PROTECTION AND DEPROTECTION OF FUSED 2-AMINO-4(3H)-PYRIMIDINONES: CONVERSION OF PTERINS AND 5-DEAZAPTERINS TO 2,4-DIAMINO DERIVATIVES

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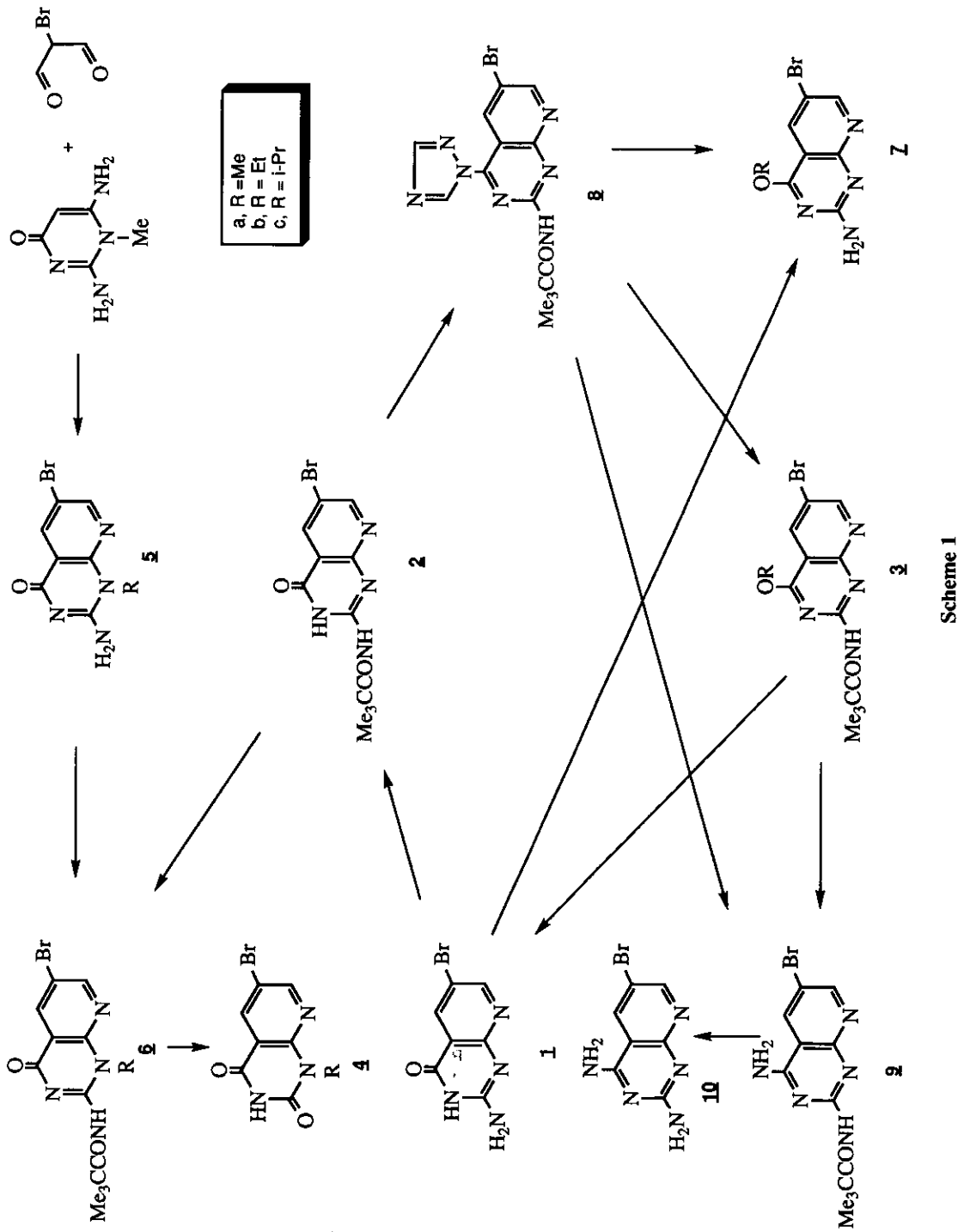
Abstract - 5-Deazapterins and pterins are readily converted to their 4-deoxy-4-amino derivatives (a lactam-to-amidine conversion) by reaction with 4-chlorophenyl phosphorodichloridate and 1,2,4-triazole to give intermediate 4-[1'-(1,2,4-triazolyl)] derivatives, followed by reaction with aqueous ammonia. Some anomalous results obtained by application of the Mitsunobu reaction (normally a lactam-to-lactim ether conversion) to 5-deazapterins are detailed.

