N651153N-SR02402. We are indebted to Dr. Charlotte Lowe-Ma of NWC for the X-ray powder pattern experiments.

Registry No. **1a**, 98778-06-4; **1b**, 98778-07-5; **1c**, 98778-08-6; **1d**, 98778-09-7; **2b**, 98778-10-0; **2c**, 98778-11-1; **2d**, 98778-12-2; **3**, 17220-38-1; (**3a**-CH_2O)$_x$, 76643-24-8; *anti*-**5a**, 98778-03-1; *amphi*-**5b**, 98778-16-6; *anti*-**5b**, 98799-23-6; *syn*-**5b**, 98778-17-7; *amphi*-**5c**, 98778-18-8; *anti*-**5c**, 98778-04-2; *syn*-**5c**, 98778-19-9; *amphi*-**5d**, 98778-20-2; *anti*-**5d**, 98778-05-3; *syn*-**5d**, 98778-21-3; **6b**, 59417-06-0; **6c**, 98778-13-3; **6d**, 98778-14-4; **7**, 97288-72-7; **9**, 98778-15-5; **10**, 97288-73-8; HON=C(Cl)C(Cl)=NOH, 2038-44-0; $H_2NCH_2CH_2NH_2$, 107-15-3; $H_3CNHCH_2CH_2NHCH_3$, 110-70-3; $(CH_3)_2CHNHCH_2CH_2NHCH(CH_3)_2$, 4013-94-9; $(CH_3)_3CNHCH_2CH_2NHC(CH_3)_3$, 4062-60-6; OHCCHO, 107-22-2.

Supplementary Material Available: Tables of the ^1H and ^{13}C NMR data for most of the compounds in this paper (2 pages). Ordering information is given on any current masthead page.

Synthesis and Properties of 7-Alkoxyfurazano[3,4-*d*]pyrimidines and Their Use in the Preparation of 4-Alkoxypteridines and N^3-Substituted Pterins[1]

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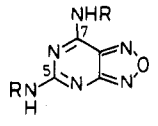
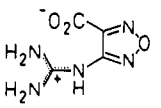
Reaction of 5-amino-7-(methylthio)furazano[3,4-*d*]pyrimidine (**4**) with a range of alcohols in the presence of bromine leads to the formation of the corresponding 5-amino-7-alkoxyfurazano[3,4-*d*]pyrimidines (**5–10**). These on hydrogenolysis afford 6-alkoxy-2,4,5-triaminopyrimidines, which can be condensed with benzil to give 2-amino-4-alkoxypteridines (**17–21**). The product from hydrogenolysis of 5-amino-7-(2-chloroethoxy)furazano-[3,4-*d*]pyrimidine (**7**), however, undergoes intramolecular cyclization to a 2,3-dihydrooxazolo[3,2-*c*]pyrimidinium compound (**23**), which behaves as a heteronuclear resonance stabilized ambident cation. Reaction of it with nucleophiles followed by condensation with benzil leads to N^3-substituted pteridines.

The pyrimidine ring of furazano[3,4-*d*]pyrimidines is highly π-deficient,[2] and this electron deficiency is particularly marked at position 7. As a result, nitrogen substituents at position 7 of furazanopyrimidines such as **1** or **2** have been found to undergo ready replacement by



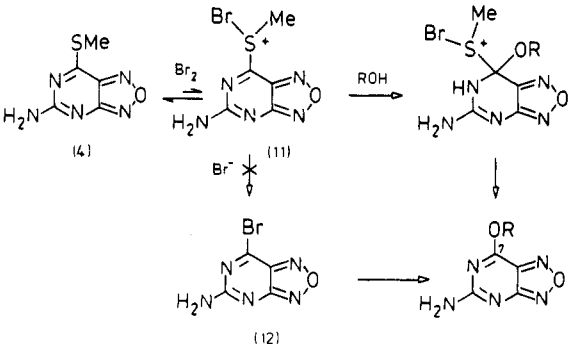
(1) R = H
(2) R = COC_6H_5



(3)

both nitrogen nucleophiles such as amines,[3,4] and carbon nucleophiles such as enolate anions.[5] Analogous replacement by alkoxide nucleophiles cannot be achieved, however. 7-Alkoxyfurazano[3,4-*d*]pyrimidines have not so far been reported, and 7(6*H*)-oxo compounds are rare.[6] For example, treatment of either **1** or **2** with ethanolic sodium ethoxide led to extensive decomposition, and no useful product could be isolated, while treatment of the same compounds with aqueous base gave 4-guanidino-3-furazancarboxylic acid (**3**), formed by hydrolytic cleavage of the pyrimidine ring.[6] In contrast, we now report that 5-amino-7-(methylthio)furazano[3,4-*d*]pyrimidine (**4**) serves as an excellent substrate for the introduction of a range of alkoxy groups into the 7 position of the furazano[3,4-*d*]pyrimidine ring system, and the resulting 7-alkoxy-5-aminofurazano[3,4-*d*]pyrimidines may be used as

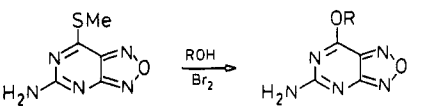
Scheme I



precursors in a convenient synthesis of 4-alkoxypteridines. These latter are potentially very useful due to their increased solubility, but have not hitherto been readily available.

