5-Hetarylmethylene-2,4-diaminopyrimidines (1)

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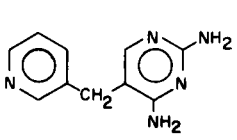
This paper details the synthesis of dimethoxypyridinealdehydes, pyrimidinealdehydes and their conversion to 2,4-diaminopyrimidines substituted in the 5-position by these heteroaromatic functions. The objective of this work was to emulate the activity recently noted for trimethoprim (2,4-diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine) against drug resistant strains of malaria (2). The extraordinarily high degree of hydrophobic binding of trimethoprim to certain dihydrofolic reductases (3) may in terms of Baker's (4) "bridge binding" concept, be a manifestation of the unshared electron pairs on the three oxygen atoms of the trimethoxybenzyl portion of the molecule. We rationalized that the diaminopyrimidines **1-3**, having a nitrogen heterocycle with unshared electron pairs in the hydrophobic binding segment of the molecule, may exhibit biological responses similar to the trimethoprim molecule.



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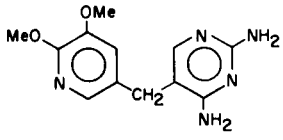

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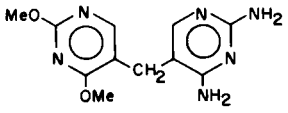

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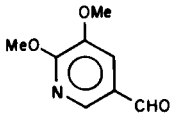

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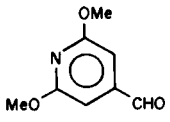

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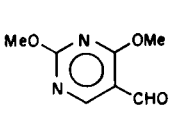

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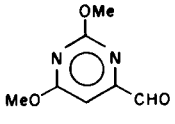

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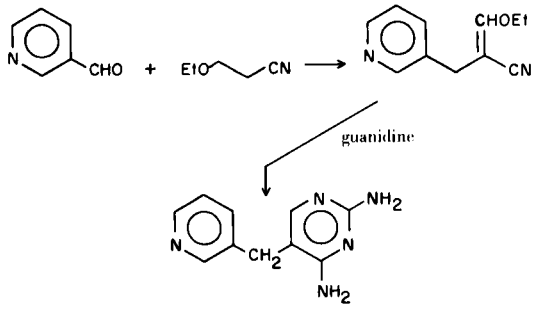
Benzyldiaminopyrimidines are conveniently prepared by sequentially condensing benzaldehydes with ethoxypropionitrile and guanidine (5). Anticipating that this apparent general synthesis would be adaptable to heteroaromatics, the aldehydes **4-7** were prepared and subjected to the reactions shown in Scheme 1.

SCHEME 1



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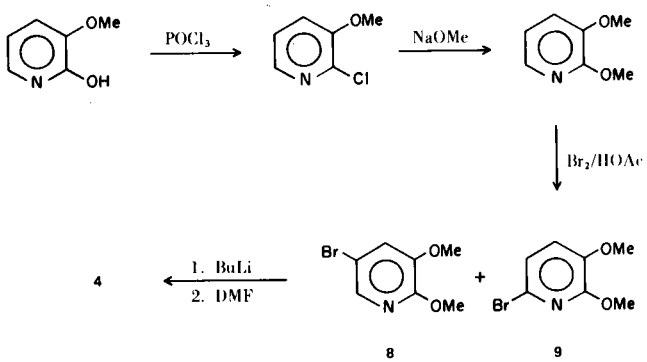
Whereas nicotinaldehyde readily undergoes the transformations shown, the isomeric pyridinealdehydes completely fail. The fate of the α- and γ-pyridinealdehydes appears to be a Cannizzaro reaction. This preference for a Cannizzaro reaction is associated with the position of the ring nitrogen and its electron withdrawing effect on the formyl group. In concert with this is the failure of **5** and **7** to condense with ethoxypropionitrile anion.

Scheme 2 summarizes the series of reactions found capable of yielding the substituted nicotinaldehyde **4**.

SCHEME 2



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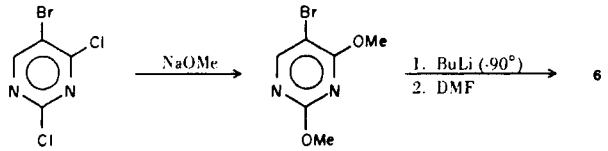
The displacement of chlorine from 2-chloro-3-methoxypyridine by methoxide ion was extremely slow in refluxing methanol, giving very low yields of product, even after 5 days. Addition of 10% DMF to the reaction mixture gave the dimethoxypyridine in 75% yield in only 2 days. This acceleration of the methanolysis is in accord with the well-known influence of aprotic materials on nucleophilic

displacements. Bromination of dimethoxypyridine in acetic acid yielded a mixture of the 5-bromo and 6-bromo isomers (5:1, respectively). Structural assignment of **8** and **9** and the product composition was based on the proton spectra.

