of ether, at ice-bath temperature, was quickly added 19.4 mmol of dichloride (2.00 g of SCl_2, 3.47 g of $PhPCl_2$, 4.91 g of $(Ph)_2SiCl_2$, 2.51 g of Me_2SiCl_2, 3.38 g of Me_2GeCl_2, and 4.28 g of Me_2SnCl_2). The reaction mixture was allowed to stir at room temperature from 4 to 12 h before washing three times with water. The ethereal solution was dried over anhydrous sodium sulfate and evaporated, and the residue was distilled at reduced pressure, except in the case of the diphenyl silyl compound which was recrystallized from diethyl ether.

Characterization of 2-*tert*-Butylbenzothiazole.[18] A yellow liquid, 2.40 g (12.6 mmol, 65%), was isolated: bp 59 °C (0.01 mm); IR (CCl_4) 3050 (w), 2960 (s), 1510 (w), 1455 (w), 1440 (m), 1365 (m), 1235 (m) cm^{-1}; ^1H NMR (CCl_4) δ 1.49 (s, 9 H), 7.0–8.0 (m, 4 H); UV (CCl_4) 258 (ϵ 10 000), 284 (ϵ 1700), 295 (ϵ 1700) nm; ^{13}C NMR ($CDCl_3$) δ 30.7, 38.3, 121.3, 122.7, 124.4, 125.7, 135.0, 153.4, 181.5; measured mass 191.9746 (rel. intensity 51.2%), calcd mass 191.9768 (dev 2.3 mmass units).

Characterization of 2-*tert*-Butyl-3-phenylbenzoazaphosphole. A yellow liquid, 2.40 g (12.6 mmol, 52%), was isolated: bp 115–117 °C (0.04 mm); IR (CCl_4) 3050 (w), 2960 (s), 1480 (m), 1445 (s), 860 (s) cm^{-1}; ^1H NMR (CCl_4) δ 1.22 (s, 9 H), 7.0–8.0 (m, 9 H); UV (CCl_4) 258 (ϵ 9000) 305 (ϵ 2400) nm; ^{13}C NMR ($CDCl_3$) 30.4 (d, J = 5.6 Hz), 40.0 (d, J = 18.5 Hz), 123.4, 125.9, 128.3 (d, J = 20.3 Hz), 128.7 (d, J = 9.2 Hz), 129.2, 129.9, 131.5 (d, J = 16.7 Hz), 134.4, 134.7, 137.6 (d, J = 10.3 Hz), 158.5 (d, J = 11.1 Hz), 198.8; measured mass 267.1153 (rel intensity 100.0%), calcd mass 267.1176 (dev 2.3 mmass units).

Characterization of 2-*tert*-Butyl-3,3-diphenylbenzoazasilole. Dry ether was added to the residue and the crystals were filtered, recrystallized from ether/pentane, and placed under high vacuum (0.005 mm) at 80 °C to remove all the ether to yield 2.08 g (6.11 mmol, 63% yield) of a white solid: mp 128–129 °C; IR ($CHCl_3$) 3050 (w), 2950 (s), 1950 (w), 1885 (w), 1815 (2), 1765 (w), 1590 (s), 1115 (s) cm^{-1}; ^1H NMR δ 1.16 (s, 9 H), 7.15–7.75 (m, 14 H); UV (CCl_4) 252 (ϵ 8400), 256 (ϵ 8400), 307 (ϵ 4400) nm; ^{13}C NMR ($CDCl_3$) δ 29.5, 40.2, 124.5, 127.0, 127.6, 128.2, 130.4, 131.7, 132.8, 135.3, 135.6, 161.0, 200.6 ppm; measured mass 341.1611 (rel intensity 86.5%), calcd mass 341.1599 (dev 1.2 mmass units).

Characterization of 2-*tert*-Butyl-3,3-dimethylbenzoazasilole. A colorless liquid, 2.22 g (10.2 mmol, 53%), was obtained: bp 86–88 °C (0.35 mm); IR ($CHCl_3$) 3050 (w), 2940 (s), 1645 (w), 1590, 1565 (w) cm^{-1}; ^1H NMR (CCl_4) δ 0.39 (s, 6 H), 1.24 (s, 9 H), 7.0–7.5 (m, 4 H); UV (CCl_4) 255 (ϵ 3500), 273 (ϵ 3600), 302 (ϵ 3600) nm; ^{13}C NMR −2.9, 28.7, 39.7, 124.1, 126.4, 129.3, 131.1, 131.4, 159.6, 201.7 ppm; measured mass 217.1284 (rel intensity 53.1%), calcd mass 217.1287 (dev. 0.3 mmass unit).

