Preparation of 8-Substituted Pyrido[2,3-*d*]pyrimidines (N5-Deazapterins)

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We report on the syntheses of some simply substituted 8-methylpyrido[2,3-*d*]pyrimidines (8-methyl-N5-deazapterins). We have found that purified triformyl methane condenses with 2-amino-6-(methylamino)pyrimidin-4(3*H*)-one (**11**) to give 6-formyl-N5-deazapterin (**10a**) in good yield. α,β-Unsaturated carbonyl compounds and their protected forms, e.g., β-halo acetals, also react with **11** in a Michael reaction to give 8-methyl-N5-deazapterins in good yield. Only one of the two possible isomeric products from reaction with the α,β-unsaturated carbonyl compounds was observed.

Introduction

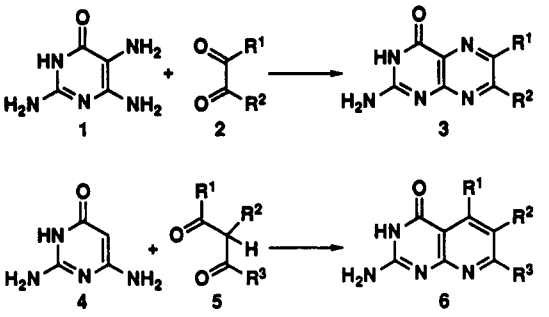
Analogues of folic acid, particularly inhibitors of DHFR, constitute a class of cytotoxic drugs, the antifolates, which are important anticancer, antimalarial, and antibacterial agents.[1] While most such inhibitors, such as methotrexate and trimethoprim, contain a 2,4-diaminopyrimidine or 2,4-diaminopteridine ring, some compounds which contain a substrate-like ring system, i.e., 2-aminopteridin-4(3*H*)-one (pterin), have been found to be inhibitors, e.g., N5-deazafolate.[2] In an investigation to design new mechanism-based compounds with biological activity for the enzyme dihydrofolate reductase (DHFR; tetrahydrofolate: $NADP^+$ oxidoreductase, EC 1.5.1.3), we have recently[3] reported a new class of substrates, the 8-substituted-pterins. Some related design considerations suggested the N5-deaza analogues as potential mechanism-based inhibitors.[4] This class of compound, which possesses an activated quinonoid structure analogous to that in the 8-substituted-pterins,[5] has not been reported previously. Synthesis of the N5-deazapteridine nucleus has been achieved previously by a number of strategies, the closest to the present work being the preparation of some N5-deaza-pteridine-2,4-(3*H*,8*H*)-diones (N5-deazalumazines) substituted by ribityl or related groups in the 8 position.[6,7]

By logical extension of the synthesis of pterins **3** where a diaminopyrimidine **1** is condensed with an α-dicarbonyl compound **2**, the most obvious route to N5-deazapterins **6** would be condensation of an aminopyrimidine **4** with a β-dicarbonyl compound **5** (Scheme I).

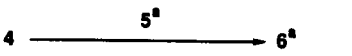
Using this approach, Robins and Hitchings[8] found that both β-diketones (**5**: R^1, $R^3 \neq H$) and β-keto aldehydes (**5**: R^1 or $R^3 = H$) reacted as expected to give **6**. As for the synthesis of pterins with unsymmetrical dicarbonyls (**2**: $R^1 \neq R^2$),[5] possible ambiguity exists in the orientation of addition of the keto aldehyde. However, they found that keto aldehydes gave **6** substituted in the 7-position rather than 5-position. In later work on the N5-deaza-8-substituted lumazines, Wood and co-workers initially reported the reverse orientation of addition of the keto aldehydes[6] but subsequently revised[7] their product assignment in conformity with ref 8 on the basis of ^1H NOE experiments. The problem of isomer assignment is not trivial even for the simplest cases involving **5** where R^1 or R^3 is methyl and R^1 or R^3 is hydrogen (i.e., 3-keto-2-R^2-butanal) because protons of both 5-methyl and 7-methyl groups in N5-deaza-8-substituted lumazines undergo deuterium exchange.[9] By contrast, in the analogous pterin syntheses possible 6-methyl or 7-methyl products can be distinguished by deuterium exchange of the 7-methyl protons only.[5]

Bernetti et al.[10] used malondialdehydes **5a** (R^1, $R^3 = H$) to prepare 6-substituted N5-deazapterins **6a** (R^1, $R^3 = H$) (Scheme II). While malondialdehyde itself is unstable and cannot be isolated from aqueous solution, C2 substituted malondialdehydes bearing a strong electron withdrawing group,[11,12] or a bulky substituent[13] are isolable

Scheme I



Scheme II



[a] $R^1 = R^3 = H$; $R^2 = NO_2$, CO_2Et, H from in situ deprotection of malonaldehyde bis(diethyl acetal).