Fused 2-amino-4(3H)-pyrimidinones in general, and pterins (2-amino-4(3H)-pteridinones) and 5-deazapterins in particular, are renowned for their insolubility and resulting chemical intransigence which is a consequence of extraordinarily strong intermolecularly hydrogen-bonded crystal lattices which are not susceptible to solvation.[2-4] Because of our intense current interest in folic acid and 5-deazapterin chemistry, we have become interested in chemical modifications of these systems which might be termed "protection/solubilizing functionalization". For example, pivaloylation of the 2-amino group has been shown to impart considerable solubility to 5-deazapterins and to pterins and has made possible synthetic transformations impossible to carry out on the parent systems.[5-8] A standard methodology for protection (with resulting solubilization) and activation (for nucleophilic displacement reactions at the 6-position) of the bases guanine and hypoxanthine has been either their conversion to lactim ethers (6-alkoxypurines)[9-11] by the Mitsunobu reaction,[12] or to 6-[1'-(1,2,4-triazolyl)] derivatives with 1,2,4-triazole and 4-chlorophenyl phosphorodichloridate.[13-17] Modifications of this latter methodology have found extensive use in pyrimidine chemistry as well.[14,18-24] We report in this paper our results in attempts to extend these procedures to 5-deazapterins and to pterins, and a resulting effective methodology for the conversion of fused 2-amino-4(3H)-pyrimidinones to 2,4-diamino derivatives; we also draw particular attention to deviations observed in the "normal" pattern of alkylation with the Mitsunobu reaction (*vide supra*).[25]

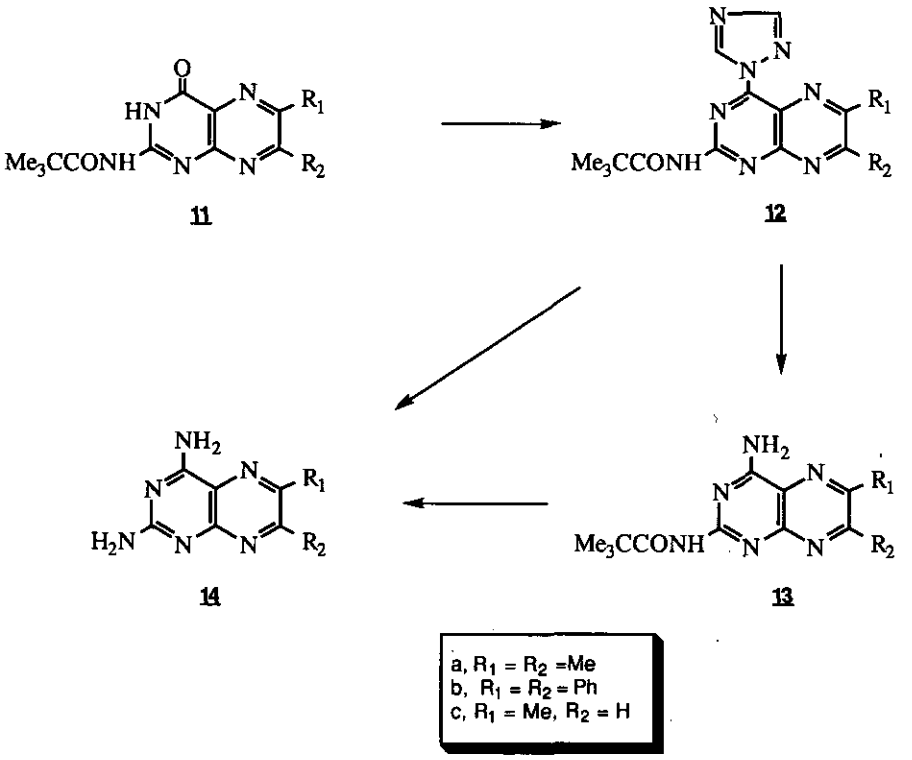
2-Amino-6-bromo-5-deaza-4(3H)-pteridinone (6-bromo-5-deazapterin) (**1**) is a key starting material for our synthesis of the extremely promising antitumor agent DDATHF,[26] but it must first be converted to its more soluble 2-pivaloyl derivative (**2**)[7] for subsequent synthetic transformations. In the anticipation that an even more soluble derivative might be obtained by conversion of **2** to a lactim ether, we examined standard Mitsunobu alkylation conditions (triphenylphosphine/diethyl azodicarboxylate/methanol) with this substrate, and indeed obtained an extremely soluble monomethyl derivative (see Scheme I). That it was not the anticipated lactim ether (**3a**), however, became readily apparent when hydrolysis yielded a mono-methyl derivative of 6-bromo-5-deazalumazine; i.e. alkylation had thus taken place on nitrogen rather than on the lactam oxygen. The assignment of structure (**4a**) to the above lumazine, and structure (**6a**) to the compound formed under the above Mitsunobu conditions, was made possible by an unequivocal synthesis of **6a**. Thus, bromomalonaldehyde[27] was condensed with 2,6-diamino-1-methyl-4(1H)-pyrimidone[28] to give 1-methyl-6-bromo-5-deazapterin (**5a**), which was then pivaloylated to give **6a**, identical in all respects with the above product of Mitsunobu alkylation. Analogous anomalous results leading to the 1-alkyl derivatives (**6b**) and (**6c**) were obtained upon Mitsunobu alkylation of **2** using ethanol and isopropanol respectively. Similarly, hydrolysis of **6b** gave **4b**. Since Mitsunobu alkylation of the parent 6-bromo-5-deazapterin (**1**) indeed led (after some 96 hours) to the lactim ethers (**7a**) and (**7b**), albeit in extremely poor yield, the acyl group on the 2-amino substituent clearly directs alkylation to N-1.