Results and Discussion

5-Amino-7-(methylthio)furazano[3,4-*d*]pyrimidine[6] (**4**), which may be prepared by the lead tetraacetate oxidation[3] of 2,4-diamino-6-(methylthio)-5-nitrosopyrimidine, is quite stable when warmed in an alcohol. If bromine (or chlorine) is added to the solution, however, a smooth reaction ensues and the corresponding 7-alkoxyfurazanopyrimidine may be isolated in yields of up to 90% (eq 1). A wide range



(1)

(4)

(5) R = CH_3
(6) R = C_2H_5
(7) R = CH_2CH_2Cl
(8) R = CH_2CH_2OH
(9) R = $CH_2(CH_2)_3CH_2OH$
(10) R = CH_2·CHOH·CH_2OH

of alcohols may be used in this reaction and products **5–10**

(1) Boyle, P. H.; Lockhart, R. J. In "Chemistry and Biology of Pteridines"; Blair, J. A., Ed.; Walter de Gruyter: Berlin, p 73.
(2) Maki, Y. *Chem. Pharm. Bull.* **1976**, *24*, 235.
(3) Taylor, E. C.; Beardsley, G. P.; Maki, Y. *J. Org. Chem.* **1971**, *36*, 3211.
(4) Crane, L. E.; Maki, Y.; Beardsley, G. P. *J. Carbohydr., Nucleosides, Nucleotides* **1980**, *7*, 281. Taylor, E. C.; Cocuzza, A. J. *J. Org. Chem.* **1979**, *44*, 302. Taylor, E. C.; Martin, S. F.; Maki, Y.; Beardsley, G. P. *J. Org. Chem.* **1973**, *38*, 2238.
(5) Crane, L. E.; Beardsley, G. P.; Maki, Y. *J. Org. Chem.* **1980**, *45*, 3827.
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0022-3263/85/1950-5127$01.50/0

Table I. Properties of 7-Alkoxy-5-aminofurazano[3,4-*d*]pyrimidines[a]

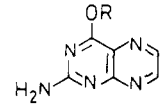
compd	mp dec, °C	% yield	λ/nm (log ε) (ethanol)	^{1}H NMR δ values (CD_3SOCD_3, 80 MHz)
5	180–81 (acetone–hexane)	94	216 (4.20) 258 (3.72) 339 (3.54)	4.15 (3 H, s, CH_3) 7.77 (2 H, br s, NH_2)
6	182–83 (acetone–water)	72	216 (4.21) 258 (3.74) 338 (3.56)	1.47 (3 H, t, J = 7 Hz, CH_3) 4.61 (2 H, q, J = 7 Hz, OCH_2) 7.73 (2 H, br s, NH_2)
7	169–70 (acetone–water)	90	216 (4.28) 260 (3.82) 340 (3.58)	4.03 (2 H, t, J = 6 Hz, CH_2Cl) 4.89 (2 H, t, J = 6 Hz, OCH_2) 7.10 (2 H, br s, NH_2)
8	177–78 (acetone–hexane)	81	214 (4.30) 260 (3.76) 340 (3.58)	3.85 (2 H, m, CH_2OH) 4.64 (2 H, t, J = 6.5 Hz, OCH_2) 5.08 (1 H, t, J = 7 Hz, OH) 7.82 (2 H, br s, NH_2)
9	156–57 (EtOH)	80	213 (4.32) 256 (3.76) 341 (3.66)	1.3–2.3 (7 H, m, $(CH_2)_3$, OH) 3.43 (2 H, m, CH_2OH) 4.57 (2 H, t, J = 6 Hz, OCH_2) 7.77 (2 H, br s, NH_2)
10	143–45 (acetone–hexane)	71	212 (4.15) 267 (3.89) 340 (3.32)	3.3–4.4 (5 H, m, $CH(OH)CH_2OH$) 4.57 (2 H, d, OCH_2) 7.80 (2 H, br s, NH_2)

[a] Compounds **5**, **8**, **9** and **10** gave C, H, N analyses within ±0.4%, and compound **6** within ±0.5%. Compound **7** gave C, H, N, and Cl analysis within ± 0.5%.

have all been prepared and characterized (Table I).

The probable mechanism of this reaction is outlined in Scheme I. Although thioethers, including heterocyclic thioethers, are known[7] to form adducts with halogen, no observable reaction occurred when the methylthio compound (**4**) was treated with bromine in an aprotic solvent, presumably reflecting the low availability of the sulfur lone pair electrons due to their interaction with the highly electron-deficient pyrimidine ring. This is consistent with the fact that the sulfur atom in **4** was found to be stable to oxidation by *m*-chloroperbenzoic acid, which is in keeping with a report[8] that the rate of oxidation of the sulfur atom in diaryl sulfides depends on the electronegativity of substituents attached at the para positions of the aryl groups. Although the sulfonium intermediate **11** was not detected, the presence of bromine is nevertheless necessary for reaction to occur between it and an alcohol. The first step of Scheme I therefore represents an equilibrium between **4** and bromine, with the position of equilibrium lying predominantly on the side of **4**. The proposed addition–elimination sequence is in harmony with Taylor's suggested mechanism[3] for transamination reactions at position 7 of these furazanopyrimidines. The 7-bromo compound **12** is not considered to be an intermediate, since no trace of it could be detected when the methylthio compound **4** was treated with bromine in a nonnucleophilic alcohol such as 2,2,2-trichloroethanol. While 2-chloroethanol did react smoothly with **4** in the presence of bromine to give product **7**, 2,2-dichloroethanol, 2,2,2-trichloroethanol, glycolic acid, and ethyl glycolate all failed to react. This is presumably because the strongly electron-withdrawing substituents in these alcohols reduce the nucleophilicity of the hydroxyl groups. As well as by the route described above, compound **5** was also prepared by lead tetraacetate oxidation of 2,4-diamino-6-methoxy-5-nitrosopyrimidine.

