7-proton visible as a doublet, J = 6.3 Hz. The 6- and 7-protons (not assigned) were observed as complex multiplets at δ 3.4–3.7. The stereochemistry of the reductions was in most cases exclusively cis, as evidenced by the small coupling constant ($J_{6,7}$ = 3.4 Hz) between the vicinal 6- and 7-protons. However, in one case (**4g**, $R^2 = NH_2$, Table II), a small proportion (16%) of the trans-reduced diastereomer was observed. The complex multiplet due to the 6- and 7-protons of this minor isomer was at slightly higher field (δ 3.13) than that of the cis derivative (δ 3.60), and the coupling constant ($J_{6,7}$ = 7.5 Hz), observed on irradiation of the methyl signals, was much larger than in the cis diastereomer. These couplings are comparable with previously observed values in the tetrahydro-6,7-dimethylpterins ($J_{6,7}$(cis) = 3.1 $J_{6,7}$(trans) = 8.3 Hz).[9]

Of the three (trifluoromethyl)pteridines **3h–j** (Table I) prepared, only the 2-ethoxy derivative **3h** gave an isolable tetrahydro derivative (**4j**); more forcing conditions (sodium cyanoborohydride in 0.2 M HCl) were required. Although UV spectra of the reaction mixtures of all three compounds showed reduction to be almost complete, only the aromatic pteridine starting material could be isolated in the case of the amino (**3i**) and dimethylamino (**3j**) derivatives. The 2-ethoxy-4-(trifluoromethyl)tetrahydro derivative **4j**, though a stable solid, tended to revert to starting material when methanolic and aqueous solutions were stored in air.

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This lesser ability of the CF_3 group to stabilize the reduced system when compared with the CO_2Et substituent may be explained by qualitative differences in their electron-withdrawing effects. Thus although CF_3 exerts a strong inductive effect, it is incapable of the kind of mesomeric stabilization (**6** ⇄ **7**) afforded by the ethoxycarbonyl group. Further, the hydrogen-bonding stabilization (**8**) available to the ethoxycarbonyl derivatives would be weak or nonexistent in the trifluoromethyl compounds.[10]

Borohydride reduction of 2-oxo-4-(ethoxycarbonyl)-pteridine, which existed as the 3,4-hydrate **9a**, was anomalous. Hydrogenation occurred in the pyrimidine rather than the pyrazine ring, with concomitant reduction of the ester group to yield the 3,4-dihydro-4-hydroxymethyl derivative **9b**. The special stability conferred by urea-type resonance on hydrated and reduced fused pyrimidines of this kind has been well documented[6] and in this case seems to outweigh the factors responsible for the stability of reduced pyrazines discussed above.

The foregoing study illustrates the effect of an electron-attracting group in stabilizing reduced pteridine derivatives. In view of the known difficulties usually experienced in the isolate and biological evaluation of hydrogenated pteridines, introduction of such substituents may represent a useful strategy in increasing the chemotherapeutic utility of analogues of reduced folates and other pterin cofactors.

Experimental Section

Melting points were determined on a Büchi capillary apparatus and are uncorrected. ^1H NMR spectra were obtained on Varian HA100, CFT-20, and T60 spectrometers. Chemical shifts (δ) are reported relative to Me_4Si (δ 0). Mass spectra were determined on a Varian MAT CH5 DF instrument at 70 eV. Analyses were performed by Atlantic Microlabs Inc., Atlanta, GA. All C, H, N and analyses not reported here were acceptable (±0.3%) and may be found with ^1H NMR data in the supplementary data section.

6,7-Dimethyl-4-(ethoxycarbonyl)pteridines 3c–j. The ethyl 2-substituted 4,5-diaminopyrimidine-6-carboxylate **5** was heated under reflux in *tert*-butyl alcohol with an excess of diacetyl. Particular reaction conditions for each compound are given in Table I. The reaction mixture was evaporated to dryness and extracted with pentane (700 mL). The pentane solution was evaporated to 70 mL, from which the products **3c–j** (40–99%) crystallized on setting aside the solution overnight in the cold. The dimethylpteridines were recrystallized from pentane or pentane/solvent mixtures as indicated.

6,7-Dimethyl-4-(ethoxycarbonyl)-5,6,7,8-tetrahydropteridines. The pteridine **3** was stirred in dry methanol with sodium borohydride, the reaction mixture was neutralized with glacial acetic acid and evaporated, and the residue was suspended in water and extracted with 2 × 20 mL of CH_2Cl_2. The residue from evaporation of the combined extracts was crystallized as indicated in Table II to yield the tetrahydro derivative **4**. A specific example is described below for the preparation of **4g**.

2-Amino-6,7-dimethyl-4-(ethoxycarbonyl)-5,6,7,8-tetrahydropteridine (4g). To a stirred solution of the pteridine **3c** (0.12 g, 0.005 mol) in dry methanol (15 mL) at room temperature was added sodium borohydride (0.15 g, 3.97 mmol). After 15 min the reaction mixture was neutralized with acetic acid and evaporated to dryness under reduced pressure at 37 °C. The residue was suspended in distilled water and extracted with 2 × 20 mL of CH_2Cl_2. The extracts were combined and evaporated to a yellow residue which was crystallized from CH_2Cl_2/pentane to give the amino compound **4g** (0.047 g, 37%): mp 206–208 °C; NMR ($CDCl_3$) (80 MHz) δ 1.16 (d, 3 H, J = 6.3 Hz), 1.19 (d, 3 H, J = 6.3 Hz), 1.40 (t, 3 H, J = 7 Hz), 3.13 (m, trans-6,7-H (16%) $J_{6,7}$ = 7.5 Hz), 3.60 (m, cis-6,7-H (84%), $J_{6,7}$ = 3.4 Hz), 4.38 (q, 2 H, J = 7 Hz), 3.34 (s, <1 H, MeOH). Anal. Calcd for $C_{11}H_{17}N_5O_2 \cdot 0.25MeOH$: C, 52.10; H, 6.99; N, 27.01. Found: C, 51.93; H, 6.82; N, 26.95.

