2-isopropyl-1,3-dithiane, 64414-34-2; isopropyl iodide, 75-30-9; 2-cyano-2-*n*-butyl-1,3-dithiane, 64414-33-1; *n*-butyl bromide, 109-65-9; 2-cyano-2-benzyl-1,3-dithiane, 64414-32-0; benzyl bromide, 100-39-0; 2-cyano-2-phenyl-1,3-dithiane, 64414-31-9; phenyl bromide, 70-11-1.

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Pteridines. 44. A Convenient Synthesis of 6-Formylpterin[1,2]

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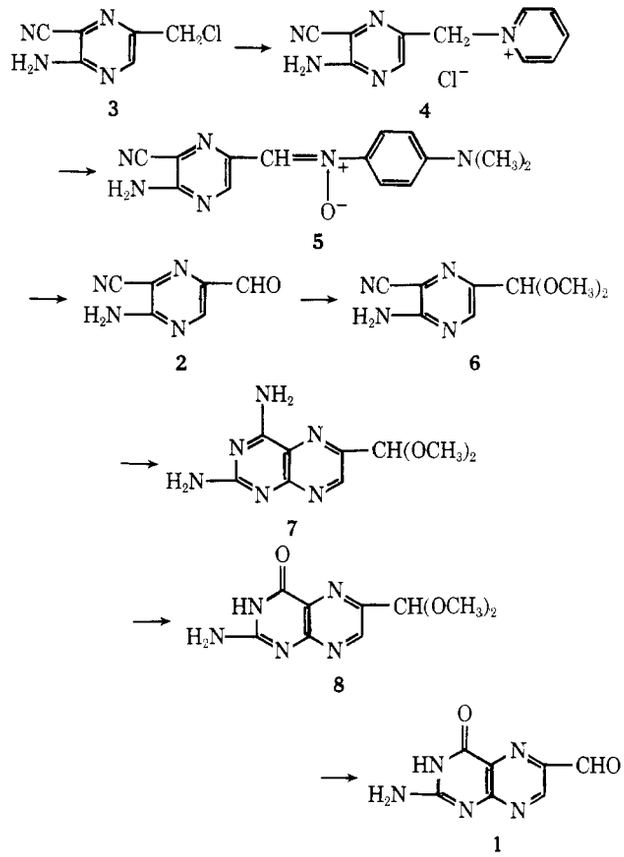
6-Formylpterin (**1**) is a key intermediate for the preparation of pteroic acid,[4,5] folic acid,[5-7] and various derivatives and analogues of the latter.[5,8-11] In addition, the formation of 6-formylpterin appears to be a characteristic of cancer cells, and its presence in urine has been reported to be diagnostic of malignancy.[12] As a consequence, a convenient synthetic route to this compound would be most desirable. Two methods recently revived from the early literature are the periodate cleavage of 6-polyhydroxyalkylpteridines[8] and the bromine–HBr cleavage of folic acid.[13] These procedures jointly suffer the obvious disadvantage of requiring complex and expensive precursors for the oxidative cleavage reactions, and the latter is clearly unacceptable for the preparation of **1** as an intermediate for the synthesis of folic acid. Alternative procedures have involved dibromination of the 6-methyl group of 6-methylpterin followed by aqueous hydrolysis,[14] and the condensation of α-bromo-β,β-diethoxypropanal with 2,4,5-triamino-6(1*H*)-pyrimidone followed by oxidation of the resulting 5,6-dihydropterin and hydrolysis of the acetal.[6] One must bear in mind, however, that all of the above procedures must of necessity give final products of dubious isomeric integrity if the inherently ambiguous condensation of a diaminopyrimidine with an unsymmetrical dicarbonyl compound (or an α-halo or hydroxy ketone) was employed at any stage of the synthesis.

Recent papers from this laboratory have described an unequivocal approach to pteridine synthesis which involves guanidine cyclization of suitably substituted pyrazine intermediates, which are prepared by unambiguous procedures.[15] Following this strategy, a 5-formylpyrazine, or a protected derivative thereof, has been sought as an intermediate for the synthesis of 6-formylpterin. One such synthon, 2-amino-3-cyano-5-oximinomethylpyrazine 1-oxide, has already been developed and utilized.[16] We now report a high-yield synthesis of 2-amino-3-cyano-5-formylpyrazine (**2**) and its conversion to 2,4-diamino-6-formylpteridine and 6-formylpterin dimethyl acetals (**7** and **8** respectively); acid hydrolysis of the latter gives **1**.

The Kröhnke method[17,18] was utilized to convert 2-amino-3-cyano-5-chloromethylpyrazine (**3**)[19] to the required aldehyde **2** in three steps. Yields for all three steps were above 90%, and the crude crystalline intermediates were pure enough in every case to be used directly in succeeding transformations. Thus, the pyridinium salt **4** was obtained from **3** and pyridine by stirring overnight at room temperature. Salt **4** reacted with *p*-dimethylaminonitrosobenzene in the presence of potassium carbonate to give the nitrone **5**, which was then hydrolyzed to **2** with cold 6 N hydrochloric acid.

