Pteridines. 43. A Facile Synthesis of 6-Chloropterin and 2,4-Diamino-6-chloropteridine[1,2]

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6-Chloropterin (**2**) and 2,4-diamino-6-chloropteridine (**5**) have been prepared by reaction of pterin 8-oxide (**1**) and 2,4-diaminopteridine 8-oxide (**4**), respectively, with acetyl chloride. Nucleophilic displacement of the 6-chloro substituent in **2** and **5** occurs smoothly with arylthiols and with alkyl mercaptides to give a series of 6-substituted pterins (**3**) and 2,4-diaminopteridines (**6**), but all attempts to react **2** or **5** with amines failed, even in the presence of reducing agents.

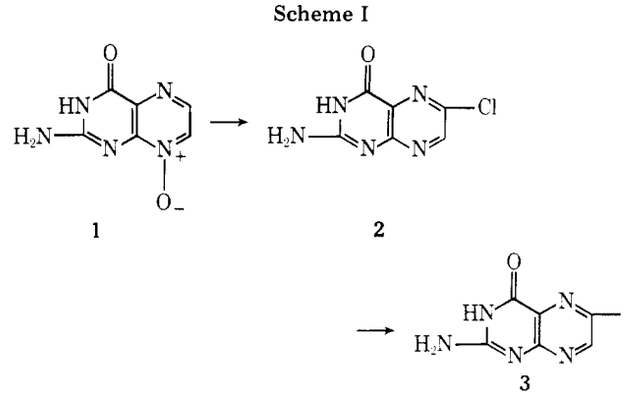
We have described in a recent series of papers[3-15] a new, general and unequivocal route to pteridine derivatives which has been utilized, inter alia, for the synthesis of 6-formylpterin,[15] 6-hydroxymethylpterin,[5] pteroic acid,[5] biopterin,[3,9] asperopterin B,[7] isoxanthopterin,[6] and xanthopterin.[6,12] In a number of these syntheses, pyrazine and pteridine *N*-oxides were utilized as key intermediates in the elaboration of the substituted pyrazine ring found in the final products. The synthesis of xanthopterin by rearrangement of pterin 8-oxide (**1**) is of particular interest, since it represents an unusual β-rearrangement reaction of a heterocyclic *N*-oxide which proceeds, in the above example, in quantitative yield under mild conditions. In the present paper, we describe extensions of this β-rearrangement reaction to the preparation of 6-chloropterin (**2**) and 2,4-diamino-6-chloropteridine (**5**) and some properties of these now readily accessible pteridine intermediates.

Treatment of a finely divided suspension of pterin 8-oxide (**1**) in trifluoroacetic acid with an excess of acetyl chloride at room temperature resulted in a vigorous exothermic reaction which was accompanied by the evolution of copious quantities of hydrogen chloride. 6-Chloropterin (**2**) hydrochloride was isolated in 98% yield upon dilution of the reaction mixture with anhydrous ether. The parent 6-chloropterin could be readily obtained in analytically pure form (91% yield) by dissolution of the hydrochloride in dilute sodium hydroxide followed by acidification with glacial acetic acid.

The above exothermic reaction could be avoided by utilizing previously chilled solvents and reagents. Phosphorus oxychloride could be used in place of acetyl chloride, but the rearrangement reaction was much slower, requiring some 60 h at room temperature. 6-Chloropterin could also be obtained from pterin 8-oxide by reaction in trifluoroacetic acid solution with diphenylimidoyl chloride. The structure of 6-chloropterin (**2**) was readily confirmed by alkaline hydrolysis to xanthopterin and by reaction with sodium methoxide to give 6-methoxypterin (**3a**) identical with an authentic sample prepared from xanthopterin by reaction with methanolic hydrogen chloride.[16]

