Pteridines. XXXVI. Syntheses of Xanthopterin and Isoxanthopterin. Application of *N*-Oxide Chemistry to Highly Functionalized Pyrazines and Pteridines[1,2]

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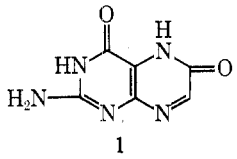
A number of new synthetic routes to xanthopterin (1) and isoxanthopterin (2) are described. Thus, 2 has been prepared from 2-amino-3-cyanopyrazine 1-oxide (7) by $POCl_3$ chlorination–deoxygenation to 2-amino-3-cyano-6-chloropyrazine (10), condensation with guanidine to give 2,4-diamino-7-methoxypteridine (11), and alkaline hydrolysis. Alternatively, 2 has been prepared from 2-amino-3-ethoxycarbonylpyrazine 1-oxide (13) by Ac_2O/AcOH rearrangement to 2-amino-3-ethoxycarbonyl-6(1*H*)-pyrazinone (15) followed by annelation of the pyrimidine ring with guanidine. Finally, 2 was readily prepared from 2,4-diaminopteridine 8-oxide (25) by reaction with pyrrolidine to give 2,4-diamino-7-(1-pyrrolidino)pteridine (26), followed by alkaline hydrolysis. Xanthopterin (1) has also been prepared by a number of new routes which use the *N*-oxide functionality for the selective positioning of appropriate substituents in the pyrazine ring. Thus, 2-amino-3-cyanopyrazine 4-oxide (17) (prepared from the isomeric 1-oxide by oxidation to the 1,4-dioxide 16 followed by selective monodeoxygenation with PCl_3) was converted to 1 by $POCl_3$/DMF deoxygenation–chlorination to give 2-amino-3-cyano-5-chloropyrazine (19), cyclization with guanidine to 2,4-diamino-6-methoxypteridine (20), and finally alkaline hydrolysis. The method of choice for the synthesis of pure xanthopterin (1), however, involves the selective, *quantitative* isomerization of pterin 8-oxide (21) with trifluoroacetic anhydride–trifluoroacetic acid. The mechanism of this remarkable *N*-oxide rearrangement is discussed, and experiments with a number of model pyrazines and pteridines are described.

The isolation, structural elucidation, and eventual synthesis of xanthopterin (1), isoxanthopterin (2), and their common oxidation product, leucopterin (3), constitute a



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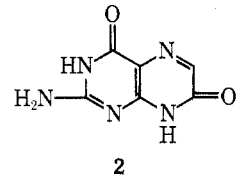

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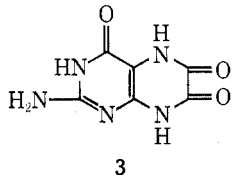

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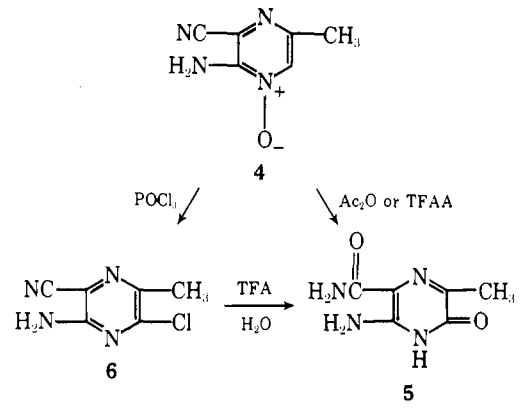
milestone in the early development of the field of pteridine chemistry.[3-5] These compounds are not only widespread insect pigments, but are also found in the skin and eyes of various fish and amphibia and have been identified as normal constituents of human urine.[6,7] The early suggestion that xanthopterin was in some way related to nutritional anemia has been well documented,[8] as has its growth-inhibiting effect on malignant tumors in mice.[9] Recent reports detailing antitumor activity of both xanthopterin and isoxanthopterin[10] and reconfirming the phenomenon of xanthopterin-stimulated renal mytosis[11] testify to the increasing attention now being directed to the importance of these naturally occurring pigments.

Both 1 and 2 have been synthesized previously by various adaptations of the conventional Isay-type synthesis of pteridines involving final construction of the pyrazine ring from preformed 2,4,5-triamino-6-hydroxypyrimidine. In every case, however, mixtures of products were obtained from which pure (?) 1 and 2 were available only with great difficulty. These conventional syntheses have been reviewed.[12] In view of the resurgence of interest in the physiological activity of these naturally occurring pigments, coupled with the deficiencies of available synthetic procedures, it is clear that simple, unequivocal synthetic routes leading to pure xanthopterin (1) and isoxanthopterin (2) would be of considerable contemporary interest and utility.

We have recently described a new synthetic approach to pteridines which involves the condensation of an α-aminonitrile with an α-oximinocarbonyl compound.[13-16] The resulting 2-aminopyrazine 1-oxides, substituted with a carboxamido, ester, or nitrile grouping at position 3, were then converted to pteridine 8-oxides by appropriate cyclization procedures. Since the ultimate objective in all of our previous syntheses was the unequivocal positioning of substituents at positions 6 and/or 7 in the final pteridine, the *N*-oxide grouping was of no intrinsic interest and was therefore removed by an appropriate deoxygenation procedure either at the pyrazine or pteridine stage. However, the widely exploited capability of the *N*-oxide grouping to facilitate both electrophilic substitution and nucleophilic displacement reactions in heterocycles,[17] coupled with the ready accessibility of both pyrazine and pteridine *N*-oxides by the above cyclization procedures, prompted us to examine the chemistry of these highly functionalized heterocyclic *N*-oxides in the hope that we could exploit them as synthetic intermediates for the facile and *regiospecific* introduction of substituents into the pyrazine and pteridine ring systems. The present paper describes the results of this investigation, which have led to several new syntheses of both xanthopterin (1) and isoxanthopterin (2) and have uncovered some novel *N*-oxide chemistry.

In order to examine the possible applicability of conventional *N*-oxide chemistry to highly functionalized pyrazine 1-oxides, the initial substrate chosen for study was the readily accessible 2-amino-3-cyano-5-methylpyrazine 1-oxide (4), available by condensation of aminomalononitrile tosylate with α-oximinoacetone.[14] Treatment of this pyrazine 1-oxide with a mixture of trifluoroacetic acid and trifluoroacetic anhydride (TFA–TFAA), or with acetic anhydride, resulted in a normal Katada rearrangement (oxygenation of the carbon α to the ring nitrogen with concomitant loss of the *N*-oxide group).[18] Conditions for the rearrangement were somewhat severe, however, and hydrolysis of the nitrile group also occurred, giving 5. It was also possible to carry out the normal phosphorus oxychloride chlorination–