The 7-alkoxyfurazanopyrimidines (**5–10**) described in Table I are all pale yellow crystalline solids. Although stable in neutral solution they are easily hydrolyzed in both aqueous acid and aqueous base, with loss of the 7-alkoxy group and concomitant cleavage of the pyrimidine ring, to give 4-guanidino-3-furazancarboxylic acid (**3**).[6] Their IR spectra are characterized by a strong sharp NH_2 stretching band at 3400–3410 cm^{-1}, and by peaks in the fingerprint region close to 870, 840, and 785 cm^{-1}. The ^{1}H NMR spectra of all these compounds are in accordance with the structures shown, and are noteworthy only for the unusually low field resonances of the protons next to the 7-oxygen atom. This deshielding reflects again the strong electron withdrawing power of the heterocyclic ring. The UV spectra of compounds **5–10** measured in ethanol show three strong absorption bands close to 215, 260, and 340 nm, as is characteristic[3] for furazano[3,4-*d*]pyrimidines. These values correlate well with the UV absorption maxima reported[9] for 2-amino-4-alkoxypteridines (**13**), and



(13)

support the generalization[10] that substitution of a –CH=CH– linkage by a heteroatom does little to disrupt the π-electronic structure of aromatic systems.

Like other furazano[3,4-*d*]pyrimidines which have been studied,[3,4,6] the 7-alkoxy compounds **5** and **6**, and also **8–10**, suffered ready hydrogenolysis of the furazan ring when stirred with a palladized charcoal catalyst in methanol or aqueous methanol solution under an atmosphere of hydrogen (Scheme II). The resulting 6-alkoxy-2,4,5-triaminopyrimidines were labile to air in the form of their free bases. Compounds **14–16**, however, were isolated as their stable sulfate salts. These 6-alkoxy-2,4,5-triaminopyrimidines all readily condensed in situ with benzil (Scheme II) to give a series of 4-alkoxypteridines (**17–21**), whose spectral and physical properties are shown in Table II. Pteridines are notoriously insoluble in most solvents and this gives rise to difficulties in the study of their chemistry. The 4-alkoxypteridines (**17–21**), however, are all very soluble in organic solvents such as chloroform, ethyl acetate, and alcohols. The alkoxy groups of com-

(7) Wilson, G. E.; Albert, R. *J. Org. Chem.* **1973**, *38*, 2156 and 2160. Furukawa, N.; Inoue, T.; Aida, T.; Oae, S. *J. Chem. Soc., Chem. Commun.* **1973**, 212. Kwart, H.; Miller, L. *J. J. Am. Chem. Soc.* **1958**, *80*, 884. Boberg, F.; Winter, G.; Schultze, G. R. *Chem. Ber.* **1956**, *89*, 1160. Bordwell, F. G.; Pitt, B. M. *J. Am. Chem. Soc.* **1955**, *77*, 572.

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(9) Pfleiderer, W.; Lohrmann, R. *Chem. Ber.* **1961**, *94*, 12.

(10) Armarego, W. In "Physical Methods in Heterocyclic Chemistry"; Katritzky, A. R., Ed.; Academic Press: New York, 1971; Vol. 3, p 70.

Scheme II

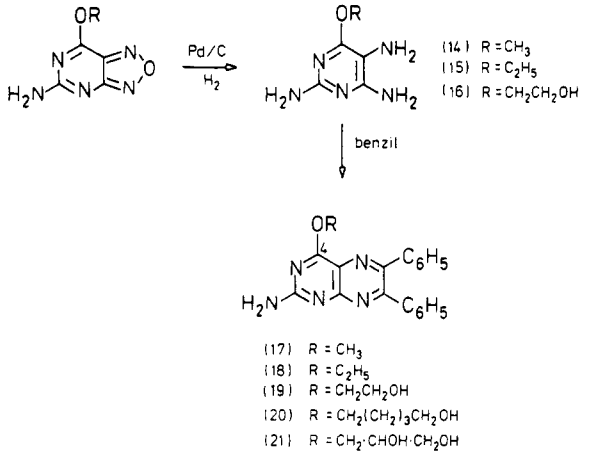
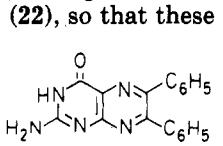


Table II. Properties of 4-Alkoxy-2-amino-6,7-diphenylpteridines[a,b]

compd	mp dec, °C	% yield	^{1}H NMR δ values (80 MHz)	NMR solvent
17	300	51	4.15 (3 H, s, CH_3) 5.60 (2 H, br s, NH_2) 7.0–7.7 (10 H, br s, Ph)	$CDCl_3$
18	300	28	1.43 (3 H, t, J = 7 Hz, CH_3) 4.58 (2 H, q, J = 7 Hz, CH_2) 7.27 (2 H, br s, NH_2) 7.37 (10 H, br s, Ph)	CD_3SOCD_3
19	239–41	40	3.84 (2 H, t, J = 5 Hz, CH_2OH) 4.59 (2 H, t, J = 5 Hz, OCH_2) 4.94 (1 H, br s, OH) 7.29 (2 H, br s, NH_2) 7.36 (10 H, br s, Ph)	CD_3SOCD_3
20	198–99	17	1.2–2.1 (7 H, m, $(CH_2)_3$, OH) 3.70 (2 H, t, J = 5 Hz, CH_2OH) 4.61 (2 H, t, J = 7 Hz, OCH_2) 5.44 (2 H, br s, NH_2) 7.27–7.70 (10 H, m, Ph)	$CDCl_3$
21	300	39	3.57 (2 H, d, J = 5 Hz, CH_2OH) 4.03 (1 H, m, CH) 4.57 (2 H, m, OCH_2) 7.39 (10 H, br s, Ph)	CD_3SOCD_3 + CD_3CO_2D

[a] Compounds **17**, **19**, **20**, and **21** gave C, H, N analyses within ± 0.4%. Compound 18 has been previously reported.[12] [b] Compounds 17–21 showed UV maxima (±2 nm) at 225, 246, 288, and 390 nm, with log ε (±0.02) 4.44, 4.43, 4.36, and 4.12, respectively.