Characterization of 2-*tert*-Butyl-3,3-dimethylbenzoazagermole. A slightly yellow, viscous oil, 3.46 g (13.2 mmol, 68%), was obtained: bp 71–74 °C (0.01 mm); IR (CCl_4) 3050 (m), 2950 (s), 1940 (w), 1905 (w), 1835 (w), 1805 (w), 1600 (m) cm^{-1}; ^1H NMR δ 0.59 (s, 6 H), 1.23 (s, 9 H), 7.0–7.6 (m, 4 H); UV (CCl_4) 253 (ϵ 4600), 265 (ϵ 4600) 293 (ϵ 3400) nm; ^{13}C NMR ($CDCl_3$) δ −1.6, 28.7, 40.5, 118.6, 124.8, 126.6, 128.6, 130.1, 131.4, 161.5, 201.3 ppm; measured mass 263.0714 (rel. intensity 30.3%), calcd mass (based on Ge, 36% abundance) 263.0729 (dev. 1.5 mmass units).

Characterization of 2-*tert*-Butyl-3,3-dimethylbenzoazastannole. A yellow viscous oil, 2.46 g (8.0 mmol, 41%), was obtained: bp 80–82 °C (0.01 mm); IR (CCl_4) 3050 (m), 2950 (s), 1940 (w), 1905 (w), 1840 (w), 1805 (w), 1595 (m) cm^{-1}; ^1H NMR (CCl_4) δ 0.52 (s, 6 H, ^{117}Sn, J = 62 Hz, ^{119}Sn, J = 66 Hz), 1.18 (s, 9 H), 7.0–7.7 (m, 4 H); UV (CCl_4) 252 (ϵ 6100), 256 (ϵ 6100) 294 (ϵ 3800) nm; ^{13}C NMR ($CDCl_3$) δ −7.1, 28.8, 41.7, 119.4, 126.0, 126.6, 127.1, 128.9, 130.1, 135.4, 159.6; measured mass 309.0560 (rel. intensity 25.9%), calcd mass (based on ^{120}Sn, 33% abundance) 309.0537 (dev. 2.3 mmass units).

Registry No.—**2** (R = *t*-Bu), 64414-13-7; **10**, 6441401206; **11**, 64414-11-5; **12**, 6625-74-7; *tert*-butyllithium, 594-19-4; phenyl isocyanide, 931-54-4; methyl iodide, 74-88-4; methyl *tert*-butyl ketone, 75-97-8; methyl *tert*-butyl ketone oxime, 2475-93-6; 2-oxo-3,3-dimethylbutanoic acid, 815-17-8; anthranilic acid, 118-92-3; *N*-(1-copper-2,2-dimethylpropylidene)benzenamine, 64414-10-4; cuprous chloride, 7758-89-6; *N*-(2,2-dimethylpropylidene)benzenamine, 26029-60-7; SCl_2, 10545-99-0; $PhPCl_2$, 644-97-3; $(Ph)_2SiCl_2$, 80-10-4; Me_2SiCl_2, 75-78-5; Me_2GeCl_2, 1529-48-2; Me_2SnCl_2, 753-73-1.

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Notes

Isocyanide–Metal Exchange.[1] The Synthesis of Masked Acyl Cyanides

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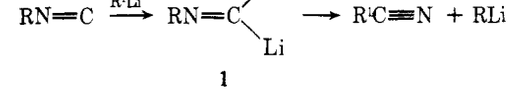
During the investigation of the synthetic utility of lithium aldimines (**1**), formed by the addition of alkyllithium reagents to isocyanides,[2] it was discovered that a number of them dissociated to produce cyanides in very good yields.[3] A detailed study of the isocyanide–metal exchange reaction showed that



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both steric and electronic effects play a role in the dissociation mechanism. Synthetically, this reaction provided a convenient route to the preparation of nitriles from lithium reagents. The use of the isocyanide–metal exchange reaction for the preparation of masked acyl cyanides is the subject of this report.