The C_6 and C_4 protons in **8** appear as doublets at 2.32 τ and 2.98 τ, respectively with J values of 2 cps. In **9** the C_4 and C_5 protons have overlapping chemical shifts and appear as a singlet at 3.17 τ. Separation of **8** and **9** was not completely successful; however, the halogen-metal interchange appeared to occur preferentially with **8** so that pure **4** was readily separated from the small quantity of the isomeric dimethoxypicolinaldehyde contaminating the reaction product.

The pyrimidinealdehyde **6** was preparable *via* the reactions shown in Scheme 3.

SCHEME 3



Formation of **6** demanded that the interchange of 5-bromo-2,4-dimethoxypyrimidine with butyl lithium be effected at very low temperatures (-90°). Slightly higher exchange temperature resulted in a rapid drop-off of yield. This thermal instability of lithiated pyrimidines has also been observed in other laboratories (6).

Both aldehydes **4** and **6** were found to be amenable to the series of reactions shown in Scheme 1, yielding the diaminopyrimidines **2** and **3**, respectively.

The isonicotinaldehyde **5** was obtained by chlorodehydroxylation of citrazinic acid, displacement of chlorine by methoxide ion and conversion of carboxy to the formyl group. Selenium dioxide oxidation of 6-methyl-2,4-dimethoxypyrimidine yielded **6**. These reactions are detailed in the Experimental section.

Antimalarial activity of **1-3** was assessed with the Gerberg (7) mosquito screen (*Plasmodium gallinaceum* in the *Aedes aegypti*). All three compounds were inactive. Compound **1** was also inactive against *P. gallinaceum* in an avian screen and against rodents parasitized with *P. berghei* (8).

EXPERIMENTAL

2-Chloro-3-methoxypyridine.

A mixture of 130 g. of 3-methoxy(1*H*)-2-pyridinone, 159 g. of phosphorus oxychloride and 160 g. of diethylaniline were refluxed for 10 hours. The cooled reaction was poured into a large volume of ice-water and extracted with ether. The oily ether residue, on recrystallization from hexane gave 65 g. (43% yield) of the titled compound, m.p. 49° (lit. (9) m.p. = 48-49°).

2,3-Dimethoxypyridine.

2-Chloro-3-methoxypyridine (42.6 g.) was refluxed for 40 hours in a solution of 56 g. of sodium methoxide in 425 ml. of methanol and 64 ml. of dimethylformamide (DMF). Filtration, solvent evaporation, and distillation of the residue gave 33 g. (55% yield) of product, b.p. 100° (17 mm).

Anal. Calcd. for $C_7H_9NO_2$: C, 60.43; H, 6.47; N, 10.07. Found: C, 60.05; H, 6.30; N, 9.87.

5-Bromo-2,3-dimethoxypyridine.

Bromine (20.8 g.) in 27 ml. of acetic acid was added to an acetic acid solution (90 ml.), at 10-12° containing 13.6 g. of 2,3-dimethoxypyridine and 10 g. of sodium acetate. The reaction was stirred for an additional hour, poured into ice-water, and neutralized with 25% sodium hydroxide. Extraction with ether, evaporation of the ether, and distillation of the residue yielded 18 g. (84% yield) of material b.p. 120-127° (2 mm). Proton spectrum of this distillation fraction indicated a 5:1 mixture of the 5-bromo and 6-bromo isomers.

5,6-Dimethoxynicotinaldehyde (**4**).

A 10% ether solution of the isomeric bromo-5,6-dimethoxypyridines was reacted with a slight excess of butyl lithium at -35°. As the exchange reaction progressed, copious amounts of a white solid formed, making stirring difficult. After addition was complete stirring was continued at -35° for 0.5 hour. A two-fold excess of DMF was added and the reaction allowed to proceed for 1 hour at -20°. The reaction was treated with an ammonium chloride solution and the product isolated in the usual manner, yield 73%, m.p. 115° (hexane).

Anal. Calcd. for $C_8H_9NO_3$: C, 57.49; H, 5.39; N, 8.38. Found: C, 57.31; H, 5.54; N, 8.21.

2,6-Dimethoxyisonicotinic Acid.

A mixture of 46.6 g. of 2,6-dichloroisonicotinic acid (10) and 65.7 g. of anhydrous sodium methoxide in 610 ml. of DMF was refluxed for 1.5 hours, diluted with an equal volume of ice-water, and acidified. The precipitated product was filtered, washed with water and dried (yield 72%), m.p. = 229-230° (lit. (11) 227-228°).

Methyl 2,6-Dimethoxyisonicotinate.

The titled compound was prepared from 2,6-dimethoxyisonicotinoyl chloride (11) and methanol in tetrahydrofuran with triethylamine as the hydrogen chloride acceptor. Recrystallization from methanol gave 75% yield, m.p. 72-73° (lit. (12) m.p. 68-69°).