Quantitative conversion of **2** to its dimethyl acetal **6** was achieved by treatment of a methanol suspension of **2** with a catalytic amount of a strong acid, e.g., anhydrous HCl, *p*-toluenesulfonic acid, or Dowex 50W-X4 cation-exchange resin (hydrogen form). It is not necessary to isolate **6**, which can be converted directly to 2,4-diamino-6-formylpteridine dimethyl acetal (**7**) by addition of guanidine to the dried methanol solution followed by heating overnight at reflux. Brief treatment of **7** with hot 5% sodium hydroxide gave 6-formylpterin dimethyl acetal (**8**), which can be hydrolyzed to **1** with either formic or trifluoroacetic acid.



The acetals **7** and **8** should find general use in the preparation of aminopterin, folic acid, and their analogues, since the respective aldehydes are readily generated in situ in the presence of acid. Thus, the UV spectrum of **8** in 1 N hydrochloric acid was identical to the reported UV spectrum of **1**.[14]

Experimental Section[20]

1-[(2-Amino-3-cyano-5-pyrazinyl)methyl]pyridinium Chloride (4). A solution of 1.0 g (5.9 mmol) of 2-amino-3-cyano-5-chloromethylpyrazine[19] in 10 mL of pyridine was stirred at room temperature for 17 h. Eighty milliliters of ether was added and the salt which had precipitated was removed by filtration, washed well with ether, and air-dried to give 1.4 g (95%) of a light gray powder, mp >300 °C (dec). One recrystallization from ethanol gave pale-yellow needles: NMR (D_2O, external Me_4Si) δ 9.0–8.0 (m, 5) (pyridinium ring), 8.47 (s, 1) (6-H), 5.85 (s, 2) ($-CH_2-$); IR (KBr) 2230 cm^{-1} (CN).

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Anal. Calcd for $C_{11}H_{10}N_5Cl$: C, 53.34; H, 4.07; N, 28.28; Cl, 14.32. Found: C, 53.39; H, 4.02; N, 28.30; Cl, 14.59.

***N*-[*p*-(Dimethylamino)phenyl]-α-(2-amino-3-cyano-5-pyrazinyl)nitrone (5).** To a suspension of 2.63 g (10.6 mmol) of the pyridinium salt **4** and 1.64 g (11.0 mmol) of *p*-dimethylaminonitrosobenzene in 50 mL of ethanol was added 8.33 g (60.4 mmol) of potassium carbonate in 30 mL of water. The reaction mixture became homogeneous, changed in color from green to brown, and the orange-brown nitrone started to separate. After 30 min of stirring at room temperature followed by ice cooling, the mixture was filtered and the collected solid was washed with water followed by ethanol and then ether and air-dried: yield 2.86 g (96%) of a dull orange powder, mp 219–222 °C (dec). Recrystallization from a large volume of acetonitrile (Norite) gave dark-orange needles: mp 227–228 °C (dec); NMR (Me_2SO) δ 2.95 (s, 6), 6.68 (d, 2), 7.72 (m, 4) (2 Ar protons + $-NH_2$), 8.15 (s, 1), 9.92 (s, 1); UV λ_{max} (acetonitrile) (log ε) 237 (4.22), 258 (sh, 3.89), 338 (4.27), 376 (4.38) nm; IR (KBr) 2230 cm^{-1} (CN).

Anal. Calcd for $C_{14}H_{14}N_6O$: C, 59.56; H, 5.00; N, 29.77. Found: C, 59.44; H, 5.06; N, 30.06.

2-Amino-3-cyano-5-formylpyrazine (2). A two-phase system containing 0.96 g (3.4 mmol) of the nitrone **5**, 60 mL of cold 6 N HCl, and 50 mL of ethyl acetate was shaken in a separatory funnel for several minutes. The organic layer was separated and the aqueous layer extracted twice with 50-mL portions of ethyl acetate. Brine (50 mL) was added to the aqueous layer, which was again extracted with 50 mL of ethyl acetate. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and evaporated to give 0.48 g (96%) of a light-gray powder, mp 202–204 °C (dec). Recrystallization from benzene (Norite) gave the aldehyde **2** as a colorless, microcrystalline solid: mp 206–208 °C (dec); NMR (Me_2SO) δ 8.32 (s, 2) ($-NH_2$), 8.70 (s, 1), 9.68 (s, 1); IR (KBr) 2240 cm^{-1} (CN).

Anal. Calcd for $C_6H_4N_4O$: C, 48.65; H, 2.72; N, 37.83. Found: C, 48.44; H, 2.80; N, 37.78.

2-Amino-3-cyano-5-formylpyrazine Dimethyl Acetal (6). To a suspension of 0.48 g (3.2 mmol) of the aldehyde **2** in 30 mL of dry methanol was added 1.0 g of Dowex 50W-X4 cation-exchange resin (hydrogen form). The mixture was stirred for 15 min to give a solution which, by TLC examination, contained one fluorescent component; all starting material had disappeared. After drying over 3A molecular sieves, the solvent was removed under reduced pressure to give 0.63 g (100%) of the desired acetal **6**, mp 91–93 °C. The acetal may be recrystallized from benzene/cyclohexane: NMR (Me_2SO) δ 3.35 (s, 6), 5.30 (s, 1), 7.43 (s, 2) ($-NH_2$), 8.42 (s, 1); IR (KBr) 2225 cm^{-1} (CN).