Preparation of the desired 4-lactim ethers (**3**) by the triazole methodology was then examined. 6-Bromo-2-pivaloylamino-4-[1'-(1,2,4-triazolyl)]-5-deazapteridine (**8**) was prepared in high yield by reaction of **2** with 1,2,4-triazole in the presence of 4-chlorophenylphosphorodichloridate. This material was readily converted to the lactim ethers (**3a-c**) by reaction at room temperature with the respective alkoxides. That these derivatives of **1** could serve both as protecting groups, and as viable intermediates for further synthetic transformations, was established by the conversion of **3a** to 2-pivaloylamino-4-amino-6-bromo-5-deazapteridine (**9**) in almost quantitative yield by stirring at room temperature for 30 minutes with dioxane/aqueous ammonia. Prolonged stirring of **9** with aqueous ammonium hydroxide removed the 2-pivaloyl grouping to give 2,4-diamino-6-bromo-5-deazapteridine (**10**). Furthermore, **3a** and **3b** were readily reconverted to **1** with aqueous methanolic sodium hydroxide.



Scheme 1

The above procedures can also be applied to pterins (Scheme 2). 6,7-Dimethylpterin,[29] 6,7-diphenylpterin, [29] and 6-methylpterin[30] were pivaloylated with pivalic anhydride/4-dimethylaminopyridine to give the much more soluble pivaloyl derivatives (**11a-c**). Compounds (**11b**) and (**11c**) were readily converted to their 4-[1'-(1,2,4-triazolyl)] derivatives (**12b**) and (**12c**) with 1,2,4-triazole and 4-chlorophenyl phosphorodichloridate; the analogous transformation failed with the 6,7-dimethyl derivative (**11a**), however, apparently because of the acidic 7-methyl group. Stirring **12b** and **12c** *at room temperature* with aqueous ammonia in dioxane for 30 minutes gave 4-amino-6,7-diphenyl-2-pivaloylaminopteridine (**13b**) and 4-amino-6-methyl-2-pivaloylaminopteridine (**13c**) respectively in almost quantitative yield; longer stirring under these conditions removed the 2-pivaloyl protecting group and generated the 2,4-diaminopteridines (**14b**) and (**14c**).