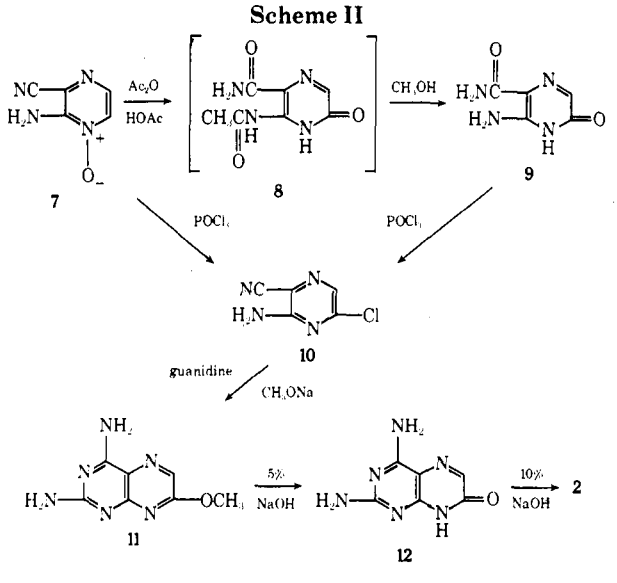
Scheme I



deoxygenation reaction on **4** to give 2-amino-3-cyano-5-methyl-6-chloropyrazine (**6**) in good yield. Hydrolysis of **6** with aqueous trifluoroacetic acid provided an alternate route to **5**. These reactions are summarized in Scheme I.

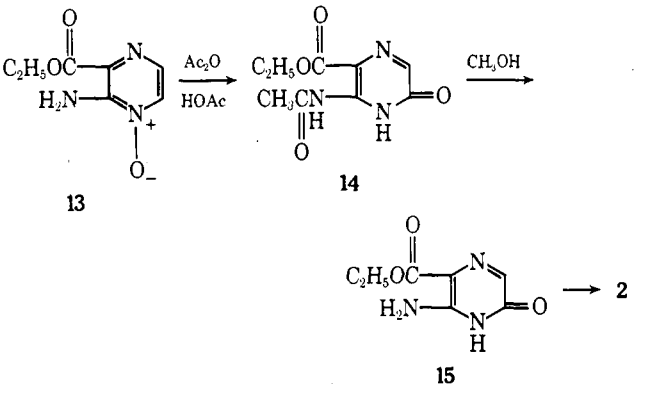
Encouraged by these preliminary results, attention was next turned to chemical transformations of 2-amino-3-cyanopyrazine 1-oxide (**7**)[14] in the hope that analogous conversions, if they could be effected, would lead to intermediates capable of cyclization to isoxanthopterin. These expectations were confirmed. Thus, treatment of **7** with acetic anhydride and acetic acid resulted in the formation of 2-acetamido-3-carbamoyl-6(1*H*)-pyrazinone (**8**), which was readily deacetylated to **9** by heating in methanol. Also, treatment of **7** with phosphorus oxychloride gave 2-amino-3-cyano-6-chloropyrazine (**10**), identical with the compound prepared from **9** with phosphorus oxychloride. The position of the chloro substituent in **10** was confirmed by its conversion to isoxanthopterin as follows. Treatment with guanidine in methanolic sodium methoxide gave 2,4-diamino-7-methoxypteridine (**11**) by simultaneous pyrimidine ring annelation and chloride displacement. Hydrolysis of **11** with 5% aqueous sodium hydroxide under reflux for 10 min then gave 2,4-diamino-7(8*H*)-pteridinone (**12**), which in turn could be hydrolyzed under more vigorous conditions (10% aqueous sodium hydroxide under reflux for 20 hr) to isoxanthopterin (**2**), identical with an authentic sample (see Scheme II).

Scheme II



An analogous Katada rearrangement was successfully effected with 2-amino-3-ethoxycarbonylpyrazine 1-oxide (**13**). Thus, treatment of **13** with a mixture of acetic anhydride and acetic acid gave 2-acetamido-3-ethoxycarbonyl-6(1*H*)-pyrazinone (**14**). Once again, the position of the new oxygen substituent on the pyrazine ring was confirmed by conversion of this compound to isoxanthopterin (**2**) by initial deacetylation to **15** with methanol, followed by cyclization with guanidine in refluxing DMF. These conversions are summarized in Scheme III.

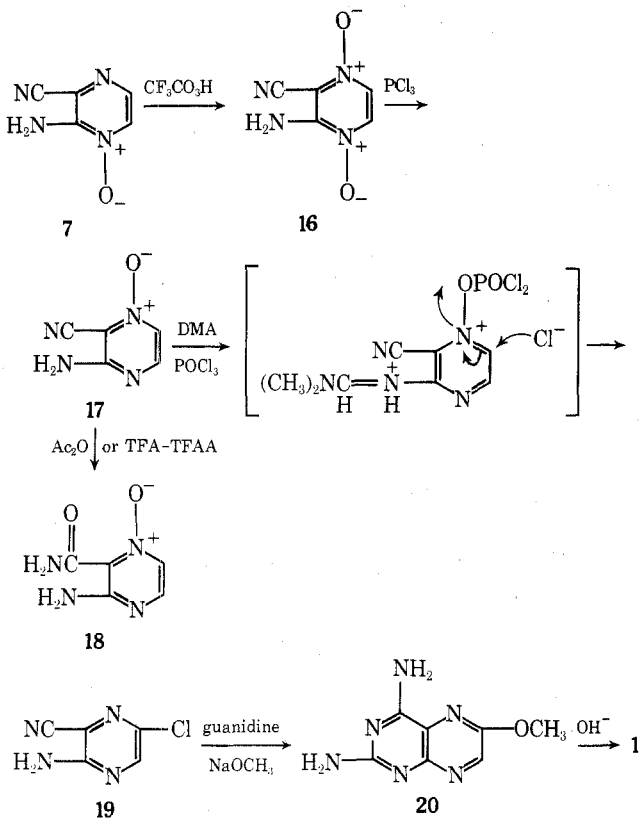
Scheme III



It would appear from the above results that conventional *N*-oxide chemistry is indeed applicable to these highly functionalized pyrazine 1-oxides, which may, as a consequence, be utilized for the introduction of substituents into the pyrazine ring α to the *N*-oxide grouping.

An extension of these rearrangement reactions to pyrazine 4-oxides should provide an attractive route to xanthopterin (**1**) and related 6-substituted pteridines. The requisite 2-amino-3-cyanopyrazine 4-oxide (**17**), although not available either by direct cyclization or by selective oxidation of 2-amino-3-cyanopyrazine, was successfully prepared by oxidation of **7** to the 1,4-dioxide **16** with pertrifluoroacetic acid, followed by selective monodeoxygenation with phosphorus trichloride. The chemical properties of this pyrazine *N*-oxide, however, proved to be strikingly different from those of its isomer (**8**). Thus, attempted rearrangement of **17** either with TFA–TFAA or with acetic anhydride, was unsuccessful; the only product isolated was the carboxamide **18** resulting from hydration of the nitrile substituent. The failure of the Katada rearrangement in this case, however, is not unreasonable, since the position of nucleophilic attack by acetate or trifluoroacetate anion is now para to the 2-amino substituent, whereas in the rearrangement of **7** to the 6-pyrazinone **9** the position of nucleophilic attack was activated by the para-situated nitrile (or carboxamide) grouping. This reasoning was reinforced by the observation that **17** could be smoothly converted to 2-amino-3-cyano-5-chloropyrazine (**19**) with phosphorus oxychloride in DMF. The success of this latter conversion presumably is due to the intermediate formation of a 2-dimethylaminomethylenamino derivative (a well-known reaction of heterocyclic amino groups with phosphorus oxychloride in DMF),[19] which, because of its greatly increased basicity, is undoubtedly protonated under the reaction conditions, thus activating the 5 position to nucleophilic addition. The product **19** was identical with an authentic sample prepared from 2-amino-3-ethoxycarbonylpyrazine by chlorination, aminolysis, and dehydration.[20] Compound **19** was then converted to xanthopterin (**1**) by reaction with guanidine in methanolic sodium methoxide to give 2,4-diamino-6-methoxypteridine (**20**) in a reaction analogous to that previously carried out on **10** (see Scheme II). Subsequent base hydrolysis of **20** then gave **1** in excellent yield. These reactions are summarized in Scheme IV.