In view of the ready accessibility of 6-chloropterin, we examined its possible utility as an intermediate for the synthesis of pterins bearing substituents at position 6 which might be introduced by the reaction of nucleophiles with what we anticipated to be a labile imidoyl chloride. An interesting example of such a 6-substituted pterin would be isofolic acid, which has been prepared by a rather laborious route commencing with a 6-chloro-5-nitropyrimidine.[17] To our intense disappointment, all attempts to displace the chloro substituent in 6-chloropterin by amines failed. Ammonia, benzylamine, para-substituted benzylamines (i.e., *p*-carboxybenzylamine), and 3,4-dichlorobenzylamine all failed to react under mild conditions, while the use of more strenuous conditions led only to extensive decomposition. However, 6-

Scheme I



1 **2** **3**

a, R = OCH_3	g, R = SC_6H_4COOH-*p*
b, R = SCH_3	h, R = SC_6H_4Cl-*p*
c, R = SO_2CH_3	i, R = $SO_2C_6H_4Cl$-*p*
d, R = SC_6H_5	j, R = $SC_6H_4CH_3$-*p*
e, R = $SO_2C_6H_5$	k, R = $SO_2C_6H_4CH_3$-*p*
f, R = $SCH_2C_6H_5$	l, R = H

chloropterin reacted smoothly with sodium methyl mercaptide in methanol solution to give 6-methylthiopterin (**3b**), which could be smoothly oxidized to the corresponding sulfone (**3c**) with alkaline potassium permanganate. Despite the fact that methylthio and methylsulfonyl substituents are both considerably more reactive to nucleophilic displacement than halogens,[18] attempted reaction of either substrate with amines led to extensive decomposition, and no 6-substituted aminopterins could be isolated.

6-Chloropterin also reacted smoothly with thiophenol in dimethylformamide solution under reflux to give 6-phenylthiopterin (**3d**) in 85% yield. Under the same conditions, 6-methylsulfonylpterin could be converted in 71% yield to 6-phenylthiopterin. 6-Benzylthiopterin (**3f**) could similarly be prepared either from **2** or from **3c**. Additional 6-arylthiopterins prepared from 6-chloropterin and aryl mercaptans are described under the Experimental Section (see Scheme I).

The failure of 6-chloropterin to react with amines is surprising, since a wide variety of 2-, 4-, 6-, and 7-chloropteridines are known to undergo such displacements.[19-23] It seems evident that the halogen at position 6 in **2** is severely deactivated both by the 2-amino substituent and probably by anion formation in the pyrimidine ring by reaction with the amine. An attempt was made to overcome the deactivating influence of the 2-amino group by initial conversion of 6-chloropterin into its 2-acetyl derivative, but subsequent reaction with amines led only to deacetylation.

Both 6- and 7-chloropteridines, which do not possess deactivating substituents in the pyrimidine ring, react readily with nucleophiles;[21-23] 6-chloropteridine is thought to undergo displacement, at least in part, via a covalent solvate arising under the reaction conditions by addition of the attacking

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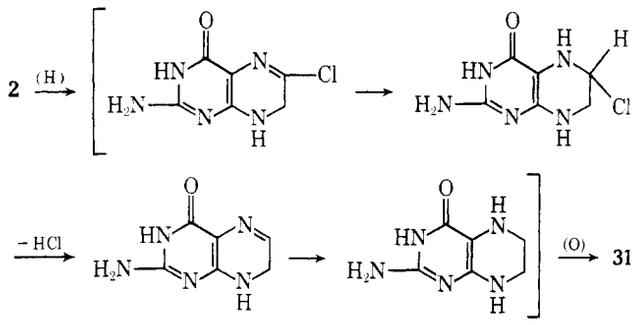
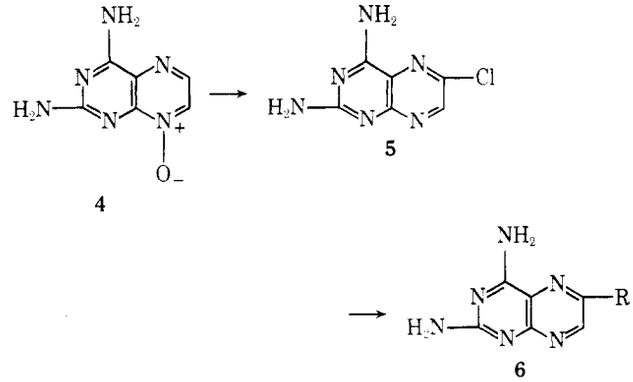
Scheme II