Scheme 2

A standard transformation in the folate field has been the preparation of pterins or 5-deazapterins from the corresponding 2,4-diamino derivatives either by acidic or basic hydrolysis of the 4-amino group.[2,3] The reverse transformation (which, *inter alia*, converts thyidylate synthase or glycineamide ribonucleotide formyltransferase inhibitors to dihydrofolate reductase inhibitors) has previously been effected either by heating pterins with phenylphosphorodiamidate at 215 °C,[31] or by chlorination or thiation of the 4-lactam grouping, followed by amination; none of these procedures is satisfactory or general.[2,3] The present alternative methodology should prove to be of considerable utility in this area of heterocyclic chemistry.[32]

EXPERIMENTAL SECTION

6-Bromo-1-methyl-2-pivaloylamino-5-deaza-4(1H)-pteridinone (6a): Method A. To a mixture of **2** (0.65 g, 2 mmol), triphenylphosphine (0.78 g, 3 mmol) and diethyl azodicarboxylate (0.47 ml, 3 mmol) in anhydrous tetrahydrofuran, (35 ml) was added methanol (0.17 ml, 4.2 mmol). The resulting pale yellow homogeneous reaction mixture was stirred at room temperature for 3 h. Solvent was removed under reduced pressure and the residual oil was passed over a silica gel column (60-200 mesh) with 10% ethyl acetate in hexanes as eluent. Concentration of the first fraction gave 0.35 g (51%) of a white solid as the major product; mp 144-145 °C; ^{1}H nmr (300 MHz, CDCl3) δ 1.27 (s, 9 H), 3.86 (s, 3 H), 8.56 (d, 1 H), 8.73 (d, 1 H): Anal. Calcd for $C_{13}H_{15}N_4O_2Br$: C, 46.03; H, 4.46; N, 16.52; Br, 23.56. Found: C, 46.03; H, 4.41; ; N, 16.41; Br, 23.80.

Method B. A suspension of 2,6-diamino-1-methyl-4(1H)-pyrimidone[28] (1.4 g, 1 mmol) and bromomalonaldehyde[27] (1.5 g, 1 mmol) in concentrated hydrochloric acid (0.5 ml) and ethanol (50 ml) was heated under reflux for 24 h. The brown reaction mixture was then filtered hot to remove residual solid, and the filtrate was concentrated under reduced pressure to give 1.8 g (70%) of crude 2-amino-6-bromo-1-methyl-5-deaza-4(1H)-pteridinone (**5a**). A mixture of **5a** (1.0 g, 3.9 mmol) and 4-dimethylaminopyridine (0.05 g, 0.4 mmol) in pivalic anhydride (10 ml) was heated under reflux for 1 h, cooled to room temperature and ether (25 ml) added. The resulting brown precipitate was collected by filtration, washed well with ether and dissolved in chloroform (10 ml). Filtration through a pad of silica gel (230-400 mesh) with 7% ethyl acetate in hexanes and concentration of the filtrate gave a white solid which was collected by filtration, washed with ether and dried; yield 0.46 g (35%), mp 144-145 °C. This material was identical in every respect with **6a** prepared by Method A.

6-Bromo-1-ethyl-2-pivaloylamino-5-deaza-4(1H)-pteridinone (6b): From **2** (0.65 g, 2 mmol), triphenylphosphine (0.78 g, 3 mmol) and diethyl azodicarboxylate (0.47 ml, 3 mmol) in anhydrous tetrahydrofuran (35 ml) and absolute ethanol (0.2 ml, 4.2 mmol) as described above; yield 0.42 g (60%); mp 120-121 °C; ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.28 (s, 9 H), 1.33 (t, 3 H), 4.63 (q, 2 H), 8.56 (d, 1 H), 8.76 (d, 1 H): Anal. Calcd for $C_{14}H_{17}N_4O_2Br$: C, 47.61; H, 4.85; N, 15.86. Found: C, 47.68; H, 4.83; N, 15.94.

6-Bromo-1-isopropyl-2-pivaloylamino-5-deaza-4(1H)-pteridinone (6c): From **2** (0.324 g, 1 mmol), triphenylphosphine (0.393 g, 1.5 mmol) and diethyl azodicarboxylate (0.24 ml, 1.5 mmol) and isopropanol (0.5 ml) in anhydrous tetrahydrofuran (25 ml) as described above; yield 0.22 g (60%); mp 145-146 °C; ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.28 (s, 9 H), 1.66-1.69 (d, 6 H), 6.06 (m, 1 H), 8.56 (d, 1 H), 8.73 (d, 1 H): Anal. Calcd for $C_{15}H_{19}N_4O_2Br$: C, 49.06; H, 5.21; N, 15.26. Found: C, 48.94; H, 5.26; N, 15.10.