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(1) *Folate Antagonists as Therapeutic Agents*; Sirotnak, F. M., Burchall, J. J., Ensminer, W. B., Montgomery, J. A., Eds.; Academic Press: New York, 1984; Vols. 1 and 2.
(2) Palmer, D. C.; Skotniki, J. S.; Taylor, E. C. *Progr. Med. Chem.* **1988**, *25*, 85.
(3) Thibault, V.; Koen, M. J.; Gready, J. E. *Biochemistry* **1989**, *28*, 6042.
(4) Gready, J. E., unpublished results.
(5) Pfleiderer, W. In *Comprehensive Heterocyclic Chemistry—The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds*; Boulton, A. J., McKillop, A., Eds.; Pergamon Press: New York, 1984; Vol. 3.
(6) Paterson, T.; Wood, H. C. S. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1041.
(7) Wood, H. C. S.; Wrigglesworth, R.; Yeowell, D. A.; Gurney, F. W.; Hurlbert, B. S. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1225.
(8) Robins, R. K.; Hitchings, G. H. *J. Am. Chem. Soc.* **1958**, *80*, 3449.
(9) Al-Hassan, S. S.; Kulick, R. J.; Livingstone, D. B.; Suckling, C. J.; Wood, H. C. S.; Wrigglesworth, R.; Ferrone, R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2645.
(10) Bernetti, R.; Mancini, F.; Price, C. C. *J. Org. Chem.* **1962**, *27*, 2863.

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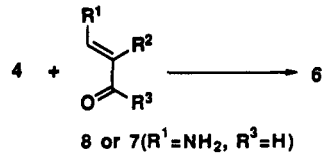
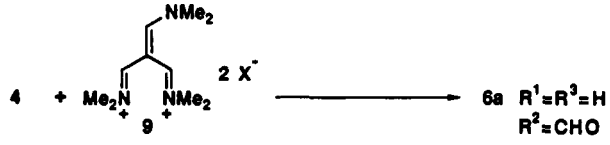
Scheme III



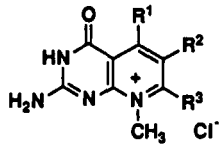
8 or 7(R^1=NH_2, R^3=H)

Scheme IV



as keto–enol tautomeric mixtures. β-Enaminocarbonyls **7** as C3 bridging units were used by Stark and Breitmaier[14–16] (Scheme III; **6** R^1 = H), but this method has been little used.[15] As a modification, Wood and coworkers[6,7] used α,β-unsaturated carbonyl compounds **8** (Scheme III), which are synthetic equivalents of β-dicarbonyl compounds (Scheme I). Temple et al.[15] prepared N5-deaza analogues of aminopterin, methotrexate, and folic acid by reductive alkylation of diethyl (*p*-aminobenzoyl)-L-glutamate with 6-formyl-N5-deazapterin **6a** (R^2 = CHO) prepared by condensation of the pyrimidine **4** with crude unhydrolyzed triformylmethane **9** (Scheme IV).

Although the synthesis and purification of triformylmethane, a C2-substituted malondialdehyde **5a** (R^1 = R^3 = H, R^2 = CHO), was first reported by Arnold,[17] Temple et al. found this isolation method poorly reproducible but were able to successfully use the unhydrolyzed precursor **9** (X = Cl^-).[15] However, because of these problems with triformylmethane, Taylor et al.[18] developed another multistep synthesis of **6a** via the 6-bromo and 6-styryl derivatives.



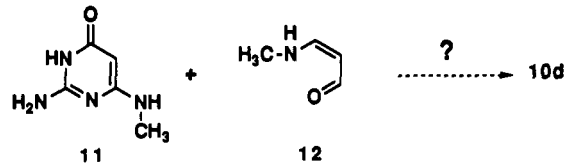
10

In our attempts to prepare the new class of 8-substituted derivatives of N5-deazapterins **10**, we investigated the literature methods in Schemes I–IV focusing on the 8-methyl compounds with variable combinations of methyl substituents in the 5, 6, and 7 positions.