Scheme III



a, R = SC_6H_5
b, R = SC_6H_4Cl-*p*
c, R = $SC_6H_4CH_3$-*p*
d, R = $SC_6H_4C_2H_5$-*o*
e, R = $SC_6H_4C_2H_5$-*p*
f, R = $SC_6H_4C_3H_7$-*n*-*p*
g, R = $SC_6H_4C_4H_9$-*n*-*p*
h, R = SC_6H_4Cl-*o*
i, R = $SC_6H_4C_3H_7$-*i*-*o*
j, R = $SC_6H_4COOC_2H_5$-*p*
k, R = SCH_3
l, R = $SCH_2COOC_2H_5$
m, R = $SCH_2C_6H_5$
n, R = $SCH_2C_6H_4Cl$-*o*
o, R = $SCH_2C_6H_4COOCH_3$-*p*

amine across the 7,8 position.[21] The ease of hyrolysis of 6-amino- and 6-alkylaminopteridines has also been attributed to an initial acid-catalyzed covalent hydration of the 7,8-imine bond.[21,24] We therefore briefly investigated the possible intermediate conversion of 6-chloropterin into 6-chloro-7,8-dihydropterin in the presence of an added nucleophile in the hope that nucleophilic displacement would, by analogy, be facilitated. The reaction of 6-chloropterin with sodium dithionite in aqueous ammonium hydroxide led only to the formation of pterin (**31**) upon oxidative workup. It seems reasonable to suggest that the formation of pterin under these conditions is the result of an initial reduction (as anticipated) of the 7,8 double bond followed, however, by further reduction of the 5,6 imine bond, dehydrohalogenation, and (probably) further reduction to 5,6,7,8-tetrahydropterin; oxidation would then give pterin (see Scheme II). Similarly, 6-chloropterin was reduced with sodium borohydride; oxidative workup again gave pterin. An attempt to convert 6-chloropterin into 6-aminopterin by catalytic reduction in the presence of ammonia also failed;[25] pterin was the only product, in addition to unchanged starting material, isolated upon oxidative work. However, striking apparent substantiation of the enhanced reactivity of the 6-chloro substituent in a 7,8-dihydro derivative was found in the reaction of 6-chloropterin with thiophenol at room temperature in the presence of sodium bisulfite. 6-Phenylthiopterin (**3d**) was formed in 97% yield, and these very mild conditions contrast with the many hours of refluxing required for the same nucleophilic displacement in the absence of added sodium bisulfite.

A parallel can be drawn between our observations with 6-chloropterin and the report by Johnston, Broadbent, and Parish[26] that 2,4,7-triamino-6-methylsulfonylpteridine failed to undergo displacement of the methylsulfonyl group upon treatment with amines (only amine displacement was observed), although the methylsulfonyl substituent was smoothly displaced by reaction with thiophenol or *p*-chlorothiophenol. These results, combined with our own observations, point to a unique role of sulfur nucleophiles in displacement reactions with this type of 6-substituted pteridine derivative. It was attractive to postulate that the facile displacement of 6-chloro- and 6-methylsulfonyl substituents from these pteridine derivatives by sulfur nucleophiles might be occurring via a radical anion process, which has now been well established for some "nucleophilic displacement reactions" involving sulfur nucleophiles and certain halo-substituted π-deficient heterocycles.[27] However, no evidence to support this postulate could be obtained; the above displacement reactions proceed normally and in comparable yields in the presence of a variety of radical trapping agents (azobenzene, hydroquinone, *p*-dinitrobenzene, 1,1,4,4-tetraphenyl-1,3-butadiene).