6-Bromo-1-methyl-5-deazalumazine (4a): Sodium hydroxide (0.18 g, 4.5 mmol) was dissolved in 60 % aqueous methanol (50 ml) and **6a** (0.27 g, 0.798 mmol) was added. The resulting suspension was heated to reflux to give a clear solution. Refluxing was continued for 12 hr and the reaction mixture was then cooled, neutralized with glacial acetic acid (0.26 ml), and the resulting solution concentrated under reduced pressure. The white solid which separated was collected by filtration, washed thoroughly with water and dried; yield 0.18 g (88%); mp 259-260 °C; ^{1}H nmr (300 MHz, Me_2SO-d_6) δ 3.46 (s, 3 H), 8.36 (d, 1 H), 8.78 (d, 1 H): Anal. Calcd for $C_8H_6N_3O_2Br$: C, 37.65; H, 2.37; N, 16.48; Br, 30.95. Found: C, 37.97; H, 2.52; N, 16.57; Br, 31.40.

6-Bromo-1-ethyl-5-deazalumazine (4b): From **6b** (0.28 g, 0.824 mmol), sodium hydroxide (0.18 g, 4.5 mmol) and 60% aqueous methanol (50 ml) as described above; yield 0.19 g (86%); mp 264-265 °C; ^{1}H nmr (300 mHz, $CDCl_3$) δ 1.29-1.33 (t, 3 H), 4.36-4.41 (q, 2 H), 8.56 (d, 1 H), 8.73 (d, 1 H): Anal. Calcd for $C_9H_8N_3O_2Br$: C, 40.02; H, 2.99; N, 15.56; Br, 29.58. Found: C, 40.27; H, 3.06; N, 15.76; Br, 29.80.

6-Bromo-2-pivaloylamino-4[1'-(1,2,4-triazoloyl)]-5-deazapteridine (8): To a pale yellow solution of **2** (0.324 g, 1 mmol) and 1,2,4-triazole (0.207 g, 3 mmol) in dry pyridine (5 ml) was added p-chlorophenylphosphoro-dichloridate (0.25 ml, 1.5 mmol), and the homogeneous pale yellow solution was stirred at room temperature under nitrogen. A light crystalline precipitate separated within a few minutes. Stirring was continued for 24 h, and the reaction mixture was then taken up in methylene chloride (100 ml) and the resulting solution washed with 2% aqueous hydrochloric acid followed by water. The organic extract was dried (anhyd. $MgSO_4$) and concentrated under reduced pressure to

give 0.35 g (93%) of a pale yellow solid; mp 284-285 °C; ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.35 (s, 9 H), 8.31 (d, 1 H), 8.46 (bs, 1 H), 9.20 (d, 1 H), 9.63 (s, 1 H), 9.96 (s, 1 H). Anal. Calcd for $C_{14}H_{14}N_7OBr$: C, 44.70; H, 3.75; N, 26.06. Found: C, 45.00; H, 3.84; N, 25.87.

6-Bromo-4-methoxy-2-pivaloylamino-5-deazapteridine (3a): To a solution of sodium (0.025 g, 1.1 mmol) in absolute methanol (10 ml) was added **8** (0.374 g, 1 mmol), and the resulting homogeneous reaction mixture was stirred at room temperature for 15 min and then neutralized by the addition of glacial acetic acid (0.04 ml). Concentration under reduced pressure, trituration of the residual white solid with water and filtration gave 0.31 g (92%) of fine needles; mp 110-112 °C; ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.32 (s, 9 H), 4.26 (s, 3 H), 8.30 (bs, 1 H), 8.50 (d, 1 H), 9.01 (d, 1 H): Anal. Calcd for $C_{13}H_{15}N_4O_2Br$: C, 46.03; H, 4.46; N, 16.52; Br, 23.56. Found: C, 46.15; H, 4.46; N, 16.47; Br, 23.82.