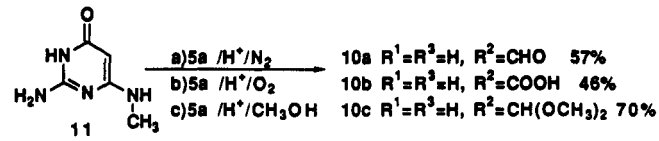
Results and Discussion

Attempts at Enaminoacrolein Approach (Scheme III). Our first attempt at the preparation of **10** (R^1 = R^2 = R^3 = H) was based on the work of Stark and Breitmaier.[14] As the mechanism of the condensation was not clear and an 8-methyl substituent was required in the product, it was necessary that both the pyrimidine **11** and the aminoacrolein **12** be substituted with an *N*-methyl group

Scheme V



Scheme VI



(Scheme V). Initial deprotection of malonaldehyde bis(diethyl acetal) to ethoxyacrolein[19] followed by reaction with a number of methylamine equivalents (methylamine hydrochloride, methylamine in water or methanol solution, and methylamine gas) failed to give the desired amine **12**. This method to deazapterins was not pursued further.

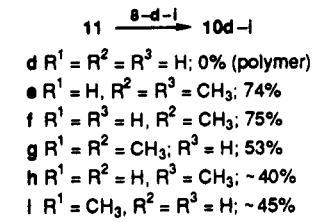
Triformylmethane Approach (Scheme IV). Our work had as its starting point the report of a new method[20] for isolating triformylmethane as the tetrafluoroborate salt (Scheme IV; X = BF_4^-), which we confirmed could be purified, stored, and reproducibly hydrolyzed to give triformylmethane in reasonable yield (40–60%). A subsequent reported isolation by Arnold[21] as the perbromide salt (Scheme IV; X = Br_3^-) was thus not pursued. We envisaged that the deazaaldehyde product **10a** from this condensation could be used to give both the 6-methyl compound **10f** (Scheme VII) by reduction and also the unsubstituted compound **10d** by decarboxylation[22] of the corresponding carboxylic acid **10b** (Scheme VI). Condensation to give **10a** in water solution was facile (method a) at room temperature, but exclusion of oxygen was necessary to avoid oxidation to the acid **10b** (Method b). Use of methanol in place of water as solvent (method c) led to recovery of the corresponding dimethyl acetal **10c** as determined by X-ray crystallography.[23]

Oxidation of the aldehyde by permanganate or hydrogen peroxide could not be achieved cleanly and was abandoned as unnecessary due to the facile autoxidation under method b. Decarboxylation of the acid to give **10b** could be achieved by refluxing in diphenyl ether for 30 min but not cleanly or in good yield (30%). This method was also abandoned with the development of a different procedure described next.

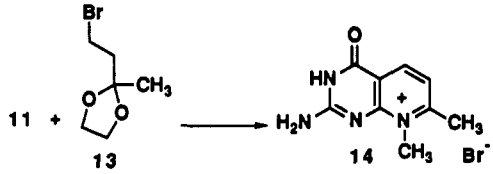
α,β-Unsaturated Carbonyl Approach (Scheme III). In order to prepare 8-methyl-N5-deazapterins bearing simple substituents (i.e., methyl groups) in the 5-, 6-, and/or 7-positions, the potentially more flexible method of Wood[7] was utilized (Scheme VII). This method was also attractive as the α,β-unsaturated carbonyl compounds were readily available. Using this methodology we were able to easily prepare the hydrochlorides of **10f**, **10g**, and **10e**. As shown in Scheme VII, reaction with acrolein in an attempt to prepare **10d** gave only polymeric material.