We have extended the above series of reactions to the preparation of a series of 2,4-diamino-6-arylthio- and 2,4-diamino-6-alkylthiopteridines by utilization of 2,4-diamino-6-chloropteridine (**5**) which was prepared by acetyl chloride/F_3AcOH rearrangement of 2,4-diaminopteridine 8-oxide (**4**).[12] In contrast to the reaction of pterin 8-oxide with acetyl chloride (which was instantaneous at room temperature), this latter reaction required 24 h at room temperature. The crude product was obtained (as its hydrochloride) by precipitation with ether; 2,4-diamino-6-chloropteridine itself was readily prepared by neutralization of a suspension of the salt in water. This compound has been made previously by a six-step sequence of reactions starting from 2-amino-3-carbomethoxypyrazine;[28] the present route, which gives 2,4-diamino-6-chloropteridine (**5**) in only three steps from noncyclic starting materials, is much more convenient.

As was the case with 6-chloropterin, all attempts to convert 2,4-diamino-6-chloropteridine into 6-amino derivatives by reaction either with primary alkylamines or with aromatic amines led only to extensive decomposition. In an independent study, Elslager had recently reported[29] that only dialkylamines reacted satisfactorily with 2,4-diamino-6-chloropteridine. By contrast, however, 2,4-diamino-6-chloropteridine reacts smoothly with substituted thiophenols or sodium alkyl mercaptides (thus paralleling the behavior of 6-chloropterin as described above) (see Scheme III). These latter results appear to be confirmed by recent observations of Elslager.[29]

Experimental Section

6-Chloropterin (2) from Pterin 8-Oxide (1). By Reaction with Acetyl Chloride/F_3AcOH. A suspension of 8.0 g of pterin 8-oxide[6,12] in 40 mL of acetyl chloride was cooled to −60 °C, and 40 mL of trifluoroacetic acid (F_3AcOH), precooled to −60 °C, was added. The mixture was sealed in a glass pressure bottle and gradually warmed to room temperature. The pterin 8-oxide slowly dissolved, and after about 2 min at room temperature a pale yellow solid started to precipitate from the reaction mixture. It was stirred at room temperature for an additional 45 min, the pressure bottle opened (careful! HCl is released), the suspension diluted with dry ether, and the pale yellow solid collected by filtration and dried in vacuo. The yield of 6-chloropterin hydrochloride was 10.4 g (98%).

6-Chloropterin was prepared by dissolution of the above hydrochloride (1.0 g) in 10 mL of 5% cold sodium hydroxide solution. After 15 min of stirring at room temperature, the clear pale yellow solution was filtered and the filtrate acidified with glacial acetic acid. After stirring for 30 min, the resulting suspension was filtered, and the collected solid was washed thoroughly with water and then with acetone and dried at 100 °C (0.01 mm) for 1 h: yield 765 mg (91%); mp >330 °C.

6-Chloropterin could also be prepared from pterin 8-oxide by stirring at room temperature for 60 h in a solution of F_3AcOH with

an excess of phosphorus oxychloride (94% yield) or by stirring at room temperature for 6 h with diphenylimidoyl chloride in F_3AcOH solution (73% yield).

Hydrolysis of 6-Chloropterin to Xanthopterin. A solution of 100 mg of 6-chloropterin in 10 mL of 5% sodium hydroxide solution was heated under gentle reflux for 15 h. The cooled solution was filtered and the filtrate acidified with glacial acetic acid. The orange precipitate which separated was collected by filtration, washed with water and then with acetone, and dried at 100 °C (0.01 mm) for 5 h to give 860 mg (91%) of an orange solid which was shown to be identical (TLC) with an authentic sample of xanthopterin.