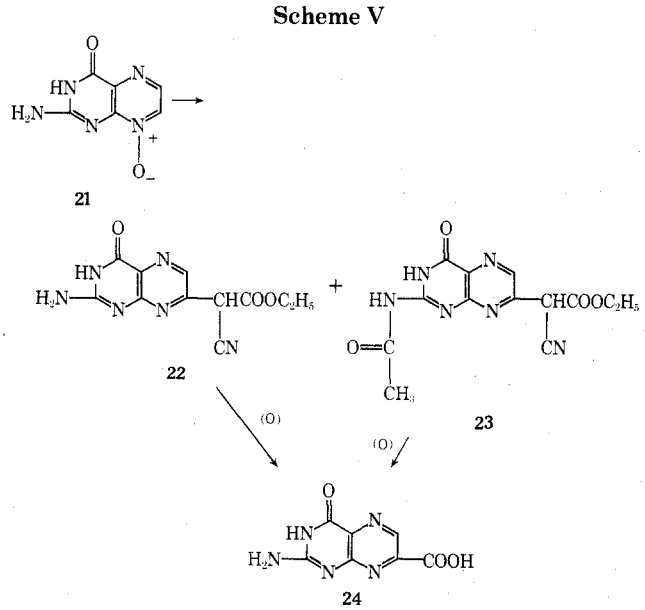
Scheme IV



Having thus achieved some measure of success in chemical transformations of these highly functionalized pyrazine *N*-oxides, attention was then turned to the possible synthetic utility of pteridine 8-oxides in the anticipation that analogous transformations leading to 7-substituted pteridines would be possible. Initial experiments, indeed, confirmed this expectation, but they also underscored the danger of direct extrapolation of results from one ring system to the other.

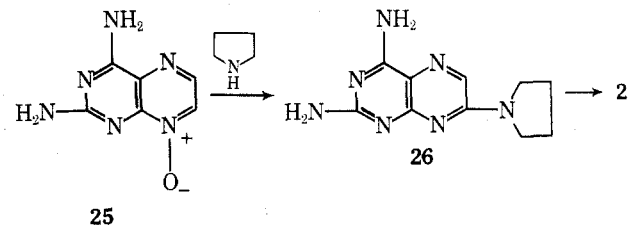
Treatment of a suspension of pterin 8-oxide (**21**) in anhydrous HMPA with acetic anhydride and ethyl cyanoacetate gave a mixture of **22** and **23** (see Scheme V). Attachment of the carbon side chain to position 7 of the pteridine nucleus was readily confirmed by the conversion of both **22** and **23** to pterin-7-carboxylic acid (**24**) by oxidation with potassium permanganate. This conversion of **21** to the 7-substituted pterins **22** and **23** thus corresponds to a normal *N*-oxide rearrangement utilizing an active methylene compound as the nucleophile, which results in the formation of a new carbon–carbon bond at a position α to the ring nitrogen.[21]

Scheme V



Similarly, it has also been possible to convert a pteridine 8-oxide into isoxanthopterin (**2**) as follows. 2,4-Diaminopteridine 8-oxide (**25**)[14] on treatment with neat pyrrolidine at 90° for 16 hr gave 2,4-diamino-7-(1-pyrrolidino)pteridine (**26**), which was then converted in a single step to **2** by hydrolysis with 10% aqueous sodium hydroxide (Scheme VI).