(11) Trofimenko, S. *J. Org. Chem.* **1963**, *28*, 3243.
(12) Torii, S.; Inokuchi, T.; Kubota, M. *Synthesis* **1986**, 400.
(13) Reichardt, C.; Wurthwein, E. U. *Chem. Ber.* **1974**, *107*, 3454.
(14) Stark, E.; Breitmaier, E. *Tetrahedron* **1973**, *29*, 2209.
(15) Temple, C., Jr.; Elliott, R. D.; Montgomery, J. *J. Org. Chem.* **1982**, *47*, 761.
(16) Stark, E.; Kraas, E.; Tjoeng, F.-S.; Jung, G.; Breitmaier, E. *Chem. Ber.* **1974**, *107*, 2537.
(17) Arnold, Z. *Collect. Czech. Chem. Commun.* **1961**, *26*, 3051.
(18) Taylor, E. C.; Yoon, C.-M. *Synth. Commun.* **1988**, *18*(11), 1187.
(19) Klinko, V.; Protopopova, T.; Smirnov, N.; Skoldinov, A. *Zhur. Obsch. Khim.* **1962**, *32*, 2961.
(20) Keshavarz-K, M.; Cox, S. D.; Angus, R. O.; Wudl, F. *Synthesis* **1988**, *8*, 641.
(21) Budesinsky, M.; Fieldler, P.; Arnold, Z. *Synthesis* **1989**, 858.
(22) *The Chemistry of Heterocyclic Compounds. Fused Pyrimidines: Part 3. Pteridines*; Brown, D. J., Ed.; John Wiley and Sons: New York, 1988.
(23) Koen, M. J.; Gready, J. E.; Hambley, T. W., to be published.

Scheme VII



Scheme VIII



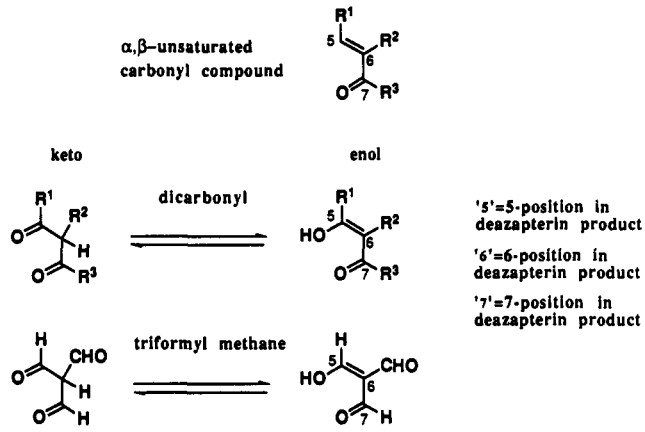
However, we were able to successfully prepare 8-methyl-N5-deazapterin (**10d**) using the method of Bernetti et al.[10] with malonaldehyde bis(diethyl acetal). It is not known if the reactive species is the fully deprotected malonaldehyde (i.e., reaction as in Scheme II) or whether the partially deprotected ethoxyacrolein (EtOCH=CHCHO)[19] undergoes condensation with the pyrimidine **11** (i.e., analogously to Scheme III). Problems were encountered in attempts to prepare the 7,8-dimethyl- (**10h**) and 5,8-dimethyl-N5-deazapterins (**10i**) by this method. In each case, product could be identified in the complex reaction mixture using both UV/vis and ^{1}H NMR spectroscopies but could not be isolated. Filtration of the flocculent solid which formed on addition of diethyl ether to the reaction mixture gave only a gummy oil.

However, we were able to obtain 7,8-dimethyl-N5-deazapterin hydro*bromide* (**14**) by reaction of the pyrimidine with the methylvinyl ketone (MVK) equivalent, 2-(β-bromoethyl)-2-methyl-1,3-dioxalane (**13**)[24] (Scheme VIII), although the yield was not high (56% yield). We were intrigued as to which functional group of MVK had to be protected in order to give clean product. Reaction with 4-bromo-2-butanone (only the double bond protected) also gave the desired product. Indeed, reaction of MVK with the pyrimidine, and addition of HBr, rather than HCl, also gave the product. In each case the products had identical ^{1}H NMR and UV/vis spectra. On the basis of this result, it would seem fair to suggest that MVK polymerization is preferred over reaction with **11** to give deazapterin product.

Confirmation of the 5,6,8- (**10g**) and 6,7,8- (**10e**) isomer assignments was made on the basis of NOE experiments. Enhancements upon irradiation of the following groups of **10e** were, for the *N*-CH_3 group, 7-CH_3 10%, 6-CH_3 5%, and 5-H −2%, for the 7-CH_3 group, *N*-CH_3 0%, 6-CH_3 0%, and 5-H 0%, and for the 6-CH_3 group, 5-H 26%, 7-CH_3 11%, and *N*-CH_3 0%. These data support the assumption that steric crowding has pushed the 7-methyl group out of plane, while the slight negative NOE in the 5-H resonance from *N*-CH_3 irradiation indicates other more complicated polarization transfer processes are occurring. Enhancements upon irradiation of the following groups of **10g** were, for the *N*-CH_3 group, 7-H 14%, 6-CH_3 0%, and 5-CH_3 0%, and for the 6-CH_3 group, *N*-CH_3 0%, 7-CH_3 12%, and 5-CH_3 8%.