6-Methoxypterin (3a). A solution of 500 mg of crude 6-chloropterin hydrochloride in methanolic sodium methoxide (prepared from 500 mg of metallic sodium in 100 mL of methanol) was heated under reflux for 24 h, cooled, and filtered, and the filtrate was evaporated to dryness under reduced pressure. The solid residue was triturated with glacial acetic acid and filtered, and the collected solid was washed thoroughly with water and then with acetone and dried at 100 °C (0.01 mm) for 5 h to give 310 mg (63%) of a bright-orange solid identified as 6-methoxypterin by comparison with an authentic sample prepared by the method of Pfleiderer.[16]

6-Methylthiopterin (3b). A solution of 5.0 g of 6-chloropterin in methanolic sodium methyl mercaptide (prepared from 5 g of sodium in 500 mL of methanol and an excess of methyl mercaptan) was heated under reflux for 24 h. The reaction mixture was then heated an additional 30 min with decolorizing charcoal and filtered, and the filtrate was evaporated to a small volume under reduced pressure. The residue was dissolved in 500 mL of warm water and filtered, and the filtrate was acidified with glacial acetic acid. The pale-yellow solid which separated was collected by filtration, washed well with water and then with acetone, and dried at 100 °C (0.01 mm) for 5 h: yield 5.2 g (98%) of a microcrystalline orange solid; mp > 330 °C.

6-Methylsulfonylpterin (3c). A cold, stirred solution of 100 mg of 6-methylthiopterin in 10 mL of water containing 100 mg of sodium hydroxide was treated with 200 mg of potassium permanganate, and the reaction mixture was stirred at room temperature for 45 min. At the end of this time, TLC analysis showed no residual starting material and the presence of a new, bright-blue fluorescent material. Excess oxidant and precipitated MnO_2 were removed by bubbling in sulfur dioxide until the reaction mixture was colorless. It was then made alkaline by the addition of sodium hydroxide solution, precipitated MnO_2 was removed by filtration, and the filtrate was acidified with glacial acetic acid. The product which precipitated was collected by filtration, washed well with water, ethanol, and finally ether, and dried to give 85 mg (74%) of a colorless solid, mp >330 °C. The analytical sample was prepared by dissolution in DMF followed by precipitation by the addition of diethyl ether.

6-Phenylthiopterin (3d). Method A. From 6-Chloropterin. A hot solution of 500 mg of 6-chloropterin in 200 mL of DMF was treated with 3 mL of thiophenol, and the solution was heated under reflux for 3 h, by which time TLC analysis showed the displacement reaction to be complete. The hot reaction mixture was treated with 100 mg of Norite and 200 mg of Celite, heated for an additional 5 min, and filtered hot. Cooling of the filtrate resulted in the separation of a bright-yellow solid. The mixture was cooled at 0 °C overnight and then filtered to give 0.58 g (85%) of a microcrystalline yellow solid, mp >330 °C.

Method B. From 6-Methylsulfonylpterin. A hot solution of 100 mg of 6-methylsulfonylpterin in 25 mL of DMF was treated with 2.5 mL of thiophenol, and the mixture was heated under reflux for 2 h. It was worked up as described above under method A to give 80 mg (71%) of 6-phenylthiopterin, identical in every respect with the product obtained by method A.

Method C. From 6-Chloropterin in the Presence of Sodium Bisulfite. A suspension of 100 mg of 6-chloropterin in 30 mL of water and 5 mL of THF containing 1 mL of thiophenol and 1 g of sodium bisulfite was stirred at room temperature for 24 h and then filtered. The collected solid was washed thoroughly with water followed by ethanol: yield 133 mg (97%) of 6-phenylthiopterin, identical in every respect with the product obtained by methods A and B as described above.