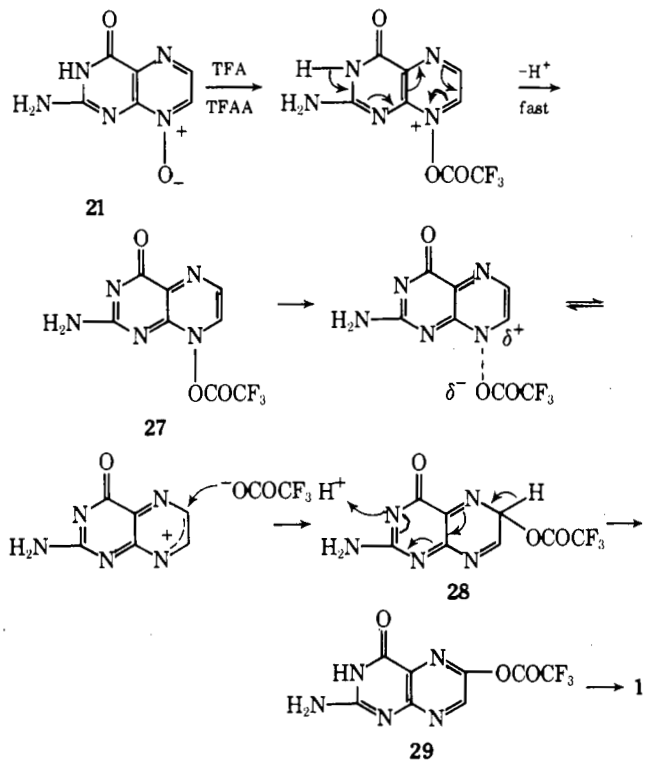
Scheme VI



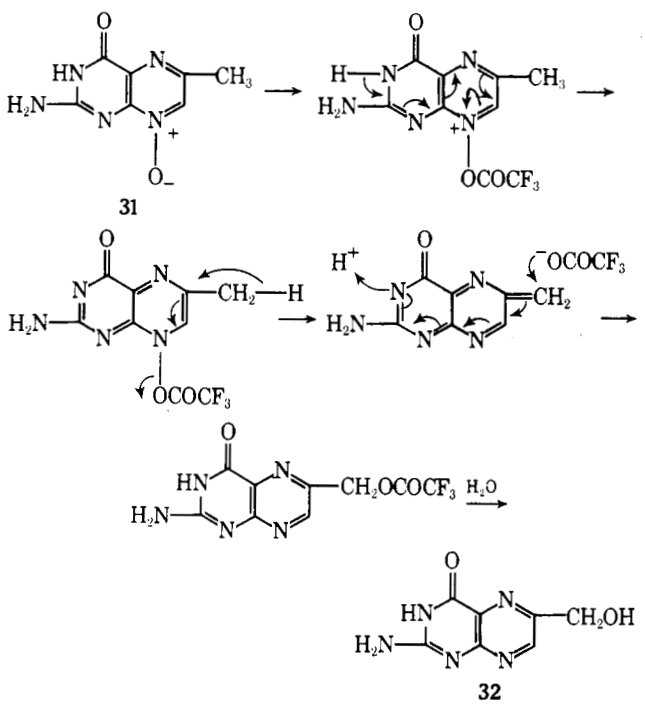
Until this point, it appeared that the chemistry of pteridine *N*-oxides was analogous to the conventional chemistry described above for the highly functionalized pyrazine *N*-oxides. It did not seem unreasonable, therefore, to expect that pterin 8-oxide (**21**) should undergo a normal Katada rearrangement with acetic anhydride (or related reagents) to give isoxanthopterin (**2**). However, this was not to be the case. No reaction of **21** either with acetic anhydride or with mixtures of acetic anhydride and acetic acid could be detected even upon prolonged (48 hr) reflux. Additionally, no reaction was observed with acetyl chloride, dichloroacetyl chloride, or benzoyl chloride in DMF or pyridine under a wide range of reaction conditions. However, **21** dissolved almost immediately in a 50:50 mixture of TFA–TFAA at 50° to give a bright yellow solution. The NMR spectrum of an aliquot of this yellow solution consisted of a single, sharp singlet at δ 8.60, and there was no trace of starting material (**21** exhibits two well-resolved doublets at δ 8.35 and 8.50, J = 4.5 Hz). When **21** was dissolved in TFA–TFAA at room temperature, the initial NMR spectrum of the reaction mixture showed both the resolved doublets of **21** and the above singlet. Over the course of 3–4 hr, however, the absorptions due to **21** slowly disappeared, with concurrent strengthening of the singlet at δ 8.60, until the final spectrum was identical with that obtained from the reaction of **21** with TFA–TFAA at 50°. The reaction mixture was worked up in the usual manner (evaporation of solvents followed by basic hydrolysis) to give, to our intense surprise, *xanthopterin* (**1**), not isoxanthopterin. *N*-Oxide rearrangements to a position β to the ring nitrogen are known in heterocyclic chemistry, although mixtures of the normal α-rearrangement products along with the abnormal β-rearrangement products are usually obtained.[22] The above conversion of **21** to **1**, which takes place in essentially quantitative yield, is most unusual in that it gives no trace of the "normal" product. It now represents the method of choice for the preparation of pure xanthopterin (**1**).

It seems probable that this unexpected conversion proceeds via intermediate **27**, which undergoes an allylic rearrangement of the trifluoroacetoxy group as shown (see Scheme VII). The extreme ease of this rearrangement may well be due to substantial *N*-trifluoroacetoxy bond heterolysis in the transition state leading from **27** to **28**, and its ir-

Scheme VII



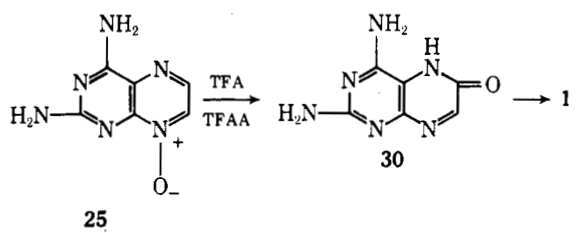
Scheme IX



reversibility may reasonably be attributed to the formation of a C–O bond at the expense of the much weaker N–O bond in **27**. Such a reaction pathway appears to be general in allylic rearrangements involving highly stabilized leaving groups, and an analogous pathway is well documented for other β-rearrangement reactions of heterocyclic *N*-oxides.[22]

2,4-Diaminopteridine 8-oxide (**25**) followed a parallel rearrangement pathway, but forcing conditions (refluxing TFA–TFAA, 5 hr) were required. The product of rearrangement was 2,4-diamino-6(5*H*)-pteridinone (**30**), alkaline hydrolysis of which provided an alternative although less satisfactory route to xanthopterin (**1**) (see Scheme VIII). Significantly, neither 2,4-diamino-6-methylpteridine

Scheme VIII



8-oxide nor 6-methylpterin 8-oxide (**31**) (in which the position β to the *N*-oxide is effectively blocked) could be induced to rearrange "normally" under any conditions; instead, they suffered mainly rapid decomposition to intractable tars. However, careful chromatography of the decomposition products from **31**, although revealing no trace of the product expected from a normal Katada rearrangement, did establish the presence of 6-hydroxymethylpterin (**32**).[23] The formation of this material is reasonably interpreted as shown in Scheme IX.

For reasons which are not clear at this point, 2,4-diaminopteridine 8-oxide (**25**), in contrast to its pyrazine precursor (**8**), proved to be completely unreactive toward phosphorus oxychloride–DMF. Similarly, 2,4-diamino-6-methylpteridine 8-oxide was also recovered unchanged under the same conditions. By contrast, however, 2,4-diamino-6-oximinomethylpteridine 8-oxide has been shown[15] to undergo a facile normal chlorination–deoxygenation reaction (accompanied by dehydration of the oximino grouping) to give 2,4-diamino-6-cyano-7-chloropteridine. It would appear that the presence of an electron-withdrawing group at position 6 is required for the phosphorus oxychloride chlorination–deoxygenation reaction of pteridine 8-oxides.

It is apparent from the above results that conventional *N*-oxide chemistry can be applied to highly functionalized pyrazine and pteridine *N*-oxides, but that subtle changes in structure, even at sites remote from the reaction center, can lead to drastic changes both in the rate and in the mode of the ensuing reactions. More detailed mechanistic studies of these transformations are in progress, and the inherent synthetic potentialities involved are currently under active exploration.

Experimental Section

2-Amino-3-carbamoyl-5-methyl-6(1*H*)-pyrazinone (5). Method A. Rearrangement of 2-Amino-3-cyano-5-methylpyrazine 1-Oxide (4) with Trifluoroacetic Acid–Trifluoroacetic Anhydride (TFA–TFAA). A solution of 1.0 g of **4** in 20 ml of TFA was treated with 5 ml of TFAA and stirred under reflux for 90 min. The reaction mixture was then cooled and poured into 150 ml of water at 0°, and the separated solid was collected by filtration to give 0.8 g (44%) of 2-trifluoroacetamido-3-carbamoyl-5-methyl-6(1*H*)-pyrazinone. The analytical sample was prepared by recrystallization from DMF–$CHCl_3$: mp 280–290° dec; NMR (CF_3COOH) δ 1.90 (3, s, C_5CH_3).

Anal. Calcd for $C_8H_7F_3N_4O_3$: C, 36.37; H, 2.67; N, 21.21. Found: C, 36.39; H, 2.90; N, 20.94.

A suspension of the crude 2-trifluoroacetamido-3-carbamoyl-5-methyl-6(1*H*)-pyrazinone above was refluxed for 2 hr in 100 ml of methanol. Evaporation of the solvent to a small volume followed by cooling and subsequent filtration afforded 0.4 g (85%) of 2-amino-3-carbamoyl-5-methyl-6(1*H*)-pyrazinone (**5**): mp 276–278°; NMR (CF_3COOH) δ 1.96 (3, s, C_5CH_3).