(24) Hsung, R. P. *Synth. Commun.* **1990**, *20*(8), 1175.

Scheme IX



General Discussion

The major problem in N5-deazapterin syntheses has been the development of a suitably functionalized, yet stable, C3 unit. It would appear that the formation of the deazapterin skeleton from a pyrimidine and the C3 units discussed here is best described as a Michael addition. The α,β-unsaturated carbonyl compounds employed are classic Michael acceptors. The β-dicarbonyls are in equilibrium with their corresponding tautomeric α,β-unsaturated carbonyl forms. The bromo compound **13** is a β-halo carbonyl compound which can undergo base-catalyzed elimination to furnish the protected α,β-unsaturated carbonyl compound in situ. Protection of methyl vinyl ketone as the bromo acetal **13** was necessary as MVK itself was too prone to polymerization to be useful.

The orientation of addition, as determined by Wood[7] and confirmed by ourselves using NOE, supports the aforementioned analysis. The Michael addition results in products whose orientation is the opposite of that obtained in Skraup and Doebner–von Miller syntheses of quinolines.[25] It is possible to identify an identical functional group in all, except the MVK equivalent used here, of the commonly employed C3 units used in N5-deazapterin syntheses (Scheme IX). Each C3 adduct possesses an α,β-unsaturated carbonyl substructure, either explicitly or as a tautomer. It is this α,β-unsaturated portion which best explains the orientation of addition. Although there exists the possibility of isomeric products being obtained from these reactions, experimentally this has been found not to be the case. As stated earlier, the unsubstituted deazapterin **10d** is formed by reaction of pyrimidine **11** with malonaldehyde bis(diethyl acetal). It is likely that the acetal deprotects in situ to furnish ethoxyacrolein **8** (R^1 = OEt, R^2 = R^3 = H), which can react to give the product. Wood[7] proposed a rule that the most reactive position of the pyrimidine, the 5-position, will condense with the most reactive site in the C3 fragment, but we propose a revision of this rule by saying that the 6-amino nitrogen will condense with the carbonyl group which is least tautomerized in the enol form. This revised rule is not meant to imply a mechanism for the order of the condensation which is still under investigation.

In our preparations of simply substituted 8-methyl-N5-deazapterins use of α,β-unsaturated carbonyl compounds as the C3 unit has been the most successful approach. We have also demonstrated the use of purified triformyl-

(25) Jones, G. In *Quinolines Part 1*; Vol. 32 of *The Chemistry of Heterocyclic Chemistry*; Jones, G., Ed.; Wiley-Interscience: London, 1977.

methane in the synthesis of deazapterins. The successful use of protected MVK in deazapterin synthesis opens the possibility of using a wide range of other Michael acceptors. These 8-substituted N5-deazapterins are much easier to work with than the corresponding 8-R-pterins,[26,27] although they share many physical properties which are discussed separately.[28] Biological activity with DHFR will also be reported separately.[29]

Experimental Section

^{1}H NMR and UV/vis spectra were recorded on Bruker AS200 and Varian Cary-3 spectrometers. Mass spectra were recorded on an A.E.I MS9 spectrometer at 70 eV with DS30 data handling system for high-resolution spectra. Microanalyses were performed by Australian Microanalytical Service, National Analytical Labs, Victoria, Australia. Reversed-phase flash silica was prepared by the method of Kuhler and Lindsten.[30] 2-Amino-4,6-dihydroxypyrimidine starting material[31] was from Aldrich. In common with our experience for the hydrochloride salts of 8-substituted pterins, it was difficult to obtain clean microanalytical results because of the presence of fractional amounts of HCl and H_2O: EIHRMS data are reported in most cases.