Anal. Calcd for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.40; H, 5.30; N, 29.07.

2,4-Diamino-6-formylpteridine Dimethyl Acetal (7). A solution of guanidine in methanol was prepared by dissolving 0.10 g (4.4 mmol) of sodium in 20 mL of dry methanol, followed by the addition of 0.42 g (4.4 mmol) of guanidine hydrochloride. This was added to a solution of 0.62 g (3.2 mmol) of the acetal **6** in 30 mL of methanol, and the mixture was heated under reflux for 18 h. It was then concentrated to a small volume under reduced pressure, cooled at −20 °C, and filtered to give 0.67 g (84%) of **7** as a light yellow powder, mp 248 °C (dec). The product was obtained in the form of bright-yellow beads, mp 254–255 °C (dec) upon recrystallization from methanol (Norite): NMR (Me_2SO) δ 3.33 (s, 6), 5.35 (s, 1), 6.67 (br s, 2), 7.57 (br s, 2), 8.72 (s, 1); UV λ_{max} (MeOH) (log ε) 261 (4.37), 284 (sh, 3.73), 368 (3.85) nm.

Anal. Calcd for $C_9H_{12}N_6O_2$: C, 45.76; H, 5.12; N, 35.58. Found: C, 45.52; H, 5.02; N, 35.81.

6-Formylpterin Dimethyl Acetal (8). A mixture of 0.52 g of 2,4-diamino-6-formylpteridine dimethyl acetal (**7**) in 20 mL of 5% aqueous sodium hydroxide was heated gently at reflux for 10 min. The resulting clear solution was filtered through sintered glass and the filtrate neutralized with acetic acid. The yellow solid which separated was collected by filtration and washed with water, ethanol, and then ether and air dried to give 0.49 g (94%) of **8** as a yellow solid, mp >330 °C. The analytical sample was prepared by recrystallization from DMF: NMR (Me_2SO) δ 3.33 (s, 6), 5.37 (s, 1), 6.93 (br s, 2), 8.63 (s, 1); UV λ_{max} (0.1 N NaOH) (log ε) 256 (4.41), 282 (sh, 3.86), 360 (3.89) nm; λ_{max} (0.1 N HCl) (log ε) 248 (4.05), 318 (3.96), 335 (sh, 3.83) nm.

Anal. Calcd for $C_9H_{11}N_5O_3$: C, 45.57; H, 4.67; N, 29.53. Found: C, 45.67; H, 4.86; N, 29.66.

6-Formylpterin (1). A mixture of 0.49 g of 6-formylpterin dimethyl acetal (**8**), 10 mL of 97% formic acid, and 1 mL of water was allowed to stand at room temperature for 30 min, poured into 15 mL of water, and neutralized with concentrated ammonium hydroxide. The yellow precipitate was collected by filtration and washed with water, ethanol, and then ether to give 0.36 g (91%) of **1** as a yellow microcrystalline solid, mp >330 °C. IR and UV spectra and TLC behavior were identical with those of an authentic sample: NMR (F_3AcOH external Me_4Si) δ 8.92 (s, 1), 9.65 (s, 1).[16]

Registry No.—**1**, 712-30-1; **2**, 64440-74-0; **3**, 40127-91-1; **4**, 64440-75-1; **5**, 64440-76-2; **6**, 64440-77-3; **7**, 64440-78-4; **8**, 59453-01-9; pyridine, 110-86-1; *p*-dimethylaminonitrosobenzene, 138-89-6; guanidine, 113-00-8.

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Preparation and Crystal Structure of 6-Acetyl-1-iodocodeine

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In conjunction with the development of a radioimmunoassay for morphine and related compounds[1] we were interested in preparing a sample of ring A specifically iodinated morphine. We found that the methods previously used for obtaining chloro-[2] or bromomorphine[3] or fluorocodeine[4] did not lead to the iodo derivative.

With positive iodine (ICl in Me_2SO), a trace of iodinated product was formed with both morphine and codeine as starting materials. With codeine, a trace of iodinated product was also formed when the conditions of tyrosine (protein) iodination were employed (chloramine T and sodium iodide in water buffered at pH 6.9).[5] Surprisingly, iodine monochloride in 0.1 N HCl with codeine produced a 67% yield of iodocodeine (**2**). This was later increased to 80–90% with the use of chloramine T and sodium iodide but again only when the reaction was carried out in 0.1 N HCl. While the reaction with codeine can be carried out quite smoothly, no readily defined reaction occurs with morphine under these conditions and iodomorphine (**5**) was therefore prepared by demethylation of iodocodeine. To avoid the possibility of deiodinaton, the demethylation was effected using boron tribromide.[6] Lastly, the preparation of iodocodeine-^{125}I (**4**) was readily accomplished using $Na^{125}I$ in the procedure shown below.

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