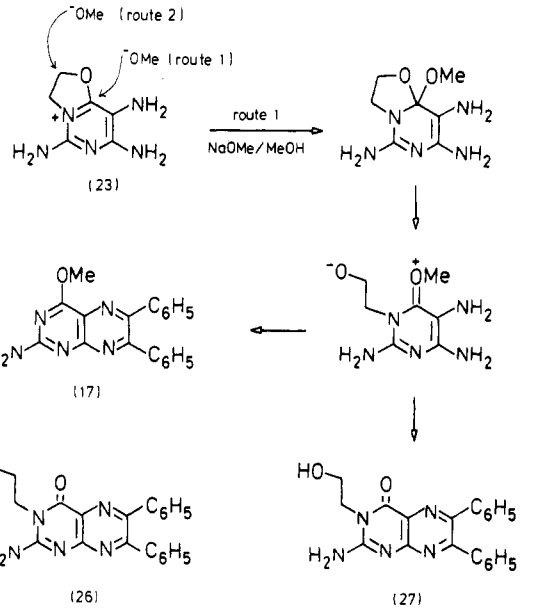
pounds (**17**–**21**) can be readily removed by mild acid or alkaline hydrolysis, to regenerate the highly insoluble 6,7-diphenylpterin (**22**), so that these compounds are in



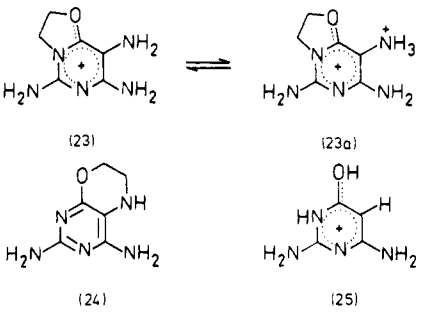
(22)

effect solubilized, protected, derivatives of the biologically important pterin system. It was suggested several years ago by Pfleiderer[9] that their favorable solubility properties could be exploited to overcome some of the problems in the handling of pteridines, and a few 4-alkoxypteridines have already been described in the literature.[9,11,12] Existing methods for their synthesis are limited in scope, however, and the present route via 7-alkoxyfurazano[3,4-*d*]pyrimidines is much more versatile.

Scheme III



When 5-amino-7-(2-chloroethoxy)furazano[3,4-*d*]pyrimidine (**7**) was hydrogenated over a palladium catalyst, an alkali labile sulfate salt was obtained which could be crystallized from 2 M sulfuric acid. This salt contained the highly resonance-stabilized oxazolo[3,2-*c*]pyrimidinium cation (**23**), formed by intramolecular cyclization of the intermediate 2,4,5-triamino-6-(2-chloroethoxy)pyrimidine which could not be isolated. Cyclization occurred exclusively towards the ring nitrogen atom, leading to the heteronuclear stabilized cation **23**. No trace could be



(2)

detected of the 8-oxapteridine (**24**). The ultraviolet absorption spectrum of **23** in 0.1 M hydrochloric acid showed three maxima, at 214, 264, and 288 nm, which is quite a different pattern from that observed for 6-alkoxy-2,4,5-triaminopyrimidines. When measured in water solution the peak at 264 nm disappeared, while in 2 M HCl solution (pH −0.3) the peak at 288 nm disappeared. This speaks for the existence of a dication **23a** at pH −0.3, absorbing at 264 nm, a monocation **23** at pH 7, absorbing at 288 nm, and a mixture of the two at pH 1. The observed absorption maximum of the monocation (**23**) at 288 nm correlates with that reported for analogous resonance-stabilized cations.[13] The observed absorption maximum of the dication **23a** at 264 nm correlates with that of model compound **25**, which

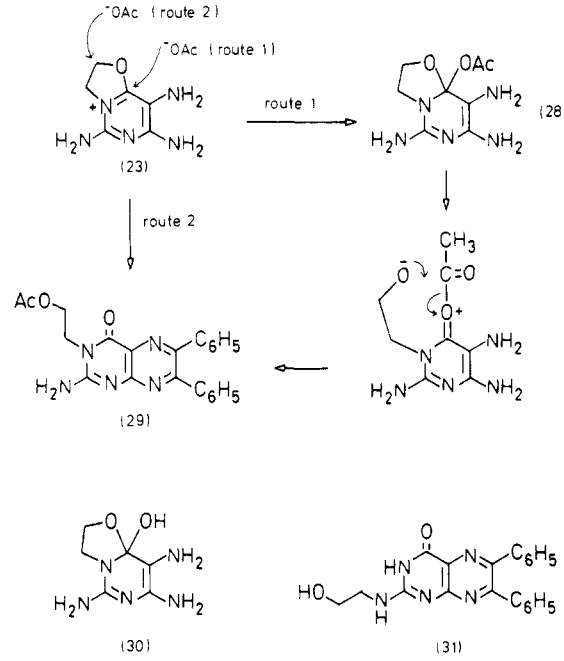
(11) Roth, B.; Smith, J. M.; Hultquist, M. E. *J. Am. Chem. Soc.* **1951**, *73*, 2869.
(12) Kaldrikyan, M. A.; Danagulyan, G. G.; Khekoyan, A. V.; Arsenyan, F. G.; Aroyan, A. A. *Arm. Khim. Zh.* **1976**, *29*, 337.
(13) Lipkin, D.; Lovett, E. G. *J. Org. Chem.* **1975**, *40*, 1713.

absorbs[14] at 265 nm. This suggests that protonation of monocation **23** occurs on the 5-amino group (eq 2), since the $-NH_3^+$ group is known to be transparent in the ultraviolet.[15]