Preparation of 2-Amino-6-formyl-8-methylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one Hydrochloride (8-Methyl-6-formyl-N5-deazapterin-HCl, 10a). 2-Amino-6-(methylamino)pyrimidin-4(3*H*)-one (0.25 g, 1.78 mmol) (11) prepared as reported[31] was dissolved in hot (60 °C) degassed water (250 mL) under a nitrogen atmosphere. Freshly sublimed triformyl methane[19] (0.18 g, 1.78 mmol) and dilute degassed hydrochloric acid (5 mL, 0.1 M) were added, and stirring was continued for 2 h. The water was removed at reduced pressure to give the crude product which was redissolved in degassed water (ca. 5 mL) and filtered through a short reversed-phase silica column[30] (eluent methanol/water (8:1)) collecting the intermediate fluorescent-blue fractions, which were then freeze-dried and recrystallized from methanol to give **10a** as a light yellow powder (0.24 g, 56%, mp > 350 °C): ^{1}H NMR (DMSO-d_6) δ 3.98 (s, NCH_3), 8.76 (d, J = 2.1 Hz, C7-*H*), 9.26 (d, J = 2.1, C5-*H*), 9.90 (s, 6-C*H*O); UV (pH 1) λ_{max}, nm (log ϵ) 216 (4.29), 245sh (3.89), 285sh (4.07), 299 (4.19), 353 (4.11); EIHRMS m/e calcd for $C_9H_8N_4O$ (M^+ - HCl) 204.0647, found 204.0644.

Preparation of 2-Amino-8-methylpyrido[2,3-*d*]pyrimidine-6-carboxylic Acid (8-Methyl-N5-deazapterin-6-carboxylic Acid, 10b). The pyrimidine 11 (0.25 g, 1.78 mmol) was dissolved in hot (60 °C) water (250 mL). Freshly sublimed triformyl methane (0.18 g, 1.78 mmol) and dilute hydrochloric acid (5 mL, 0.1 M) were added, and stirring was continued for 2 h as air was drawn through the solution. On cooling, the insoluble product was collected at the pump and then recrystallized from water to give **10b** as white microneedles (0.17 g, 46%, mp > 350 °C). Preparation by this method of aerial oxidation was superior to attempted oxidation of **10a** by either permanganate or hydrogen peroxide: ^{1}H NMR (DMSO-d_6) δ 4.08 (s, NCH_3), 8.82 (d, J = 1.84 Hz, C7-*H*), 9.42 (d, J = 1.84, C5-*H*), 12.72 (bs, COO*H*); UV (pH 1) λ_{max}, nm (log ϵ) 217 (4.22), 247 (3.72), 294 (4.27), 349 (4.01); EIHRMS m/e calcd for $C_8H_8N_4O$ (M^+ - CO_2) 176.0698, found 176.0690.

Preparation of 2-Amino-6-(dimethoxymethyl)-8-methylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one Hydrochloride (8-Methyl-6-(dimethoxymethyl)-N5-deazapterin-HCl, 10c). The pyrimidine 11 (0.695 g, 4.97 mmol) was dissolved in hot (60 °C) methanol (150 mL) under N_2. Freshly sublimed triformyl methane (0.496 g, 4.97 mmol) and dilute hydrochloric acid (5 mL, 0.1 M) were added, and the mixture was stirred for 12 h. The methanol was removed at reduced pressure to give the crude product which, after purification by RP silica as for **10a**, was recrystallized from methanol/methanolic-HCl and activated charcoal to give **10c** as yellow-brown prisms (0.57 g, 40%, mp > 350 °C): ^{1}H NMR (D_2O) δ 3.48 (s, 2 × -OCH_3), 4.13 (s, NCH_3), 5.64 (s, C6-C*H*), 8.76 (d, J = 2.1 Hz, C7-*H*), 8.78 (d, J = 2.1, C5-*H*); UV (pH 1) λ_{max}, nm (log ϵ) 217 (4.28), 250sh (3.84), 281 (4.21), 352 (4.02). Anal. Calcd for $C_{11}H_{15}ClN_4O_3$: C, 46.08; H, 5.27; Cl, 12.37; N, 19.55. Found: C, 46.01; H, 5.49; Cl, 12.77; N, 19.28.