6-Phenylsulfonylpterin (3e). A solution of 100 mg of 6-phenylthiopterin in 4 mL of glacial acetic acid containing 4 drops of concentrated hydrochloric acid was treated with 0.5 mL of 30% hydrogen peroxide, and the reaction mixture was stirred at room temperature for 30 min. By the end of this time, TLC analysis showed only one compound (not starting material) to be present. The reaction mixture was diluted with 20 mL of water, and the precipitated solid was collected by filtration, washed with ethanol and then with ether, and dried in vacuo at 100 °C to give 94 mg (75%) of a very light yellow solid, mp >330 °C.

6-Benzylthiopterin (3f). Method A. From 6-Chloropterin. A solution of 5.00 g of 6-chloropterin in a methanolic solution of sodium benzyl mercaptide (prepared from 1 g of sodium, 500 mL of methanol, and 6 g of benzyl mercaptan) was heated under reflux for 30 h. At the end of this time, the copious pale-yellow solid which had separated was collected by filtration and washed with methanol and then with ether. The filtrate was heated for an additional 42 h with an additional quantity of sodium benzyl mercaptide (prepared from 1 g of sodium, 50 mL of methanol, and 6 g of benzyl mercaptan). At the end of this time, the reaction was apparently (by TLC) complete. Solvent was removed by evaporation under reduced pressure, the residue was triturated with glacial acetic acid, and the product was collected by filtration. The combined solids were then recrystallized from 1 L of DMF to give 5.93 g (83%) of bright-yellow platelets, mp >330 °C.

Method B. From 6-Methylsulfonylpterin. A hot solution of 100 mg of 6-methylsulfonylpterin in 25 mL of DMF and 2.5 mL of benzyl mercaptan was heated under reflux for 22 h. At the end of this time, TLC analysis indicated that starting material was absent and that only one product had been formed. The bright-orange solution was cooled and filtered, and the collected solid was washed with ether and recrystallized from DMF to give 83 mg (70%) of a bright-orange microcrystalline solid identical in every respect with the material prepared above by method A.

6-(*p*-Carboxyphenylthio)pterin (3 g). Method A. From 6-Chloropterin. A hot solution of 500 mg of 6-chloropterin in 200 mL of DMF containing 3 g of *p*-carboxythiophenol was heated under reflux for 5 h, decolorized with 100 mg of Norite and 200 mg of Celite, and filtered hot. The product crystallized from the hot filtrate upon cooling and was collected by filtration, washed with ethanol and then with ether, and dried in vacuo at 100 °C: yield 0.63 g (80%) of a bright-yellow microcrystalline solid; mp >330 °C.

Method B. From 6-Methylsulfonylpterin. A solution of 100 mg of 6-methylsulfonylpterin and 166 mg of *p*-carboxythiophenol in 15 mL of DMF was heated under reflux for 42 h and evaporated to dryness under reduced pressure, and the filtrate was triturated with methanol and filtered. The collected product was dissolved in DMF (charcoal) and precipitated by the addition of methanol: yield 95 mg (77%) of a bright-yellow solid identical in every respect with the compound prepared as described above by method A.

6-(*p*-Chlorophenylthio)pterin (3h). This compound was prepared as a bright-yellow microcrystalline solid, mp >330 °C, in 88% yield from 500 mg of 6-chloropterin and 3 g of *p*-chlorothiophenol in 200 mL of DMF (reflux for 45 min) and was isolated as described above under the preparation of **3d.**

6-(*p*-Chlorophenylsulfonyl)pterin (3i). This compound was prepared in 94% yield by oxidation of 6-*p*-chlorophenylthiopterin with hydrogen peroxide in a mixture of aqueous acetic acid and concentrated hydrochloric acid as described above under the preparation of **3e.**

6-(*p*-Methylphenylthio)pterin (3j). This compound was prepared in 87% yield from 6-chloropterin and *p*-thiocresol in DMF, as described above under the preparation of **3d.**