2-Ethoxy-6,7-dimethyl-5,6,7,8-tetrahydro-4-(trifluoromethyl)pteridine (4j). 2-Ethoxy-6,7-dimethylpteridine (**3h**; 0.03 g, 0.11 mmol) was suspended in 0.2 M HCl (30 mL) and sodium cyanoborohydride (1.0 g, 15.9 mmol) was added in small portions over 2 h. The reaction mixture was stirred for 1 h at room temperature, adjusted to pH 8 with 6 M NaOH, and extracted with 3 × 30 mL of methylene chloride. The combined extracts were evaporated and the residue was crystallized from methylene chloride/pentane (1:1) to yield the tetrahydro derivative (**4j**; 0.005 g, 16%); mp 154–155 °C; mass spectrum (70 eV, 115 °C), m/e 276.1213 (M^+, 100%); $C_{11}H_{15}F_3N_4O$ requires 276.1198; NMR ($CDCl_3$) δ 1.16 (d, 1 H, J = 6.3 Hz), 1.20 (d, 1 H, J = 6.3 Hz), 1.34 (t, 3 H, J = 7 Hz), 3.66 (m, 2 H) 3.99 (br s, 1 H), 4.76 (q, 2 H, J = 7 Hz) 5.71 (br s, 1 H).

6,7-Dimethyl-4-(ethoxycarbonyl)-4-hydroxy-1,2,3,4-tetrahydropteridin-2-one (9a). 4,5-Diamino-1,2-dihydro-6-(ethoxycarbonyl)pyrimidin-2-one[8] (0.5 g, 2.5 mmol) was heated under reflux with diacetyl (0.5 mL) for 15 min. The cooled solution was evaporated under reduced pressure to 3 mL, when the pteridine **9a** (0.25 g, 35%) crystallized as pale yellow prisms which decomposed gradually without melting at >200 °C: NMR (Me_2SO-d_6) δ 1.13 (t, 3 H, J = 7 Hz); 2.34 (s, 3 H), 2.38 (s, 3 H), 4.12 (q, 2 H, J = 7 Hz), 6.8 (s, 1 H), 8.30 (s, 1 H), 10.19 (s, 1 H). Anal. Calcd for $C_{11}H_{14}N_4O_4 \cdot H_2O$: C, 46.47; H, 5.67; N, 19.71. Found: C, 46.62; H 5.59; N, 19.80.

6,7-Dimethyl-4-(hydroxymethyl)-1,2,3,4-tetrahydropteridin-2-one (9b). The foregoing (ethoxycarbonyl)pteridine **9a** (0.10 g, 0.376 mmol) was stirred in dry methanol (10 mL) during the addition of sodium borohydride (0.16 g, 4.23 mmol) portionwise over 20 min. The reaction mixture was neutralized with glacial acetic acid, and the resulting solid was filtered off and washed with methanol to yield the reduced pteridine (0.051 g, 64.9%) as a white solid: mp 245–250 °C; NMR (Me_2SO-d_6, 80 mHz) δ from Me_4Si 2.34 (s, 6 H), 3.58 (q, 2 H), 4.32 (m, 1 H), 4.84 (t, 1 H), 6.95 (br s, 1 H), 9.47 (br s, 1 H). Anal. Calcd for $C_9H_{12}N_4O_2 \cdot 0.4H_2O$: C, 50.18; H, 5.99; N, 26.01. Found: C, 50.42; H, 5.88; N, 25.75.

Acknowledgment. We thank Dr. R. W. Morrison for helpful discussions and encouragement, Dr. B. S. Hurlbert, A. Ragouzeous, and R. Crouch for NMR spectra, Dr. D. Brent. B. Soltmann and R. Johnson for mass spectra, and S. K. Wrenn for technical assistance.

Registry No. **3c**, 93683-57-9; **3d**, 93683-58-0; **3e**, 93683-59-1; **3f**, 93683-60-4; **3g**, 93683-61-5; **3h**, 93683-48-8; **3i**, 93683-62-6; **3j**, 93683-63-7; *cis*-**4e**, 93683-51-3; *cis*-**4f**, 93683-52-4; *cis*-**4g**, 93683-49-9; *cis*-**4h**, 93683-50-2; *cis*-**4i**, 93683-53-5; **4j**, 93683-54-6; **5c**, 60914-72-9; **5d**, 90084-94-9; **5e**, 90769-45-2; **5f**, 18204-20-1; **5g**, 90649-37-9; **5h**, 32706-24-4; **5i**, 2927-10-8; **5j**, 32706-22-2; **9a**, 93683-55-7; **9b**, 93683-56-8; 2,3-butanedione, 431-03-8; 4,5-diamino-1,2-dihydro-6-(ethoxycarbonyl)pyrimidin-2-one, 89897-53-0.

Supplementary Material Available: Elemental analyses on compounds **3c–j** and **4e–i**; ^1H NMR spectra on compounds **3c–j** and **4e–j** (3 pages). Ordering information is given on any current masthead page.

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Preparation of (*Z*)-1,4-Diphenylcyclohexane

Samuel G. Levine* and Angelita S. Ng

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204

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In line with our interest in the stereochemical properties of (arene)chromium tricarbonyl (CT) complexes,[1] we undertook to determine the conformational energy of a complexed phenyl group. This objective seemed most amenable to approach by Eliel's "counterpoise" method[2]

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