Preparation of 2-Amino-8-methylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one Hydrochloride (8-Methyl-N5-deazapterin-HCl, 10d). Reaction of the pyrimidine 11 with acrolein **8d** gave polymeric material in less than 2 min; this method was abandoned. The pyrimidine 11 (0.25 g, 1.78 mmol) was suspended in a mixture of methanol (10 mL) and water (40 mL). Malonaldehyde bis(diethyl acetal) (0.43 mL, 0.39 g, 1.78 mmol) and methanolic-HCl (saturated solution, 5 drops) were added, and the resultant suspension was heated at 70 °C for 48 h. After removal of methanol at reduced pressure, the aqueous phase was extracted with chloroform (2 × 20 mL). The aqueous phase was taken to dryness on the rotary, recrystallized from ethanol, and purified by RP chromatography to give **10d** as a cream solid (0.20 g, 53%, mp > 350 °C): ^{1}H NMR (D_2O) δ 4.13 (s, NCH_3), 7.41 (dd, $^3J_{C6\text{-}H,C7\text{-}H}$ = 6.4 Hz, $^3J_{C6\text{-}H,C5\text{-}H}$ = 7.8 Hz, C6-*H*), 8.67 (dd, $^3J_{C7\text{-}H,C6\text{-}H}$ = 6.4 Hz, $^4J_{C7\text{-}H,C5\text{-}H}$ = 1.58 Hz, C7-*H*), 8.82 (dd, $^3J_{C5\text{-}H,C6\text{-}H}$ = 7.8 Hz, $^4J_{C5\text{-}H,C7\text{-}H}$ = 1.58 Hz, C5-*H*); UV (pH 1) λ_{max}, nm (log ϵ) 216 (4.25), 242sh (3.79), 276 (4.11), 347 (3.97); EIHRMS m/e calcd for $C_8H_8N_4O$ (M^+ - HCl) 176.0698, found 176.0695.

Preparation of 2-Amino-6,7,8-trimethylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one Hydrochloride (6,7,8-Trimethyl-N5-deazapterin-HCl, 10e). The pyrimidine 11 (0.25 g, 1.78 mmol) was suspended in freshly prepared methyl isopropenyl ketone[32] (2.2 g, 26.4 mmol, 15 equiv) and stirred at 25 °C for 3 h. Dilute hydrochloric acid (5 mL, 0.1 M) was added and stirring continued for a further 14 h before the crude mixture was taken to dryness on the rotary evaporator and recrystallized from ethanol to give **10e** as white needles (0.35 g, 83%, mp > 350 °C). Unambiguously confirmed by NOE experiments (see text): ^{1}H NMR (D_2O–DSS) δ 2.47 (s, C6-CH_3), 2.77 (s, C7-CH_3), 4.13 (s, NCH_3), 8.52 (s, C5-*H*); C7-CH_3 undergoes deuterium exchange virtually quantatively in less than 5 min at pD 11; UV (pH 1) λ_{max}, nm (log ϵ) 219 (4.29), 280 (4.12), 355 (4.06). Anal. Calcd for $C_{10}H_{11}ClN_4O$: C, 49.89; H, 5.40; Cl, 14.73; N, 23.20. Found: C, 49.93; H, 5.36; Cl, 14.56; N, 23.53.

Preparation of 2-Amino-6,8-dimethylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one Hydrochloride (6,8-Dimethyl-N5-deazapterin-HCl, 10f). The pyrimidine 11 (0.115 g, 0.82 mmol) was suspended in freshly distilled methacrolein (5 mL, 4.24 g, 61 mmol, 75 equiv) and stirred at 30 °C for 12 h. Dilute hydrochloric acid (5 mL, 0.1 M) was added and stirring continued for a further 2 h. The mixture was filtered at the pump to remove polymerized methacrolein. The aqueous phase was extracted with chloroform (2 × 20 mL). The filtrate was taken to dryness on the rotary evaporator and recrystallized from ethanol to give **10f** as white needles (0.139 g, 75%, mp > 350 °C): ^{1}H NMR (D_2O) δ 2.40 (s, C6-CH_3), 4.07 (s, NCH_3), 8.53 (d, J = 1.84 Hz, C7-*H*), 8.65 (d, J = 1.84, C5-*H*); UV (pH 1) λ_{max}, nm (log ϵ) 218 (4.23), 278 (4.15), 354 (3.94); EIHRMS m/e calcd for $C_9H_{10}N_4O$ (M^+ - HCl) 190.0854, found 190.0852.