Anal. Calcd for $C_6H_8N_4O_2$: C, 42.85; H, 4.80; N, 33.32. Found: C, 42.72; H, 4.76; N, 33.55.

Method B. Rearrangement of 2-Amino-3-cyano-5-methylpyrazine 1-Oxide (4) with Acetic Acid–Acetic Anhydride. A solution of 0.5 g of **4** in 10 ml of acetic acid was treated with 7 ml of acetic anhydride and refluxed for 90 min. The reaction mixture

was then taken to dryness and any remaining acetic anhydride was destroyed by the addition of a small amount of ethanol and evaporation. The residue was recrystallized from ethanol to give 0.4 g (64%) of 2-acetamido-3-carbamoyl-5-methyl-6(1*H*)-pyrazinone: mp 238–239°; NMR (CF_3COOH) δ 2.01 (3, s, acetyl), 1.99 (3, s, C_5 CH_3).

Anal. Calcd for $C_8H_{10}N_4O_3$: C, 45.71; H, 4.80; N, 26.66. Found: C, 45.53; H, 4.76; N, 26.35.

A suspension of the crude 2-acetamido-3-carbamoyl-5-methyl-6(1*H*)-pyrazinone above in 30 ml of methanol was refluxed for 3 days. The resulting solution was cooled and the crystals which separated were collected by filtration to give 0.15 g (40%) of **5**, mp 275–276°, identical with the material prepared by method A above.

2-Amino-3-cyano-5-methyl-6-chloropyrazine (6). A suspension of 3.0 g of 2-amino-3-cyano-5-methylpyrazine 1-oxide (**4**) in 30 ml of DMF was treated dropwise with 6.0 ml of phosphorus oxychloride, maintaining the temperature between 80 and 90° (cold water bath). After addition was complete, the reaction mixture was stirred at 80–90° in a preheated oil bath for 10 min and then poured into 300 ml of water at 0°. The resulting solution was allowed to stand overnight before filtering and drying to give 3.0 g of crude product. Recrystallization from ethanol afforded 2.5 g (74%) of **6**: mp 228–229°; NMR (CF_3COOH) δ 2.07 (3, s, C_5 CH_3).

Anal. Calcd for $C_6H_5N_4Cl$: C, 42.74; H, 2.99; N, 33.23; Cl, 21.03. Found: C, 42.87; H, 2.89; N, 33.44; Cl, 21.23.

2-Amino-3-carbamoyl-6(1*H*)-pyrazinone (9). A suspension of 5.0 g of 2-amino-3-cyanopyrazine 1-oxide (**7**)[14] in 100 ml of acetic acid and 68 ml of acetic anhydride was refluxed for 2 hr. The reaction mixture was then evaporated to dryness under reduced pressure and any remaining acetic anhydride was destroyed by the addition of a small volume of ethanol followed by evaporation to dryness. Recrystallization of the residue from methanol afforded 4.7 g (65%) of 2-acetamido-3-carbamoyl-6(1*H*)-pyrazinone (**8**), mp 257–259° dec. The analytical sample, recrystallized twice from ethanol, melted at 258–259° dec, NMR (CF_3COOH) δ 7.61 (1, s, H_5), 2.01 (3, s, acetyl).

Anal. Calcd for $C_7H_8N_4O_3$: C, 42.86; H, 4.11; N, 28.56. Found: C, 42.67; H, 4.02; N, 28.70.

A suspension of 3.50 g of the above 2-acetamido-3-carbamoyl-6(1*H*)-pyrazinone in 600 ml of methanol was heated under reflux for 4.5 days. The reaction mixture was then treated with animal carbon, filtered, and concentrated to a small volume to give 2.66 g (96.5%) of **9**: mp 338°; NMR (CF_3COOH) δ 7.22 (1, s, H_5).

Anal. Calcd for $C_5H_6N_4O_2$: C, 38.96; H, 3.92; N, 36.25. Found: C, 39.04; H, 4.02; N, 36.35.

2-Amino-3-cyano-6-chloropyrazine (10). Method A. A suspension of 3.0 g of 2-amino-3-cyanopyrazine 1-oxide (**7**)[14] in 30 ml of DMF was stirred in an ice–water bath while 6.0 ml of phosphorus oxychloride was added dropwise between 5 and 10°. After addition was complete the reaction mixture was stirred for a further 16 hr at room temperature and then poured into ice water. After standing for 24 hr, the aqueous suspension was filtered and the residue was recrystallized from ethyl acetate–petroleum ether (bp 60–80°) to give 1.8 g (52%) of **10**. The analytical sample, recrystallized from ethanol, melted at 194–196°, NMR (CF_3COOH) δ 7.59 (1, s, H_5).

Anal. Calcd for $C_5H_3N_4Cl$: C, 38.85; H, 1.95; N, 36.25; Cl, 22.94. Found: C, 38.70; H, 1.95; N, 36.50; Cl, 22.85.

Method B. A suspension of 0.3 g of 2-amino-3-carbamoyl-6(1*H*)-pyrazinone (**9**) in 50 ml of DMF was stirred in an ice–water bath while 0.6 ml of phosphorus oxychloride was added dropwise between 5 and 10°. After addition was complete the reaction mixture was stirred at 70–80° for 80 min, and then at room temperature overnight. A brown precipitate was produced which was recovered by filtration, washed with water, and dried. Recrystallization from ethyl acetate–petroleum ether afforded 0.07 g (23%) of **10**, mp 192–194°, which was identical in all respects with the sample prepared by method A above.

2,4-Diamino-7-methoxypteridine (11). To a methanolic solution of guanidine (prepared from 1.2 g of sodium in 80 ml of methanol and 1.9 g of guanidine hydrochloride) was added 1.4 g of 2-amino-3-cyano-6-chloropyrazine (**10**). The reaction mixture was refluxed for 17 hr, cooled, and filtered to give 1.4 g (74%) of **11** as a yellow solid. Recrystallization from methanol gave 1.3 g of colorless crystals: mp 240–250°; NMR (DMSO-d_6) δ 7.88 (1, s, H_6), 3.86 (3, s, $-OCH_3$); uv λ_{max} (0.1 *N* HCl) 336 nm (log ε 4.13), 332 (4.16), 325 (4.19), 248 (4.23), 221 (4.13).

Anal. Calcd for $C_7H_8N_6O$: C, 43.75; H, 4.20; N, 43.73. Found: C, 43.92; H, 4.32; N, 43.79.

2,4-Diamino-7(8*H*)-pteridinone (12). A suspension of 0.25 g of 2,4-diamino-7-methoxypteridine (**11**) in 20 ml of 5% aqueous sodium hydroxide was stirred under reflux for 10 min, after which time all material had dissolved. Cooling followed by neutralization with 6 *N* HCl afforded an off-white solid which was recovered by filtration, redissolved in dilute aqueous sodium hydroxide solution, filtered (animal carbon), and reprecipitated at pH 4 to give 0.23 g (99%) of **12**. The sample was analytically pure as obtained: mp >400°; NMR (CF_3COOH) δ 7.68 (1, s, H_6); uv λ_{max} (0.1 *N* NaOH) 357 nm (sh, log ε 4.06), 345 (4.10), 280 (sh, 3.94), 263 (4.18), 219 (4.52).