6-(*p*-Methylphenylsulfonyl)pterin (3k). This compound was prepared in 90% yield by oxidation of 6-(*p*-methylphenylthio)pterin with hydrogen peroxide in a mixture of aqueous acetic acid and concentrated hydrochloric acid as described above for the preparation of **3e.**

Reduction of 6-Chloropterin in the Presence of Amines. Formation of Pterin (31). A solution of 50 mg of 6-chloropterin in 10 mL of ammonium hydroxide was heated to reflux, a solution of 100 mg of sodium dithionite in 2 mL of water was added dropwise over a period of 1 h, and the reaction mixture was heated under reflux for 8 h. By this time, all starting material had disappeared. The mixture was cooled, the pH was adjusted to 13 with sodium hydroxide, and 200 mg of potassium permanganate dissolved in 10 mL of water was added. After several minutes of stirring, sulfur dioxide was bubbled into the reaction mixture until excess oxidant and precipitated MnO_2 had dissolved. The suspended colorless solid was then collected by filtration, washed well with alcohol and then with ether, and recrystallized from DMF to give 20 mg (50%) of pterin, identical in every respect with an authentic sample.

Repetition of the above experiment utilizing sodium borohydride rather than dithionite as the reducing agent gave identical results.

Pterin was also the sole product formed by catalytic reduction of a solution of the sodium salt of 6-chloropterin in dry methanol in the presence of 10% Pd/C catalyst and an excess of benzylamine, followed by oxidative workup as described above.

2,4-Diamino-6-chloropteridine (5). A suspension of 1.0 g of 2,4-diaminopteridine 8-oxide[6,12] in 5 mL of trifluoroacetic acid and

5 mL of acetyl chloride was stirred at room temperature for 24 h. During this time the starting material slowly dissolved, and the product then started to precipitate from the reaction solution. The resulting mixture was diluted with 200 mL of ether, and the pale-yellow hydrochloride of 2,4-diamino-6-chloropteridine was collected by filtration, washed with ether, dried, and then converted into the free base by dissolution in water followed by neutralization with cold dilute sodium hydroxide. The precipitated solid was collected by filtration, washed thoroughly with water and then with ethanol and ether, and dried: yield 1.0 g (91%); mp >330 °C. The analytical sample was prepared by vacuum sublimation at 250 °C, followed by recrystallization of the sublimate from DMF.

2,4-Diamino-6-phenylthiopteridine (6a). A solution of 2.0 g of 2,4-diamino-6-chloropteridine in a mixture of 50 mL of DMF and 4 g of thiophenol was heated under reflux for 20 min, by which time TLC showed the absence of starting material. The hot reaction solution was diluted with ether, and the precipitated solid was collected by filtration, washed with ether, and dried. Excess acid was removed by trituration with a solution of triethylamine in ether; the solid was again collected by filtration, washed thoroughly with water and then with ethanol, and dried: yield 1.3 g (47%); mp > 330 °C. The analytical sample was prepared by dissolution in DMF followed by precipitation with ether.

The following compounds were prepared in the same manner as described above.

2,4-Diamino-6-(*p*-chlorophenylthio)pteridine (6b): 39% yield; mp >330 °C (after sublimation at 250 °C) (0.05 mm).

2,4-Diamino-6-(*p*-methylphenylthio)pteridine (6c): 34.5% yield; mp >330 °C (from DMF).

2,4-Diamino-6-(*o*-ethylphenylthio)pteridine (6d): 66% yield; mp >330 °C (from aqueous methanol).

2,4-Diamino-6-(*p*-ethylphenylthio)pteridine (6e): 69.5% yield; mp >330 °C (from DMF).

2,4-Diamino-6-[*p*-(*n*-propylphenylthio)]pteridine (6f): 52% yield; mp >330 °C (from DMF).

2,4-Diamino-6-[*p*-(*n*-butylphenylthio)]pteridine (6g): 56.5% yield; mp >330 °C (from DMF).

2,4-Diamino-6-(*o*-chlorophenylthio)pteridine (6h): 65% yield; mp >330 °C (from DMF).