The heteronuclear stabilized cation **23** is an ambident cation, susceptible to attack by nucleophiles at either of the carbon atoms attached to the isoxazoline oxygen atom. In Scheme III these two reaction pathways are shown as routes 1 and 2. The general principles governing this type of reaction have been comprehensively reviewed by Hünig,[16] and an ambident cation similar to **23** has been studied in detail by Lipkin and Lovett.[13] We examined the behavior of cation **23** under three sets of reaction conditions, namely with sodium methoxide in methanol, with methanol containing sulfuric acid, and with sodium acetate in aqueous methanol. Since the 2,4,5-triaminopyrimidines formed initially in these reactions were labile to air, it was found convenient to react them with benzil *in situ*, without isolation, to give the corresponding 6,7-diphenylpteridines, which were isolated and characterized. The results showed that the course of the reaction depended upon the nature of the nucleophile, in agreement with observations made by other workers.[13,16] For example, when **23** was allowed to react with methanolic sodium methoxide in presence of benzil (see Scheme III), that is, with a hard anionic nucleophile, the ensuing reaction proceeded exclusively by route 1. This was shown by the isolation of 2-amino-4-methoxy-6,7-diphenylpteridine (**17**) and 2-amino-3-(2-hydroxyethyl)-6,7-diphenylpteridine (**27**) as the only products formed. Any attack by route 2 would have led to the formation of 2-amino-3-(2-methoxyethyl)-6,7-diphenylpteridine (**26**), and no trace of this product could be detected. Under acidic conditions on the other hand, route 2 appears to be the major pathway, for compound **26** was the main product isolated when cation **23** was allowed to react with methanol containing sulfuric acid, followed by treatment of the resulting mixture with benzil. Pteridines **17** and **27** were also formed as minor products in this reaction, however, so that under these conditions too some attack by the neutral methanol molecule must proceed via route 1. Finally, when **23** was treated with sodium acetate in aqueous methanol followed by benzil, the main product isolated was the N^3-(2-hydroxyethyl)pteridine **27**. By analogy with $H_2{}^{18}O$ labelling experiments carried out by Lipkin and Lovett,[13] product **27** most likely arises here by route 1 attack of either hydroxide ion or water, through intermediate **30**. A small amount of 2-amino-3-(2-acetoxyethyl)-6,7-diphenylpteridine (**29**) was also obtained. This was most probably formed by route 2 attack of acetate ion on the ambident cation **23** as shown in Scheme IV, although its formation via route 1 intermediate **28** by an intramolecular acyl transfer reaction cannot be ruled out.[17]

The pteridine products **26**, **27**, and **29** were identified by their spectroscopic and chemical properties. They are all N^3-substituted 6,7-diphenylpterins, and show the same ultraviolet absorption pattern as does N^3-methyl-6,7-diphenylpterin.[18] The spectra are the same at pH 7 as they are at pH 9.2, showing the absence of an ionizable lactam proton at N^3, and suggesting the location of the side chain at this position. This last point was confirmed by heating

Scheme IV



compound **27** in sodium hydroxide solution, when it underwent a Dimroth rearrangement, to give the rearranged product **31**.

Experimental Section

NMR spectra were measured either on a Bruker WP-80 instrument at 80 MHz, or a Jeol PMX-60 instrument at 60 MHz. Chemical shifts were determined relative to tetramethylsilane as an internal standard. UV spectra were recorded using a Pye Unicam SP-200 spectrophotometer, and IR spectra using a Perkin-Elmer 298 spectrophotometer. Elemental analyses of the furazanopyrimidines were best carried out with tungstic oxide to ensure complete combustion.

Preparation of 7-Alkoxy-5-aminofurazano[3,4-*d*]pyrimidines (5–10). A suspension of 5-amino-7-(methylthio)-furazano[3,4-*d*]pyrimidine (**4**) (1.0 g) in the appropriate dried alcohol (15 mL) was stirred and warmed to about 50 °C. A solution of bromine (1 g) in either the same alcohol (4 mL) or in carbon tetrachloride (4 mL) was added in small portions in such a way that the bromine color in the reaction mixture had disappeared before more bromine was added. Addition of bromine was continued until all the starting material had reacted, as shown by TLC on silica plates, using ethyl acetate/hexane (3:2) as solvent. The reaction mixture was then cooled and poured with vigorous stirring into a mixture of ethyl acetate (300 mL) and solid sodium hydrogen carbonate (3 g). After the mixture had been stirred for 5 min, saturated aqueous sodium chloride (20 mL) was added and the mixture stirred for a further 10 min. The organic layer was separated, washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and evaporated to give a yellow solid. The yields and properties of products **5–10** are summarized in Table I.

5-Amino-7-methoxyfurazano[3,4-*d*]pyrimidine (5). Lead tetraacetate was added in portions over a period of 30 min under an atmosphere of nitrogen to a deaerated solution of 2,4-diamino-6-methoxy-5-nitrosopyrimidine[9] (97 mg, 0.58 mmol) in acetic acid (10 mL). The mixture was stirred at room temperature under nitrogen for a further 14 h, by which time the purple color of the nitrosopyrimidine had disappeared. The resulting yellow solution was evaporated under reduced pressure and the residue chromatographed on a column of silica, by eluting first with methanol/chloroform (1:2) and then with methanol/chloroform (1:1), to give **5** (80 mg, 83%), identical with the sample of the same product prepared as described above.

Hydrogenation of 7-Alkoxy-5-aminofurazano[3,4-*d*]pyrimidines (5, 6, and 8). A solution of the 7-alkoxy-5-aminofurazano[3,4-*d*]pyrimidine (1.0 g) in deaerated methanol (50 mL)

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and water (50 mL) was hydrogenated at atmospheric temperature and pressure over a 10% palladized charcoal catalyst (100 mg) until hydrogen uptake ceased (ca. 3 h). The catalyst was removed by filtration under nitrogen, and the pH of the filtrate brought to 1 with aqueous sulfuric acid. The pyrimidinium sulfate was precipitated in 90–95% yield by the addition of ethanol/ether. 2,4,5-Triamino-6-(2-hydroxyethoxy)pyrimidinium sulfate hemihydrate (**16**) had mp >300 °C dec; UV (0.1 M HCl) 228 (log ε 3.87), and 277 (log ε 4.11); (0.1 M NaOH) 244 (log ε 3.82), and 287 (log ε 3.93). Anal. Calcd for $C_6H_{13}N_5SO_6 \cdot 0.5H_2O$: C, 24.7; H, 4.8; N, 24.0. Found: C, 24.3; H, 4.65; N, 23.8. The sulfate salts of **14**,[11] and of **15**,[11] were similarly obtained and had UV spectra identical with that of **16**.