Anal. Calcd for $C_6H_6N_6O$: C, 40.45; H, 3.39; N, 47.18. Found: C, 40.21; H, 3.19; N, 47.06.

Isoxanthopterin (2) by Hydrolysis of 2,4-Diamino-7-methoxypteridine (12). A suspension of 0.30 g of **12** in 20 ml of 10% aqueous sodium hydroxide was stirred under reflux for 20 hr. The reaction mixture was then diluted with 30 ml of water, decolorized with animal carbon, filtered, and adjusted to pH 4 with 6 *N* hydrochloric acid to give a white, crystalline solid. A second recovery of the precipitated solid from dilute NaOH solution by addition of HCl to pH 4 afforded 0.23 g (82%) of analytically pure isoxanthopterin, mp >300°, identical in all respects with an authentic sample.

2-Amino-3-ethoxycarbonylpyrazine 1-Oxide (13). A suspension of 17.7 g of finely powdered glyoxime and 59.4 g of ethyl α-aminocyanoacetate tosyl salt in 355 ml of water was stirred at room temperature for 45 hr. The resulting solution was extracted several times with chloroform, and the combined extracts were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to give a yellow, crystalline solid. Recrystallization from ethanol then gave 6.1 g (17%) of **13**: mp 194–195°; NMR (CF_3COOH) δ 8.37 (1, d), 7.82 (1, d, H_5, H_6), 4.23 (2, q), 1.02 (3, t, OC_2H_5).

Anal. Calcd for $C_7H_9N_3O_3$: C, 45.90; H, 4.95; N, 22.94. Found: C, 46.18; H, 5.07; N, 23.06.

2-Acetamido-3-ethoxycarbonyl-6(1*H*)-pyrazinone (14). A suspension of 5.0 g of 2-amino-3-ethoxycarbonylpyrazine 1-oxide (**13**) in 66 ml of acetic anhydride and 100 ml of acetic acid was refluxed with stirring for 1.5 hr. The reaction mixture was then taken to dryness and treated with ethanol in the usual manner to give a brown solid after evaporation. Recrystallization from ethanol gave 3.7 g (60%) of **14**, mp 157–159°. The analytical sample, mp 158–160°, was recrystallized from ethanol: NMR (CF_3COOH) δ 7.73 (1, s, H_5), 4.08 (2, q), 0.99 (3, t, $-OC_2H_5$), 2.01 (3, s, acetyl CH_3).

Anal. Calcd for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.92; N, 18.66. Found: C, 47.96; H, 4.93; N, 18.96.

2-Amino-3-ethoxycarbonyl-6(1*H*)-pyrazinone (15). A suspension of 0.48 g of 2-acetamido-3-ethoxycarbonyl-6(1*H*)-pyrazinone (**14**) in 50 ml of ethanol was refluxed for 18 hr. The reaction mixture was then treated with animal carbon, filtered, and evaporated to dryness. Recrystallization of the residue from ethanol afforded 0.32 g (82%) of **15**, mp 226–228°. The analytical sample, recrystallized from ethanol, melted at 228–230°: NMR (CF_3COOH) δ 7.15 (1, s, H_5), 4.11 (2, q), 0.98 (3, t, $-OC_2H_5$).

Anal. Calcd for $C_7H_9N_3O_3$: C, 45.09; H, 4.95; N, 22.94. Found: C, 45.94; H, 4.87; N, 23.12.

Isoxanthopterin (2) by Cyclization of 2-Amino-3-ethoxycarbonyl-6(1*H*)-pyrazinone (15). To a methanolic solution of guanidine (prepared from 0.11 g of sodium in 20 ml of methanol and 0.48 g of guanidine hydrochloride) was added 0.30 g of **15** and the reaction mixture was refluxed with stirring for 1 hr. The solvent was then removed under reduced pressure and 10 ml of DMF was added to the residue. Refluxing for an additional 4.5 hr gave crude isoxanthopterin as an off-white precipitate. This was purified by precipitation from an alkaline solution with HCl in the usual manner to give 0.04 g (14%) of **2**, identical in all respects with an authentic sample.

2-Amino-3-cyanopyrazine 1,4-Dioxide (16). To a stirred, ice-cold solution of 12 ml of 30% hydrogen peroxide in 100 ml of trifluoroacetic acid was added 5.0 g of 2-amino-3-cyanopyrazine 1-oxide (**7**). Stirring at room temperature was then continued until the solution showed a negative starch–iodide reaction (ca. 18 hr). A further 8 ml of 30% hydrogen peroxide was then added at 0°, and stirring was continued a further 24 hr (starch–iodide test positive). The solvent was removed under reduced pressure below 40° to give a yellow, semicrystalline solid which was triturated with ice-cold ethanol and filtered after overnight refrigeration to give 2.9 g of crude **16**: mp 255° dec; NMR (CF_3COOH) δ 8.07 (1, d), 7.44 (1, d, H_5, H_6).

Anal. Calcd for $C_5H_4N_4O_2$: C, 39.48; H, 2.65; N, 36.84. Found: C, 39.57; H, 2.58; N, 37.00.

2-Amino-3-cyanopyrazine 4-Oxide (17). To an ice-cold suspension of 1.0 g of 2-amino-3-cyanopyrazine 1,4-dioxide (**16**) in 30 ml of tetrahydrofuran was added 1.4 g of phosphorus trichloride in 10 ml of tetrahydrofuran. The reaction mixture was stirred at 25° for 3.5 hr, the solvent was removed by evaporation under reduced pressure, and the residue was triturated with 50 ml of water. Filtration afforded crude **17**, mp 258–260°. The analytical sample was recrystallized from methanol to give 0.6 g (67%) of **17**: mp 262–263°; NMR (CF_3COOH) δ 7.79 (1, d), 7.37 (1, d, H_5, H_6).

Anal. Calcd for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.17. Found: C, 44.33; H, 2.89; N, 40.90.

2-Amino-3-carbamoylpyrazine 4-Oxide (18). A solution of 0.3 g of 2-amino-3-cyanopyrazine 4-oxide (**17**) in 1.5 ml of TFAA and 7.5 ml of TFA was stirred under reflux for 5 hr. The reaction mixture was then cooled and poured into water, and the aqueous solution was taken to dryness under reduced pressure. Ethanol was added to the residue and again removed by evaporation. The semicrystalline solid thus obtained was recrystallized from methanol to give 0.07 g (21%) of 2-amino-3-carbamoylpyrazine 4-oxide (**18**), mp 230–232°. The analytical sample, mp 230–232°, was recrystallized from methanol: NMR (CF_3COOH) δ 7.53 (1, d), 7.29 (1, d, H_5, H_6).