2,4-Diamino-6-(*o*-isopropylphenylthio)pteridine (6i): 74% yield; mp >330 °C (from DMF).

2,4-Diamino-6-(*p*-carbethoxyphenylthio)pteridine (6j): 76% yield; mp >330 °C (from DMF).

2,4-Diamino-6-methylthiopteridine (6k). A solution of 2 g of sodium in 1 L of dry methanol was saturated with methyl mercaptan, and to this solution was added 1 g of 2,4-diamino-6-chloropteridine. The reaction mixture was heated under reflux for 3 h and evaporated to dryness, the residual solid was triturated with water and filtered, and the collected solid was dried and recrystallized from DMF to give 760 mg (72%), mp >300 °C.

2,4-Diamino-6-(carbethoxymethylthio)pteridine (6l). A solution of 0.5 g of 2,4-diamino-6-chloropteridine in sodium methoxide (prepared from 0.5 g of sodium in 660 mL of dry methanol) containing 3 g of ethyl thioglycolate was heated under reflux for 16 h and then worked up as described above: yield 375 mg (51%); mp >300 °C.

2,4-Diamino-6-benzylthiopteridine (6m). This compound was prepared as described above for the 6-(carbethoxymethylthio) derivative except for the substitution of benzyl mercaptan for ethyl thioglycolate: yield 79%; mp >300 °C.

2,4-Diamino-6-(*o*-chlorobenzylthio)pteridine (6n): 54% yield; mp >300 °C.

2,4-Diamino-6-(*p*-carbomethoxybenzylthio)pteridine (6o): 70% yield; mp >300 °C.

Registry No.—**1**, 42346-89-4; 1 HCl, 64507-67-1; **2**, 64507-68-2; **3a**, 64507-69-3; **3b**, 64507-70-6; **3c**, 64507-71-7; **3d**, 58858-76-7; **3e**, 64507-72-8; **3f**, 58858-80-3; **3g**, 64507-73-9; **3h**, 64507-74-0; **3i**, 64507-75-1; **3j**, 58858-78-9; **3k**, 64507-76-2; **3l**, 2236-60-4; **4**, 42346-93-0; **5**, 17714-06-6; **6a**, 58858-77-8; **6b**, 64507-77-3; **6c**, 58858-79-0; **6d**, 64507-78-4; **6e**, 64507-79-5; **6f**, 58858-83-6; **6g**, 64507-80-8; **6h**, 64507-81-9; **6i**, 58858-82-5; **6j**, 64507-64-8; **6k**, 64507-63-7; **6l**, 64507-62-6; **6m**, 58858-81-4, **6n**, 64507-61-5; **6o**, 64535-86-0; acetyl chloride, 75-36-5; xanthopterin, 119-44-8; sodium methoxide, 124-41-4; sodium methyl mercaptide, 5188-07-8; thiophenol, 108-98-5; sodium benzyl mercaptide, 3492-64-6; benzyl mercaptan, 100-53-8; *p*-carboxythiophenol, 1074-36-8; *p*-chlorothiophenol, 106-54-7; *p*-thiocresol, 106-45-6; *o*-ethylthiophenol, 4500-58-7; *p*-ethylthiophenol, 4946-13-8; *p*-propylthiophenol, 4527-44-0; *p*-butylthiophenol, 4946-15-0; *o*-chlorothiophenol, 6320-03-2; *o*-isopropylthiophenol, 6262-87-9; *p*-carbethoxythiophenol, 28276-32-6; methyl mercaptan, 74-93-1; ethyl thioglycolate, 623-51-8; *o*-chlorobenzylthiol, 39718-00-8; *p*-carbomethoxybenzylthiol, 6302-65-4.

References and Notes

(1) For the previous paper in this series, see: E. C. Taylor and J. V. Berrier, *Heterocycles*, **6**, 449 (1977).
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