Preparation of 4-Alkoxy-2-amino-6,7-diphenylpteridines (17–21). A solution of the appropriate 7-alkoxy-5-aminofurazano[3,4-*d*]pyrimidine, (**5,6** or **8–10**), (1.0 g), in deaerated 50% aqueous methanol (100 mL) was hydrogenated at atmospheric temperature and pressure over a 10% palladized charcoal catalyst until hydrogen uptake ceased (ca. 3 h). The catalyst was removed by filtration under nitrogen and a 50% molar excess of benzil added to the filtrate. The mixture was refluxed for 2–4 h under nitrogen and was then evaporated to dryness. The solid residue was extracted with warm hexane to remove unreacted benzil and was then chromatographed on a column of silica gel, by eluting with ethanol/dichloromethane (1:19). The main product from the column was the desired 4-alkoxy-2-amino-6,7-diphenylpteridine, which could be crystallized from ethanol. The yields and properties of products **17–21** are summarised in Table II.

2,3-Dihydro-5,7,8-triaminooxazolo[3,2-*c*]pyrimidinium Sulfate (23). The chloroethoxy compound **7** (200 mg, 0.93 mmol) in deaerated 50% aqueous methanol (25 mL) was hydrogenated at atmospheric temperature and pressure over a 10% palladized charcoal catalyst until hydrogen uptake ceased (ca. 2 h). Aqueous sulfuric acid (10%, 10 mL) was added and the catalyst was then removed by filtration. Ethanol (20 mL) and ether (20 mL) were added to the filtrate which was then allowed to stand at 0 °C for 4 h. The crystals which separated were collected and recrystallized from oxygen-free aqueous ethanol containing sulfuric acid, to give hydrated **23** (255 mg, 92%), mp >300 °C dec; IR (nujol) 3520, 3330, 3120 (NH_2), 2660 (NH_3), 1708, 1575, 1075, and 900 cm^{-1}; UV (2 M HCl) 223 sh (log ε 3.88), and 264 nm (log ε 3.84); UV (0.1 M HCl) 214 (log ε 4.16), 264 (log ε 3.69), and 288 nm (log ε 3.30); UV (H_2O) 218 (log ε 4.34) and 288 (log ε 3.84); ^1H NMR (60 MHz; CD_3SOCD_3) 4.21 (2 H, t, J = 7 Hz), 4.69 (2 H, t, J = 7 Hz). Anal. Calcd for $C_6H_9N_5O.H_2SO_4 \cdot 1.5H_2O$: C, 24.7; H, 4.8; N, 24.0. Found: C, 24.6; H, 4.9; N, 23.7.

Reaction of the 2,3-Dihydro-5,7,8-triaminooxazolo[3,2-*c*]pyrimidinium Cation (23) with Sodium Methoxide. The chloroethoxy compound **7** (504 mg, 2.33 mmol) in deaerated methanol (50 mL) was hydrogenated at atmospheric temperature and pressure over a 10% palladized charcoal catalyst (100 mg) until hydrogen uptake ceased (ca. 2 h). The catalyst was removed by filtration and 0.4 M methanolic sodium methoxide (10 mL) together with benzil (1.033 g) added to the filtrate. The solution was refluxed for 2 h, and was then cooled and neutralized with dilute methanolic sulfuric acid. Removal of solvent and chromatography of the residue on silica gel using ethanol/dichloromethane (1:19) as eluant, gave **17** (153 mg, 20%), see Table II, and **27** (260 mg, 43%), mp 260–62 °C dec; IR (nujol) 3430 and 3330 (NH_2 and OH), 1670 (C=O), 1610, 1545, 1450, and 1365 cm^{-1}; UV (EtOH) 228 (log ε 4.38), 248 (log ε 4.31), 299 (log ε 4.40), and 382 nm (log ε 4.10); UV (0.1 M HCl) 232 (log ε 4.44), 281 (log ε 4.23), and 366 nm (log ε 4.23); UV (0.1 M borax buffer, pH 9.2) 226 (log ε 4.37), 243 (log ε 4.32), 295 (log ε 4.36), and 380 nm (log ε 4.05); UV (H_2O) 224 (log ε 4.45), 243 sh (log ε 4.34), 295 (log ε 4.39), and 380 nm (log ε 4.16); ^1H NMR (80 MHz; CD_3SOCD_3) 3.76 (2 H, m, CH_2OH), 4.18 (2 H, t, J = 5 Hz, CH_2CH_2OH), 5.09 (1 H, br t, J = 5 Hz, OH), and 7.2–7.8 (12 H, m, 2 × Ph and NH_2). Anal. Calcd for $C_{20}H_{17}N_5O_2 \cdot H_2O$: C, 63.65; H, 5.1; N, 18.6. Found: C, 63.8; H, 4.8; N, 18.35.