Anal. Calcd for $C_5H_6N_4O_2$: C, 38.96; H, 3.92; N, 36.35. Found: C, 38.79; H, 3.92; N, 36.65.

2-Amino-3-cyano-5-chloropyrazine (19).[20] To a stirred suspension of 1.0 g of 2-amino-3-cyanopyrazine 4-oxide (**17**) in 10 ml of DMF (held at 5–10°) was added 2.0 ml of phosphorus oxychloride. After addition was complete, the reaction mixture was stirred at 80–90° for 10 min, cooled, and poured into 10 ml of water at 0°. The aqueous mixture was stirred at room temperature for an additional 16 hr and cooled to give a crystalline precipitate of crude **19** which was collected by filtration. A further crop of crystals could be recovered from the filtrate by extraction with ethyl acetate, drying (Na_2SO_4), and removal of the solvent under reduced pressure. The combined materials were crystallized from ethyl acetate–petroleum ether to give 0.70 g (61%) of **19**: mp 152–154°; NMR (CF_3COOH) δ 7.81 (1, s, H_6).

Anal. Calcd for $C_5H_3N_4Cl$: C, 38.83; H, 1.96; N, 36.91; Cl, 22.22. Found: C, 38.89; H, 1.90; N, 36.63; Cl, 22.24.

2,4-Diamino-6-methoxypteridine (20). To a methanolic solution of guanidine (prepared from 0.35 g of sodium in 25 ml of methanol and 0.36 g of guanidine hydrochloride) was added 0.50 g of 2-amino-3-cyano-5-chloropyrazine (**19**). The suspension was stirred under reflux for 5 hr, cooled, and filtered, and the crude product was recrystallized from DMF–methanol to give 0.39 g (62%) of bright yellow **20**: mp >300°; NMR (CF_3COOH) δ 8.07 (1, s, H_7), 3.67 (3, s, $-OCH_3$); uv λ_{max} (0.1 *N* HCl) 362 nm (log ϵ 3.92), 353 (3.97), 274 (3.87), 248 (4.30).

Anal. Calcd for $C_7H_8N_6O$: C, 43.75; H, 4.20; N, 43.73. Found: C, 44.00; H, 4.16; N, 44.06.

Xanthopterin (1) by Hydrolysis of 2,4-Diamino-6-methoxypteridine (20). A suspension of 0.30 g of **20** in 20 ml of 10% aqueous sodium hydroxide was refluxed with stirring for 21 hr. The reaction mixture was then diluted with water, treated with animal carbon, and filtered. The pH of the filtrate was adjusted to 4 with acetic acid to give 0.26 g (93%) of bright yellow **1**. One precipitation from aqueous ammonia with dilute hydrochloric acid gave 0.24 g (86%) of xanthopterin monohydrate, mp >300°, identical in all respects with an authentic sample.

Pterin 8-Oxide (21). A suspension of 1.00 g of 2,4-diaminopteridine 8-oxide (**25**)[14] in 100 ml of 5% NaOH was heated under reflux until complete solution was achieved, and then for additional 5 min (total heating time 30 min). The yellow solution was then brought to pH 3 with 6 *N* HCl and allowed to stand for 30 min before filtering, washing thoroughly with water, and drying to yield 0.98 g (98%) of bright yellow **21**, identical with an authentic sample prepared by pertrifluoroacetic acid oxidation of pterin.[24]

Ethyl α-(Pterin-7-yl)-α-cyanoacetate (22). To a suspension of 0.15 g of pterin 8-oxide (**21**) in 15 ml of anhydrous HMPA was added 5.0 ml of ethyl cyanoacetate followed by 2 ml of acetic anhydride, and the mixture was stirred for 12 hr at 85–90°. Filtration afforded 0.01 g of unreacted **21**. The filtrate was diluted to 100 ml with absolute ethanol and stirred for 1 hr at 25° to give 0.05 g (30%) of **22** as a yellow, crystalline solid. The analytical sample crystallized from DMF as bright yellow needles: mp >300°; ir (KBr) $\bar{\nu}$ 2200 (CN), 1684, 1700 cm^{-1}; mass spectrum *m/e* 274 ($M^{\cdot+}$), 202 (M − $COOC_2H_5$); uv λ_{max} (EtOH) 402 nm (log ϵ 4.07), 317 (3.91), 267 (3.99), 232 (3.94).

Anal. Calcd for $C_{11}H_{10}N_6O_3$: C, 48.17; H, 3.68; N, 30.65. Found: C, 48.03; H, 3.82; N, 30.75.

Ethyl α-(2-Acetylpterin-7-yl)-α-cyanoacetate (23). Overnight refrigeration of the filtrate from **22** gave 0.03 g (15%) of **23** as a bright canary yellow solid. The analytical sample, which recrystallized from DMF in the form of elongated needles, had mp >300°; ir (KBr) $\bar{\nu}$ 2220 (CN), 1660, 1700 cm^{-1}; mass spectrum *m/e* 316 ($M^{\cdot+}$), 274 (M − $COCH_3$); uv λ_{max} (EtOH) 400 nm (log ϵ 4.42), 273 (4.43), 215 (4.26).

Anal. Calcd for $C_{13}H_{12}N_6O_4$: C, 49.37; H, 3.82; N. 26.57. Found: C, 49.11; H, 3.79; N, 26.28.

Oxidation of 22 or 23 to Pterin-7-carboxylic Acid (24). To a suspension of 0.60 g of **22** or **23** in 10 ml of water was added 0.10 g of sodium hydroxide, followed by the dropwise addition of 6.0 ml of 2 *M* potassium permanganate solution with stirring over a period of 2.5 hr at 80°. The excess potassium permanganate was destroyed with sodium sulfite, and the reaction mixture was then treated with animal carbon and filtered. The pH of the filtrate was adjusted to 2 to give a yellow microcrystalline solid. After the solution was stirred at 90° for 2 hr the crystals were collected by filtration, washed with water, and dried (0.4 Torr, 110°, 24 hr) to give 0.01 g of pterin-7-carboxylic acid (**24**), identical chromatographically and spectroscopically with an authentic sample.

2,4-Diamino-7-(1-pyrrolidino)pteridine (26). A suspension of 0.20 g of 2,4-diaminopteridine 8-oxide (**25**) in 15 ml of pyrrolidine was stirred for 16 hr at 95°. After removal of the solvent on a rotary evaporator, the yellow residue was triturated with 10 ml of absolute ethanol and refrigerated at 5° for 2 hr. Filtration afforded 0.17 g (62%) of **26** as a yellow powder. The analytical sample, prepared by recrystallizing a portion of the title compound twice from ethanol, had mp >300°; NMR (DMSO-d_6) δ 7.65 (1, s, H_6), 6.83 (2, br, $-NH_2$), 5.95 (2, br, $-NH_2$), 3.45 (4, m, α-pyrrolidine), 1.86 (m, β-pyrrolidine); uv λ_{max} (0.1 *N* HCl) 364 nm (log ϵ 4.34), 287 (4.18), 263 (4.16), 220 (4.46).