6-Bromo-4-ethoxy-2-pivaloylamino-5-deazapteridine (3b): From sodium (0.025 g, 1.1 mmol), absolute ethanol (10 ml), and **8** (0.374 g, 1 mmol) as described above; yield 0.30 g (85%); mp 170-171 °C; ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.36 (s, 9 H), 1.53 (t, 3 H), 4.76 (q, 2 H), 8.26 (bs, 1 H), 8.53 (d, 1 H), 9.03 (d, 1 H): Anal. Calcd for $C_{14}H_{17}N_4O_2Br$: C, 47.61; H, 4.85; N, 15.86. Found: C, 47.88; H, 4.62; N, 16.09.

This material was readily hydrolyzed back to **1** as follows: Sodium hydroxide (0.15 g, 3.75 mmol) was dissolved in 25 ml of 60% aqueous methanol and **3b** (0.176 g, 0.5 mmol) added. The resulting solution was heated under reflux for 12 h and then cooled to room temperature, neutralized by the addition of acetic acid (0.21 ml) and concentrated under reduced pressure. The residual white solid was triturated with water, collected by filtration, washed well with water and dried to give 0.10 g (83%) of **1**, identical in all respects with authentic material.

6-Bromo-4-isopropoxy-2-pivaloylamino-5-deazapteridine (3c): From sodium (0.012 g, 0.52 mmol), isopropanol (15 ml) and **8** (0.15 g, 0.4 mmol) as described above; yield 0.13 g (88%); mp 180-181 °C; ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.37 (s, 9 H), 1.51-1.53 (d, 6 H), 5.76 (m, 1 H), 8.26 (bs, 1 H), 8.53-8.54 (d, 1 H), 9.03 (d, 1 H): Anal. Calcd for $C_{15}H_{19}N_4O_2Br$: C, 49.06; H, 5.21; N, 15.26; Br, 21.76. Found: C, 48.93; H, 5.24; N, 15.48; Br, 21.90.

4-Amino-6-bromo-2-pivaloylamino-5-deazapteridine (9): Method A. To a suspension of **8** (0.375 g, 1 mmol) in dioxane (7 ml) was added aqueous ammonia (3 ml), and the resulting thick suspension was stirred at room temperature for 30 min, concentrated under reduced pressure, and the pale yellow solid which precipitated collected by

filtration, washed with water and dried; yield 0.31 g (95%); mp 251-252 °C; ^{1}H nmr (300 MHz, Me_2SO-d_6) δ 1.16 (s, 9 H), 8.13 (bs, 2 H), 8.63 (d, 1 H), 8.88-8.93 (d, 2 H), 9.65 (s, 1 H): Anal. Calcd for $C_{12}H_{14}N_5OBr$: C, 44.46; H, 4.35; N, 21.60; Br, 24.65. Found: C, 44.12; H, 4.43; N, 21.42; Br, 24.99.
Method B: To a suspension of **3a** (0.338 g, 1 mmol) in dioxane (5 ml) was added 30 % aqueous ammonia (5 ml) and the reaction mixture was stirred at room temperature for 12 h and then worked up as described above under Method A to give 0.30 g (95%), of **9**, mp 251-252 °C, identical in all respects with material prepared by Method A.

6-Bromo-2,4-diamino-5-deazapteridine (10): A suspension of **9** (0.15 g, 0.46 mmol) and aqueous ammonia (5 ml, 30%) in dioxane (10 ml) was stirred at room temperature for five days. The suspended white solid was collected by filtration, washed thoroughly with water and dried to give 90 mg (81%) of **10**; mp >300 °C; ^{1}H nmr (300 MHz, Me_2SO-d_6) δ 6.51 (bs, 2 H), 7.59 (bs, 2 H), 8.60-8.61 (d, 1 H), 8.61 (d, 1 H). Anal. Calcd for $C_7H_6N_5Br$: C, 35.02; H, 2.52; N, 29.17; Br, 33.28. Found: C, 35.26; H, 2.68; N, 28.80; Br, 33.56.