Reaction of the 2,3-Dihydro-5,7,8-triaminooxazolo[3,2-*c*]pyrimidinium Cation (23) with Methanolic Sulfuric Acid. The chloroethoxy compound (7) (208 mg, 0.96 mmol) in deaerated methanol (20 mL) was hydrogenated at atmospheric temperature and pressure over a 10% palladized charcoal catalyst (50 mg) until hydrogen uptake ceased (ca. 2 h). The catalyst was removed by filtration, 1.8 M methanolic sulfuric acid (4 mL) added, and the solution heated under reflux for 72 h. Benzil (330 mg, 1.43 mmol) was added and refluxing was continued for a further 4 h. The reaction mixture was then neutralised with solid sodium hydrogen carbonate, and evaporated to dryness. The residue was washed with water, and the insoluble remainder chromatographed on a column of silica gel, with ethanol/dichloromethane (1:32) as eluant. Compound **27** (10 mg, 4%) was obtained, as well as a mixture containing two other products. Rechromatography of this mixture on silica gel using ethanol/hexane (1:4) as eluant gave **17** (30 mg, 9%) (see Table II) and **26** (120 mg, 32%), mp 261–62 °C dec (from EtOH); IR (nujol) 3380 (NH), 1710 (C=O), 1655, 1540, 1370, and 1115 cm^{-1}; UV (EtOH) 226 (log ε 4.40), 246 (log ε 4.33), 298 (log ε 4.42), and 380 nm (log ε 4.12); UV (0.1 M HCl) 231 (log ε 4.45), 281 (log ε 4.23), and 364 nm (log ε 4.24); UV (H_2O) 224 (log ε 4.39), 243 sh (log ε 4.30), 294 (log ε 4.37), and 381 nm (log ε 4.14); UV (0.1 M borax buffer, pH 9.2) 226 (log ε 4.39), 243 sh (log ε 4.32), 294 (log ε 4.38), and 3.81 nm (log ε 4.15); ^1H NMR (80 MHz; CD_3SOCD_3) 3.31 (3 H, s, OCH_3), 3.66 (2 H, t, J = 5.5 Hz, CH_2OCH_3), 4.30 (2 H, t, J = 5.5 Hz, NCH_2), 7.15–7.60 (10 H, m, 2 × Ph). Anal. Calcd for $C_{21}H_{19}N_5O_2$: C, 67.55; H, 5.1; N, 18.75. Found: C, 67.25; H, 5.2; N, 18.6.

Reaction of the 2,3-Dihydro-5,7,8-triaminooxazolo[3,2-*c*]pyrimidinium Cation (23) with Aqueous Sodium Acetate. The chloroethoxy compound **7** (655 mg, 3 mmol) in deaerated 50% aqueous methanol (50 mL) was hydrogenated at atmospheric temperature and pressure over a 10% palladized charcoal catalyst (100 mg) until hydrogen uptake had ceased (ca. 2 h). The catalyst was removed by filtration, sodium acetate (1.53 g) was added to the filtrate, and the mixture was refluxed for 2 h under nitrogen. Benzil (1.02 g) was then added, and the mixture was refluxed for a further 4 h under nitrogen. The reaction mixture was evaporated to dryness and the residue extracted first with water (3 × 20 mL) and then with warm hexane (3 × 20 mL) to remove excess sodium acetate and benzil, respectively. The remaining insoluble solid product was chromatographed on a column of silica gel, eluting with ethanol/dichloromethane (1:24), to give **27** (255 mg, 33%), and (**29**) (25 mg, 7%), mp 260 °C dec (from EtOH); IR (nujol) 3380 (NH_2), 1735 ($COCH_3$), 1700 (C=O), 1655, 1540, 1370, and 1240 cm^{-1}; UV (EtOH) 228 (log ε 4.38), 248 (log ε 4.30), 299 (log ε 4.41), and 383 nm (log ε 4.12); ^1H NMR (80 MHz; CD_3SOCD_3) 1.96 (3 H, s, $COCH_3$), 4.33 (4 H, br s, CH_2CH_2), 7.34–7.37 (10 H, m, 2 × Ph), and 7.61 (2 H, br s, NH_2); ^1H NMR (80 MHz; $CDCl_3$) 2.13 (3 H, s, $COCH_3$), 4.39 (4 H, br s, CH_2CH_2), 6.35 (2 H, br s, NH_2), and 7.18–7.66 (10 H, m, 2 × Ph). Anal. Calcd for $C_{22}H_{19}N_5O_3$: C, 65.8; H, 4.8; N, 17.45. Found: C, 65.8; H, 4.9; N, 17.3.

Dimroth Rearrangement of 2-Amino-3-(2-hydroxyethyl)-6,7-diphenyl-4(3*H*)-pteridinone (27). Compound **27** (112 mg, 0.3 mmol) was refluxed in 5 M aqueous sodium hydroxide (35 mL) and methanol (15 mL) for 2 h. The reaction mixture was cooled and neutralized with dilute hydrochloric acid, and after further chilling a yellow product separated. Crystallization from methanol gave **31** (72 mg, 64%) mp 274–75 °C dec; IR (nujol) 3520, 1680 (C=O), 1550, 1380, and 705 cm^{-1}; UV (EtOH) 226 sh (log ε 4.35), 251 (log ε 4.26), 299 (log ε 4.37), and 381 nm (log ε 4.07); UV (0.1 M HCl) 234 sh (log ε 4.38), 292 (log ε 4.26), and 368 nm (log ε 4.14); UV (H_2O) 229 (log ε 4.30), 246 (log ε 4.24), 274 (log ε 4.22), and 387 nm (log ε 4.12); UV (0.1 M borax buffer, pH 9.2) 227 (log ε 4.30), 281 (log ε 4.36), and 390 nm (log ε 4.13); ^1H NMR (80 MHz; CD_3SOCD_3) 3.57 (4 H, br s, CH_2CH_2), 4.95 (1 H, br s, OH), 6.95 (1 H, br s, N^2–H), 7.35 (5 H, s, Ph), 7.40 (5 H, s, Ph), and 11.36 (1 H, br s, N^3–H). Anal. Calcd for $C_{20}H_{12}N_5O_2$: C, 66.8; H, 4.8; N, 19.5. Found: C, 66.5; H, 4.9; N, 19.2.