Preparation of 2-Amino-5,6,8-trimethylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one Hydrochloride (5,6,8-Trimethyl-N5-deazapterin-HCl, 10g). The pyrimidine 11 (100 mg, 0.71 mmol) was suspended in tiglic aldehyde (ALDRICH, 1.2 g, 14.3 mmol, 20 equiv) and heated with stirring at 60 °C for 4 h. Dilute HCl (5 mL, 0.1 M) was added and stirring continued at 60 °C for 24 h. All of the solvent was removed on the rotary evaporator to give a pale yellow residue, which was recrystallized from ethanol to give **10g** as cream microneedles (0.091 g, 53%, mp > 350 °C), unambiguously confirmed by NOE experiments (see text): ^{1}H NMR (D_2O) δ 2.31 (s, C6-CH_3), 2.80 (s, C5-CH_3), 3.98 (s, NCH_3), 8.36 (s, C7-*H*); UV (pH 1) λ_{max}, nm (log ϵ) 219sh (4.12), 233 (4.20), 278 (4.06), 346 (3.86); EIHRMS m/e calcd for $C_{10}H_{12}N_4O$ (M^+ - HCl) 204.1011, found 204.1001.

Attempted Preparation of 2-Amino-5,8-dimethylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one Hydrochloride (5,8-Dimethyl-

(26) Pfleiderer, W.; Bunting, J. W.; Perrin, D. D.; Nübel, G. *Chem. Ber.* **1968**, *101*, 1072.
(27) Ivery, M. T. G.; Gready, J. E. *Biol. Chem. Hoppe-Seyler* **1992**, *373*, 1125.
(28) Ivery, M. T. G.; Gready, J. E., to be published.
(29) Ivery, M. T. G.; Gready, J. E., to be published.
(30) Kuhler, T. C.; Lindsten, G. R. *J. Org. Chem.* **1983**, *48*, 3589.
(31) Fidler, W. E.; Wood, H. C. S. *J. Chem. Soc.* **1954**, 4157.
(32) Landau, E. F.; Irany, E. P. *J. Org. Chem.* **1946**, 422.

N5-deazapterin-HCl, 10i). The pyrimidine 11 (100 mg, 0.71 mmol) was suspended in freshly distilled crotonaldehyde (7.5 mL, 6.23 g, 90 mmol, 50 equiv) and heated with stirring at 60 °C for 12 h. Dilute HCl (5 mL, 0.1 M) was added and stirring continued at 60 °C for 6 h. The mixture was extracted with chloroform (2 × 30 mL) and the aqueous phase taken to dryness on the rotary. The resultant residue could not be purified, although the ^{1}H NMR indicated the presence of the desired compound; yield based upon mass of polymer was ~45%.

Attempted Preparation of 2-Amino-7,8-dimethylpyrido-[2,3-*d*]pyrimidin-4(3*H*)-one Hydrochloride (7,8-Dimethyl-N5-deazapterin-HCl, 10h). The pyrimidine 11 (0.25 g, 1.8 mmol) was suspended in freshly distilled methyl vinyl ketone (11 mL, 9.3 g, 134 mmol, 75 equiv) and heated at 60 °C for 12 h. Dilute HCl (5 mL, 0.1 M) was added and stirring continued for a further 18 h. Removal of the solvent on the rotary evaporator gave a residue which could not be recrystallized and which by ^{1}H NMR was a mixture of polymer and product.

Preparation of 2-Amino-7,8-dimethylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one Hydrobromide (7,8-Dimethyl-N5-deazapterin-HBr, 14). The pyrimidine 11 (0.28 g, 2 mmol) was added to freshly distilled 2-(β-bromoethyl)-2-methyl-1,3-dioxolane[24] (2.14 g, 11 mmol, 5 equiv) and the mixture stirred at 60 °C under N_2 for 16 h. The brown solid which formed was filtered at the pump and washed with a little cold methanol to give a cream solid. Concentration of solvent to dryness and washing of the residue with a little ethanol produced a second crop. Recrystallization from ethanol gave 14 as fine cream needles (0.38 g, 70%, mp > 350 °C): ^{1}H NMR (D_2O) δ 2.78 (s, C7-C*H*$_3$), 4.05 (s, NC*H*$_3$), 7.34 (d, J = 8.04 Hz, C6-*H*), 8.59 (d, J = 8.04, C5-*H*); UV (pH 1) λ_{max}, nm (log ε) 215 (4.32), 279 (4.10), 348 (4.12); EIHRMS m/e calcd for $C_9H_{10}N_4O$ (M^+ - HBr) 190.0854, found 190.0854.

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Supplementary Material Available: ^{1}H NMR data for all deazapterins **10a–10g** and **14** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.