Anal. Calcd for $C_{10}H_{13}N_7$: C, 51.94; H, 5.67; N, 42.40. Found: C, 51.78; H, 5.65; N, 42.34.

Isoxanthopterin (2) by Hydrolysis of 2,4-Diamino-7-(1-pyrrolidino)pteridine (26). A suspension of 0.10 g of **26** in 20 ml of 5% NaOH solution was heated under reflux at 110° for 96 hr, and the resulting solution was cooled to 0° in an ice bath. After the pH was adjusted to 4 with 12 *N* HCl and the solution was allowed to stand for 12 hr, the solution had deposited 0.05 g (85%) of a yellowish-brown powder, which, following purification in the usual manner, gave isoxanthopterin (**2**), identical with an authentic sample.

Xanthopterin (1) by Rearrangement of Pterin 8-Oxide (21) with TFA–TFAA. A suspension of 1.0 g of pterin 8-oxide (**21**) in 5 ml of TFA and 5 ml of TFAA was stirred in an oil bath at 50°. After 20 min a homogeneous solution (bright yellow) was obtained, an aliquot of which showed only one aromatic proton (NMR). After stirring for a total of 1 hr the solution was evaporated to dryness at room temperature (10 Torr), and the residual solvent was removed under high vacuum (0.1 Torr) to give a bright yellow solid. Fifty milliliters of 10% ammonium hydroxide was added, and the resulting suspension was stirred for an additional 15 min at 50° and then dissolved by the slow addition of 1 *N* sodium hydroxide. After solution was complete, 500 mg of Darco G-60 carbon was added, and stirring was continued for an additional 20 min at 50°. Filtration through a small pad of Celite than gave a bright yellow solution, which on acidification with 6 *N* HCl to pH 3 gave the title compound as a yellow, microcrystalline precipitate. The product was collected, washed well with water and methanol, and dried overnight under high vacuum (0.1 Torr, P_2O_5) to give **1** in nearly quantitative yield. The product was shown to be pure **1** by virtue of its identical ir, uv, and paper chromatographic behavior with an authentic sample. The same rearrangement could be effected at room temperature, again in quantitative yield, but a total reaction time of 4 hr was required.

Xanthopterin (1) from 2,4-Diaminopteridine 8-Oxide (25). A suspension of 100 mg of **25** in a solution of 0.5 ml of TFAA and 3 ml of TFA was brought to reflux in an oil bath heated to 65° and stirred under these conditions for 5 hr. During this time the suspended solid slowly dissolved to give a deep red-brown solution. All solvents were then removed under reduced pressure to give 2,4-diamino-6(5*H*)-pteridinone (**30**) as a dark brown solid. This material was then dissolved in 10 ml of 5% NaOH, 100 mg of Darco G-60 carbon was added, and the mixture was heated for 24 hr in an oil bath at 100°. Filtration through a pad of Celite gave an orange-yellow solution, which upon acidification to pH 3 with 6 *N* HCl gave **1** as a gelatinous precipitate. The material was collected and

washed (water, then methanol) by centrifugation, and dried overnight under high vacuum to give 65 mg (65%) of **1**, identical with an authentic sample.

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Pteridines. XXXVIII. Synthesis of Some 2,4-Diamino-6-Substituted Methylpteridines. A New Route to Pteroic Acid[1,2]

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A versatile, flexible route to a variety of 6-substituted 2,4-diaminopteridines (**6**) and 6-substituted pterins (**7**) is described which involves the reaction of 2-amino-3-cyano-5-chloromethylpyrazine (**5**) with nucleophiles, followed by ring closure with guanidine (to give **6**), and final acid hydrolysis (to give **7**). Among the compounds conveniently prepared by this unequivocal route are 2,4-diamino-6-hydroxymethylpteridine, 6-hydroxymethylpterin, and pteroic acid. A three-component, one-pot (TCOP) condensation of aminomalononitrile tosylate, β-bromopyruvaldoxime, and added nucleophile has been developed which leads directly, in moderate yield but high purity, to 2-amino-3-cyano-5-substituted pyrazine 1-oxides (**4**).

Previous papers in this series have described a new, general, and unequivocal synthesis of 6- and/or 7-substituted pteridines from pyrazine 1-oxide intermediates, prepared by the condensation of α-aminonitriles with α-ketoaldoximes or α-oximino aldehydes.[3-5] The synthesis of 2,4-diaminopteridines substituted in position 6 with olefinic substituents suitable for final elaboration into multifunctional side chains characteristic of some of the naturally occurring pterins (i.e., biopterin, neopterin, urothion, etc.) involved (a) the preliminary formation of 2-amino-3-cyano-5-chloromethylpyrazine 1-oxide (**4a**) by the condensation of aminomalononitrile tosylate (**1**) with β-chloropyruvaldoxime (**2**), (b) deoxygenation with phosphorus trichloride to 2-amino-3-cyano-5-chloromethylpyrazine (**5a**), (c) elaboration of the olefinic side chain by means of the Wittig reaction, and (d) terminal closure of the pyrimidine ring by cyclization with guanidine.[5] The present paper describes a number of nucleophilic displacement reactions on the chloromethyl substituent in **5a**, and the elaboration of the resulting substituted methylpyrazines to a variety of new 2,4-diaminopteridines and pterins. This paper also describes new and unequivocal syntheses of pteroic acid and of 6-hydroxymethylpterin, and a convenient three-component, one-pot (TCOP) synthesis of 2-amino-3-cyano-5-substituted methylpyrazine 1-oxides.

Although the primary chloro substituent in **5a** is reactive toward nucleophiles (we have previously described its displacement by methoxide ion and by triphenylphosphine[5]), conditions must be chosen with care because of the ease of nucleophilic addition to the 3-cyano grouping. Displacement by sodium 4-chlorothiophenolate occurred smoothly in methanol solution in high yield, without concomitant addition to the extremely reactive nitrile grouping, to give **5d**. Reaction of **5a** with aromatic amines, however, proved to be more critical, and optimum reaction conditions involved the use of acetonitrile as solvent, although DMSO at higher temperatures could also be employed. Thus, reaction of **5a** with 3,4-dichloroaniline, ethyl 4-aminobenzoate, or sulfanilamide in the presence of potassium carbonate led to the formation in high yield of the pyrazines **5e, 5k,** and **5h,** respectively. Reaction of **5a** with 3,4-dichloro- and 2,4-dichlorobenzylamine, and with diethylamine, all occurred smoothly in 2-propanol solution to give the pyrazines **5f, 5g,** and **5i,** respectively. Cyclization of these pyrazine *o*-aminonitriles to the corresponding 2,4-diaminopteridines (**6**) proceeded in the normal manner with guanidine in methanol in the presence of sodium methoxide.

The conversion of 2,4-diaminopteridines to pterins [2-amino-4(3*H*)-pteridinones] by selective hydrolysis of the 4-amino group has been exploited previously.[4,6-8] Thus, alkaline hydrolysis of **6k** gave pteroic acid (**7**), identical in every respect with an authentic sample.[9] This synthesis of pteroic acid is a five-step process utilizing readily available starting materials and involving crystalline intermediates