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Registry No. **4**, 90180-93-1; **5**, 98945-30-3; **6**, 98945-31-4; **7**, 98945-32-5; **8**, 98976-64-8; **9**, 98945-33-6; **10**, 98976-65-9; **14**, 22715-33-9; **15**, 98945-34-7; **16**, 98945-35-8; **17**, 98945-36-9; **18**,

60783-59-7; **19**, 98945-37-0; **20**, 98945-38-1; **21**, 98945-39-2; **23**, 98945-41-6; **23a**, 98945-43-8; **24**, 98945-42-7; **26**, 98945-44-9; **27**, 98945-45-0; **29**, 98945-47-2; **31**, 98945-46-1; MeOH, 67-56-1; EtOH, 64-17-5; $ClCH_2CH_2OH$, 107-07-3; $HOCH_2CH_2OH$, 107-21-1; $HO(CH_2)_5OH$, 111-29-5; $HOCH_2CH(OH)CH_2OH$, 56-81-5; 2,2-dichloroethanol, 598-38-9; 2,2,2-tricholoroethanol, 115-20-8; glycolic acid, 79-14-1; ethyl glycolate, 623-50-7; 2,4-diamino-6-methoxy-5-nitrosopyrimidine, 98143-11-4; benzil, 134-81-6.

α,α-Dimethoxy-*o*-xylylene (5-(Dimethoxymethylene)-6-methylene-1,3-cyclohexadiene): Formation by 1,4-Elimination and Electrocyclic Routes and Reactions

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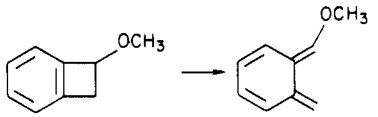
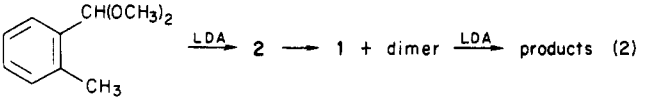
The title reactive intermediate **4**, which features an unprecedented (*Z*)-alkoxy substituent, is generated in two independent ways. The ortho ester **5** undergoes 1,4-elimination on treatment with lithium diisopropylamide, at convenient rates in the temperature range 50–70 °C. In the absence of added dienophile, **4** generated in this manner forms a spiro [2 + 4] dimer and a [4 + 4] dimer, both involving bonding between the two unsubstituted methylene groups. Diels–Alder adducts of **4** with norbornene (NB), norbornadiene, and cyclopentene are described. The ketal **8** formed from **4** and NB undergoes further 1,4-elimination, generating a new *o*-xylylene which in turn adds a second NB to yield the novel bis-adduct **11**. Thermal opening of α,α-dimethoxybenzocyclobutene (**6**) is also used to generate **4**. Rate constants for this reaction were determined over the temperature range 132–168 °C, through the use of *N*-phenylmaleimide, which efficiently traps the intermediate, thereby preventing reclosure to **6** and other decomposition reactions. The E_a for this electrocyclic opening is 33.6 kcal/mol; comparative data from the literature are discussed. In the absence of a dienophile, **4** generated in this way recloses to **6** as its major reaction pathway but also undergoes an unusual rearrangement to form methyl *o*-ethylbenzoate (**26**). The overall rate of this reaction is ca. one-tenth that of the opening of **6** to **4** and restricts the range of dienophiles which can be used to trap **4** generated from **6**. For example, even at the lowest temperature (132 °C) needed to observe electrocyclic opening, and in the presence of a very large excess of NB, competitive cycloadduct formation and rearrangement to **26** are observed. Flash vacuum pyrolysis of **6** was also briefly examined.

The elegant work of Sammes and colleagues[1] demonstrated that the thermal conversion of α-methoxybenzocyclobutene (**1**, name is common usage; IUPAC rules require the "dihydro" designation) to α-methoxy-*o*-xylylene (**2**) occurs with exclusive formation of the *E* isomer as shown in eq 1. The methoxy substituent of **1** causes a



1 2 (1)

remarkable (ca. 9 kcal/mol) lowering of the activation energy for this ring-opening reaction, compared with the unsubstituted case.[1] The methoxy system also differs from the unsubstituted material in that **2** closes readily to reform **1** under conditions where *o*-xylylene, at its steady-state concentration, undergoes preferential (second-order) dimerization and polymerization. The activation parameters for the reactions of **2** are unknown, whereas the temperature-dependent behavior of *o*-xylylene can be appreciated by consideration of these parameters as determined by Roth and co-workers.[2] We have recently shown[3] that the acetal **3** on treatment with lithium diisopropylamide (LDA) also affords **2** in high yield, and arguments were presented supporting the view that this process also forms the *E* isomer as the sole trappable (Diels–Alder) intermediate. In qualitative agreement with Sammes' observation, conversion of **2** to **1** was also demonstrated, although dimer of **2** was also formed (eq 2).



3 (2)

Very recently Kirmse, Rondan, and Houk[4] have described the effects of substituents on the formally analogous (to eq 1) cyclobutene–butadiene rearrangement; a 3-methoxy substituent lowers the activation barrier here also by ca. 9 kcal/mol and forms exclusively the (*E*)-vinyl ether (outward rotation of the alkoxy group). When an alkoxy group is constrained by orbital symmetry effects to move inward (as in *cis*-3,4-dimethoxycyclobutene), appreciable destabilization of the transition state results. Although net rate enhancement was observed for this material, the geometrically very similar 3,3-dimethoxycyclobutene undergoes rearrangement at a rate comparable to, or slightly slower than, that of the unsubstituted parent olefin.[5]

α,α-Dimethoxy-*o*-xylylene (**4**) is an especially intriguing material in this context, since it is the simplest representative of an unknown class of *o*-xylylenes, in which one alkoxy group must, in the planar structure, assume the *Z* geometry. We envisioned approaching **4** in the two ways

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(5) We thank Professor Kirmse for providing the data on 3,3-dimethoxycyclobutene (E_a = 32.8 kcal/mol; log *A* = 13.7) and permission to quote these unpublished results.

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