2-Amino-6-bromo-4-methoxy-5-deazapteridine (7a): Method A. To a solution of sodium (0.025 g, 1.1 mmol) in absolute methanol (25 ml) was added **8** (0.375 g, 1 mmol), and the resulting homogeneous pale yellow reaction mixture was stirred at room temperature for 12 h and then worked up as described above for the preparation of **3a**; yield 0.23 g (90%); mp 225-227 °C (decomp); ^{1}H nmr (300 MHz, $CDCl_3$) δ 4.11 (s, 3 H), 5.40 (bs, 2 H), 8.39 (d, 1 H), 8.92 (d, 1 H): Anal. Calcd for $C_8H_7N_4OBr$: C, 37.67; H, 2.77; N, 21.96: Br, 31.33. Found: C, 37.90; H, 2.87; N, 21.69; Br, 32.89.
Method B: To a mixture of **1** (0.12 g, 0.5 mmol), triphenylphosphine (0.2 g, 0.75 mmol) and diethyl azodicarboxylate (0.11 ml, 0.75 mmol) in anhydrous tetrahydrofuran (20 ml) was added methanol (1 ml), and the resulting suspension was stirred at room temperature for 72 h. Solvent was removed by evaporation under reduced pressure, and the concentrate was passed through a column of silica gel (60-230 mesh), with 10% ethyl acetate in hexanes as the eluent. Concentration of the eluate gave 0.03 g (25%) of **7a**, mp 225-227 °C (decomp), as a white solid, identical in all respects with the material prepared by Method A.

2-Amino-6-bromo-4-ethoxy-5-deazapteridine (7b): Method A. From sodium (0.025 g, 1.1 mmol), absolute ethanol (25 ml) and **8** (0.375 g, 1 mmol) as described above for the preparation of **7a**; yield 0.24 g (89%); mp 225-226 °C; ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.48-1.52 (t, 3 H), 4.53-4.60 (q, 2 H), 5.45 (bs, 2 H), 8.39-8.40 (d, 1 H), 8.87-8.88 (d, 1 H): Anal. Calcd for $C_9H_9N_4OBr$: C, 40.17; H, 3.37; N, 20.82. Found: C, 40.06; H, 3.25; N, 20.69.

Method B: From **1** (0.12 g, 0.5 mmol), triphenylphosphine (0.2 g, 0.75 mmol) and ethanol (1 ml) in anhydrous tetrahydrofuran, (20 ml) as described above for the preparation of **7a**, Method B; yield 0.04 g (30%) of **7b**, mp 225-226 °C, identical in all respects with the material prepared by Method A.

6,7-Dimethyl-2-pivaloylamino-4(3H)-pteridinone (11a): A yellow suspension of 6,7-dimethylpterin[29] (1.91 g, 0.01 mol) and 4-dimethylaminopyridine (0.123 g, 1 mmol) in pivalic anhydride (10 ml) was heated under reflux for 3 h, cooled to room temperature and ether (100 ml) added. The resulting brown solid was collected by filtration, washed with ether, dissolved in chloroform (100 ml) and filtered through a pad of silica gel (230-400 mesh), with 1% methanol in methylene chloride as the eluent. Concentration of the eluate gave 2.3 g (83%) of a yellow solid; mp 289-290 °C; ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.36 (s, 9 H), 2.72 (s, 3 H), 2.76 (s, 3 H), 8.30 (bs, 1 H): Anal. Calcd for $C_{13}H_{17}N_5O_2$: C, 56.72; H, 6.22; N, 25.44. Found: C, 56.50; H, 6.09; N, 25.71.

6,7-Diphenyl-2-pivaloylamino-4(3H)-pteridinone (11b): From 6,7-diphenylpterin[29] (3.15 g, 0.01 mol), 4-dimethylaminopyridine (0.123 g, 1 mmol) and pivalic anhydride (15 ml) as described above; yield 3.59 g (90%); mp 160-161 °C; ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.36 (s, 9 H), 7.30-7.43 (m, 6 H), 7.53-7.63 (m, 4 H), 8.46 (bs, 1 H): Anal. Calcd for $C_{23}H_{21}N_5O_2$: C, 69.16; H, 5.30; N, 17.53. Found: C, 68.87; H, 5.24; N, 17.38.

6-Methyl-2-pivaloylamino-4(3H)-pteridinone (11c): From 6-methylpterin[30] (0.88 g, 4.97 mmol), 4-dimethylaminopyridine (0.07 g, 0.569 mmol) and pivalic anhydride (5 ml) as described above; yield 0.55 g (40%); mp 302-303 °C (decomp); ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.33 (s, 9 H), 2.75 (s, 3 H), 8.38 (bs, 1 H), 8.72 (d, 1 H): Anal. Calcd for $C_{12}H_{15}N_5O_2$: C, 55.16; H, 5.79; N, 26.80. Found: C, 55.14; H, 5.83; N, 27.09.