The reaction of lithium aldimine (**2**), prepared by lithiation of 1,1,3,3-tetramethylbutyl isocyanide (TMBI) with triphenylmethyl isocyanide, gave the masked acyl cyanide **3**. The

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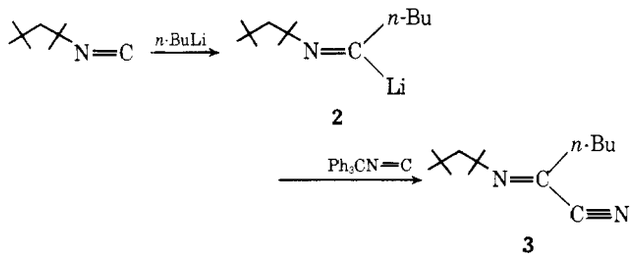
Table I. Reaction of 2-Lithio-2-cyano-1,3-dithiane with RX

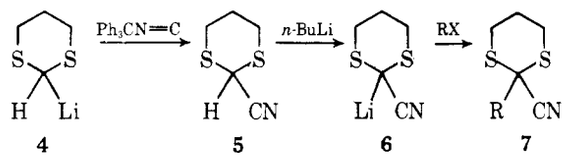
RX	CH_3I	*n*-BuBr	*i*-PrI	$PhCH_2Br$	$PhC(=O)CH_2Br$
Yield, %[a]	81	100	91	94	97

[a] Isolated yield based on **5**



yield of **3** was quite low (26%) and when *tert*-butyllithium was used instead of *n*-butyllithium for metalation only traces of product could be detected. The low yield obtained is probably due to a steric effect in the addition of **2** to triphenylmethyl isocyanide.

An attractive alternative to the masked acyl carbanion **2** was the 2-lithio-1,3-dithiane (**4**) which has been explored by Seebach.[4] Thus, when **4** was reacted with triphenylmethyl isocyanide at low temperature, the isocyanide–metal exchange reaction occurred to yield 2-cyano-1,3-dithiane (**5**) in 83%



yield.[5] The masked acyl cyanide could readily be converted to the anion **6** by reaction with butyllithium. Alkylation of **6** was easily achieved using a series of alkyl halides to yield **7** in excellent yield (Table I).

Experimental Section

Bulk solvents were distilled before use. Industrial grade dimethylformamide (DMF) was purified by distillation from barium oxide at atmospheric pressure, after discarding a forecut, the fraction with bp 150 to 152 °C being collected. Reagent grade diethyl ether and tetrahydrofuran were distilled from lithium aluminum hydride prior to use. All other reagent grade materials were used as received from the commercial suppliers unless further purification was judged necessary.

Infrared spectra were obtained with a Perkin-Elmer Model 257 grating infrared spectrophotometer. Solution spectra were run on 3% solution using either carbon tetrachloride or chloroform as solvent and employing a 0.5-mm sodium chloride cell. Nuclear magnetic resonance spectra were obtained on a Varian Associates A-60 or a Brucker 90-MHZ spectrophotometer using tetramethylsilane as internal standard. Mass spectra were obtained from a AEI Picker high-resolution mass spectrophotometer. Melting points were determined in capillary tubes using a Mel-Temp apparatus and are uncorrected. Elemental analyses were run by J. Beller's Microanalytisches Laboratorium, Gottingen, Germany.

2-Cyano-1,3-dithiane. To a stirred solution of 1.20 g (0.01 mol) of 1,3-dithiane[6] in 15 mL of dry tetrahydrofuran at −30 °C was added 8.0 mL (0.01 mol) of *n*-butyllithium in hexane (1.12 mol) dropwise under a nitrogen atmosphere. The solution was stirred at −30 °C for 1 h and then 2.69 g (0.01 mol) of triphenylmethyl isocyanide[7] in 20 mL of dry tetrahydrofuran was added dropwise. The solution turned red and was then stirred overnight at room temperature. The reaction was worked up by adding 10 mL of H_2O and then extracting with ether. The ether extract was washed with saturated salt solution, dried over anhydrous sodium sulfate, and concentrated, giving a yellow oil which was subjected to column chromatography over alumina with pentane/ether. Initially, a mixture of 10% ether in pentane was used to elute triphenylmethane; then, 20% ether eluted unreacted 1,3-dithiane, and 40% ether eluted unreacted triphenylmethyl isocyanide. Finally, using 100% ether, 2-cyano-1,3-dithiane was eluted (1.2 g, 82.8%) as a colorless solid. Recrystallization from ether–pentane gave colorless crystals; mp 86–88 °C [lit.[5] 90 °C]; IR (CCl_4) 2940 (s), 2908 (s), 2228 (m), 1435 (s), 1429 (s), 1418 (s), 1290 (m), 1280 (m), 1245 (m), 940 (m), 910 (s), 875 (m) cm^{-1}; NMR ($CDCl_3$) δ 2.08 (m, 2 H), 3.37 (m, 4 H), 4.44 (s, 1 H).