6,7-Diphenyl-2-pivaloylamino-4-[1'-(1,2,4-triazolyl)]pteridine (12b): To a suspension of **11b** (1.2 g, 3 mmol) and 1,2,4-triazole (0.621 g, 9 mmol) in pyridine (10 ml) was added 4-chlorophenyl phosphorodichloridate (0.75 g, 4.5 mmol). The reaction was then carried out and worked up as described above for the preparation of **8**: yield 0.27 g (20%); mp 232-235 °C; ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.43 (s, 9 H), 7.36-7.49 (m, 6 H), 7.57-7.60 (d, 2 H), 7.69-7.72 (d, 2 H), 8.35 (s, 1 H), 8.64 (bs, 1 H), 10.23 (s, 1 H). This compound was too unstable to give reproducible microanalytical values.

6-Methyl-2-pivaloylamino-4-[1'-(1,2,4-triazolyl)]pteridine (12c): From **11c** (0.26 g, 0.001 mol), 1,2,4-triazole (0.207 g, 0.003 mol), 4-chlorophenyl phosphorodichloridate (0.25 ml, 1.5 mmol) in pyridine (5 ml) at room temperature for 48 h, followed by workup as described above; yield 0.14 g (44%); mp >320 °C. Attempts to purify this

material by column chromatography resulted in the recovery of **11c**; it was, however, pure as judged by nmr; ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.37 (s, 9 H), 2.88 (s, 3 H), 8.31 (s, 1 H), 8.53 (bs, 1 H), 9.08 (s, 1 H), 10.15 (s, 1 H).

4-Amino-6,7-diphenyl-2-pivaloylaminopteridine (13b): From **12b** (0.1 g, 0.22 mmol), aqueous ammonia (5 ml) and dioxane (5 ml) as described above for the preparation of **9**; yield 82 mg (93%); mp 287-288 °C (decomp); ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.37 (s, 9 H), 7.30-7.43 (m, 6 H), 7.51-7.58 (q, 2 H), 7.61 (q, 2 H), 8.27 (bs, 1 H): Anal. Calcd for $C_{23}H_{22}N_6O.1/2\ H_2O$: C, 67.80; H, 5.69; N, 20.62. Found: C, 68.05; H, 5.54; N, 20.32.

4-Amino-6-methyl-2-pivaloylaminopteridine (13c): From **12c** (0.1 g, 0.32 mmol) and aqueous ammonia (3 ml) in dioxane (5 ml) as described above for the preparation of **9**; yield 80 mg (96%); mp 247-248 °C (decomp); ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.33 (s, 9 H), 2.65 (s, 3 H), 6.38 (bs, 1 H), 7.00 (bs, 1 H), 8.18 (bs, 1 H), 8.82 (s, 1 H): Anal. Calcd for $C_{12}H_{16}N_6O$: C, 55.37; H, 6.20; N, 32.29. Found: C, 54.88; H, 6.05; N, 30.66.

2,4-Diamino-6,7-diphenylpteridine (14b): A suspension of **13b** (0.15 g, 0.37 mmol) and aqueous ammonia (2 ml) in dioxane (5 ml) was stirred at room temperature for 72 h, concentrated under reduced pressure, and the yellow precipitate collected by filtration, washed thoroughly with water and dried; yield 80 mg (68%); mp 297-298 °C (lit.,[33] mp 280-283 °C); ^{1}H nmr (300 MHz, $CDCl_3$) δ 7.27 -7.40 (m, 6 H), 7.47 (q, 2 H), 7.54 (q, 2 H).

2,4-Diamino-6-methylpteridine (14c): A solution of **13c** (0.1 g, 0.38 mmol) and aqueous ammonia (5 ml, 30%) in dioxane (5 ml) was stirred at room temperature for 96 h. The bright yellow precipitate was collected by filtration, washed thoroughly with water and dried to give 60 mg (89%) of **14c**; mp >310 °C (lit.,[34] mp 314-320 °C); ^{1}H nmr (300 MHz, Me_2SO-d_6) δ 2.47 (s, 3 H), 6.46 (bs, 2 H), 7.48 (bs 2 H), 8.56 (s, 1 H).

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