Anal. Calcd for $C_5H_7S_2N$: C, 41.36; H, 4.85; N, 9.64; S, 44.17. Found: C, 41.45; H, 4.81; N, 9.72; S, 43.95.

2-Cyano-2-methyl-1,3-dithiane. To a stirred solution of 0.725 g (0.005 mol) of 2-cyano-1,3-dithiane in 25 mL of dry tetrahydrofuran at −40 to −60 °C was added, dropwise, 4.5 mL (0.005 mol) of 1.1 M *n*-butyllithium in hexane under a nitrogen atmosphere. The solution was stirred at −40 °C for 90 min and then 1.0 mL (0.016 mol) of CH_3I was added. The mixture was stirred for an additional 30 min and then overnight at room temperature. The reaction mixture was worked up by adding 10 mL of water and then extracting with ether. The ether extract was washed with saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to give 0.9 g (quantitative) of a yellow oil which was subjected to column chromatography over alumina using binary eluting mixture composed of 1:1 pentane–ether. A total of 0.65 g (81.2%) of colorless solid was collected. Recrystallization from ether–hexane gave colorless crystals: mp 51–53 °C; IR (CCl_4) 2935 (m), 2910 (s), 2830 (w), 2225 (m), 1452 (s), 1438 (s), 1430 (s), 1380 (m), 1285 (s), 1140 (s), 908 (s), 870 (m) cm^{-1}; NMR (CCl_4) δ 1.81 (s, 3 H), 1.98 (m, 2 H), 3.11 (m, 4 H).

Anal. Calcd for $C_6H_9S_2N$: C, 45.24; H, 5.74; N, 8.79; S, 40.26. Found: C, 45.38; H, 5.67; N, 8.80; S, 40.31.

2-Cyano-2-isopropyl-1,3-dithiane. The procedure described for the methylation of **4** was used. The reaction mixture was poured onto ice water and extracted with ether several times. The ether extract was washed with saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to give a yellow liquid which was subjected to column chromatography over alumina, using 10% of ether in pentane as eluent. An oil, 91% yield, was collected: IR (CCl_4) 2990 (s), 2950 (s), 2925 (s), 2238 (w), 1475 (s), 1448 (m), 1438 (s), 1405 (s), 1388 (s), 915 (m), 885 (m) cm^{-1}; NMR (CCl_4) δ 1.26 (d, 6 H, J = 7 Hz), 2.18 (m, 3 H), 3.1 (m, 4 H).

Anal. Calcd for $C_8H_{13}S_2N$: C, 51.29; H, 6.99; N, 7.48; S, 34.23. Found: C, 51.33; H, 7.02; N, 7.45; S, 34.16.

2-Cyano-2-*n*-butyl-1,3-dithiane. The procedure for methylation of **4** was used. The reaction mixture was worked up by adding 10 mL of water and extracting with ether several times. The ether extract was washed with saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to give a quantitative yield of yellow solid. The solid was taken into ether and decolorized with Norit. Evaporation of ether gave a colorless solid. Recrystallization from ether–hexane gave colorless crystals: mp 53–54 °C; IR (CCl_4) 2970 (s), 2920 (s), 2880 (s), 2240 (w), 1478 (m), 1445 (s), 1435 (s), 1428 (s), 1395 (w), 1292 (s), 1254 (w) and 915 (m) cm^{-1}.

Anal. Calcd for $C_9H_{15}S_2N$: C, 53.69; H, 7.51; N, 6.96; S, 31.84. Found: C, 53.80; H, 7.51; N, 6.95; S, 31.92.

2-Cyano-2-benzyl-1,3-dithiane. The procedure for methylation of **4** was used. The reaction mixture was worked up by adding 10 mL of water and extracting with ether several times. The ether extract was washed with saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to give a 94% yield of yellow solid. Recrystallization with ether–hexane gave colorless crystals: mp 108–110 °C; IR (CCl_4) 3078 (m), 2925 (s), 2240 (m), 1617 (w), 1510 (m), 1458 (s), 1445 (s), 1435 (s), 1428 (s), 1293 (s), 928 (m), 915 (s), and 703 (s) cm^{-1}; NMR ($CDCl_3$) δ 2.08 (m, 2 H), 2.96 (m, 4 H), 3.30 (s, 2 H), 7.38 (s, 5 H).

Anal. Calcd for $C_{12}H_{13}S_2N$: C, 61.24; H, 5.57; N, 5.95; S, 27.24. Found: C, 61.37; H, 5.52; N, 5.96; S, 27.18.

2-Cyano-2-phenacyl-1,3-dithiane. The procedure for methylation of **4** was used. The reaction mixture was worked up by adding 10 mL of water and extracting with ether several times. The ether extract was washed with saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to give a 97% yield of an orange solid which was dissolved in chloroform and decolorized twice with charcoal. Recrystallization using chloroform–hexane gave colorless crystals: mp 144–145 °C; IR ($CHCl_3$) 2920 (m), 2242 (m), 1705 (s), 1610 (s), 1592 (m), 1462 (m), 1350 (s), and 1295 (m) cm^{-1}; NMR ($CDCl_3$) δ 2.02 (m, 2 H), 3.20 (m, 4 H), 3.62 (s, 2 H), and 7.73 (m, 5 H).

Anal. Calcd for $C_{13}H_{13}S_2NO$: C, 59.28; H, 4.98; N, 5.32; S, 24.34; O, 6.08. Found: C, 59.40; H, 5.02; N, 5.45; S, 24.26; O, 6.21.

Registry No.—2-Cyano-1,3-dithiane, 33927-42-3; 1,3-dithiane, 505-23-7; triphenylmethyl isocyanide, 1600-49-3; 2-cyano-2-methyl-1,3-dithiane, 64414-35-3; methyl iodide, 74-88-4; 2-cyano-

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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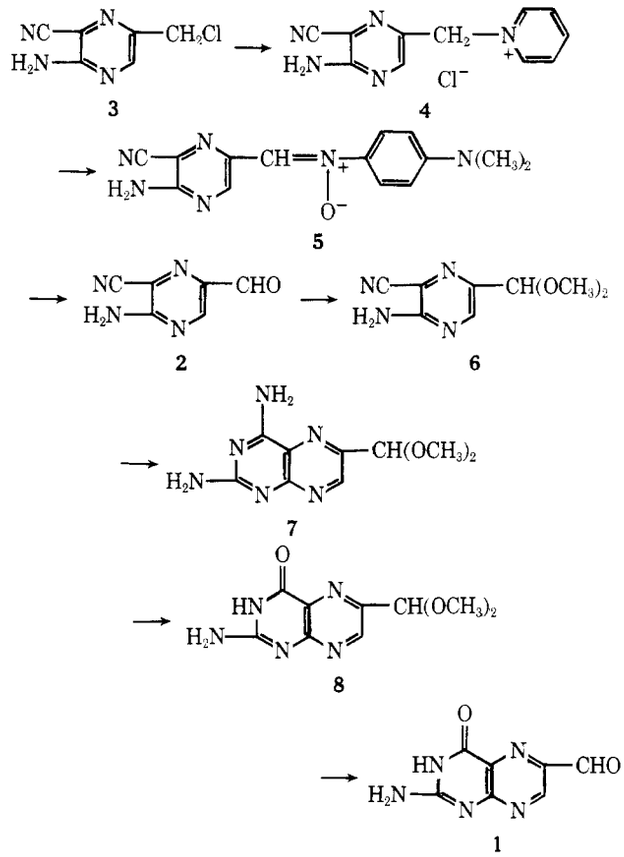
6-Formylpterin (**1**) is a key intermediate for the preparation of pteroic acid,[4,5] folic acid,[5-7] and various derivatives and analogues of the latter.[5,8-11] In addition, the formation of 6-formylpterin appears to be a characteristic of cancer cells, and its presence in urine has been reported 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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