2,6-Dimethoxy-4-pyridinemethanol.

Reduction of methyl 2,6-dimethoxyisonicotinate with lithium aluminum hydride in ether at 0° gave the pyridinemethanol in 81% yield, m.p. 61-62° (hexane).

Anal. Calcd. for $C_8H_{11}NO_3$: C, 56.80; H, 6.51; N, 8.28. Found: C, 57.16; H, 6.45; N, 7.94.

2,6-Dimethoxyisonicotinaldehyde (**5**).

Lead tetraacetate (25 g.) was added to a solution of 9.4 g. of 2,6-dimethoxy-4-pyridinemethanol in 165 ml. of pyridine. The initial deep red solution gradually faded to a pale yellow. After 3 hours at 50-60° the solution was diluted with two volumes of water, extracted with ether, and backwashed with cold dilute hydrochloric acid. Evaporation of the dried ether solution and recrystallization gave 7.3 g. of the isonicotinaldehyde, **5**, m.p. 74-75° (hexane).

Anal. Calcd. for $C_8H_9NO_3$: C, 57.49; H, 5.39; N, 8.38. Found: C, 57.26; H, 5.47; N, 8.37.

2,4-Dimethoxy-5-pyrimidinealdehyde (**6**).

A solution of 38.7 g. of 5-bromo-2,4-dimethoxypyrimidine in 450 ml. of tetrahydrofuran at -90° was reacted with 121 ml. of 1.6 *M* butyl lithium over a 10-minute period. DMF (15.9 ml.) was added all at once. The temperature was maintained at -65° for 1 hour, gradually raised to 0°, and then made slightly acidic with 2 *N* hydrochloric acid. The organic phase was separated, dried, and evaporated, yield 19 g., m.p. 123° (hexane); nmr (deuteriobenzene/deuteriochloroform): τ 0.2 (1H s, CHO); 1.31 (1H s, H_6 pyrimidine); 6.30 (3H s, OCH_3); 6.40 (3H s, OCH_3).

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.76; N, 16.67. Found: C, 50.09; H, 4.59; N, 16.60.

2,4-Dimethoxy-6-pyrimidinealdehyde (**7**).

The selenium dioxide oxidation of 2,4-dimethoxy-6-methylpyrimidine in acetic acid paralleled the procedure used to oxidize 6-methyl uracil (13), yield 20%, m.p. 107° (hexane); nmr (deuteriobenzene): τ 0.32 (1H s, CHO); 3.23 (1H s, H_5 pyrimidine); 6.29 (3H s, OCH_3); 6.45 (3H s, OCH_3).

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.76; N, 16.67. Found: C, 50.36; H, 4.97; N, 16.40.

2,4-Diamino-5-(3-pyridylmethylene)pyrimidine (**1**).

Nicotinaldehyde (100 g.) and 100 g. of ethoxypropionitrile in 300 ml. of ethanol was added to a hot solution of 44 g. of potassium ethoxide in 300 ml. of ethanol. During the addition and for 2 hours after addition was complete, ethanol was distilled from the reaction. Ether was added to the cooled reaction and the precipitated solid was filtered and dissolved in water. Extraction of the aqueous solution with ether, evaporation of the ether, and distillation gave 47.5 g. of a thick oil, boiling 140-177° (1 mm).

Reaction of 24 g. of this oil with four molar equivalents of guanidine in methanol at reflux for 18 hours yielded upon concentration and cooling 13 g. of product, m.p. 255-255.5° (ethanol).

Anal. Calcd. for $C_{10}H_{11}N_5$: C, 59.70; H, 5.47; N, 34.83. Found: C, 59.25; H, 5.48; N, 34.65.

2,4-Diamino-5-(5,6-dimethoxy-5-pyridylmethylene)pyrimidine (**2**).

The sodium ethoxide catalyzed condensation of 2.24 g. of 5,6-dimethoxynicotinaldehyde with 1.35 g. of ethoxypropionitrile, as described in the previous example, gave 1.8 g. of a thick oil, b.p. 170-190° (1 mm). Refluxing this oil in 100 ml. of methanol containing four equivalents of guanidine yielded a gummy residue after solvent evaporation. This residue was extracted with hot methylene chloride and chromatographed through a base treated silica gel column. The acetone eluate contained the titled compound, weight 0.8 g., m.p. 205-207° (ethanol-ether).

Anal. Calcd. for $C_{12}H_{15}N_5O_2$: C, 55.17; H, 5.75; N, 26.82. Found: C, 55.50; H, 6.12; N, 26.52.

2,4-Diamino-5-(2,4-dimethoxy-5-pyrimidylmethylene)pyrimidine (**3**).

Condensation of 17.5 g. of 2,4-dimethoxy-5-pyrimidinecarboxaldehyde with 10.3 g. of ethoxypropionitrile in 300 ml. of ethanol containing 4.36 g. of potassium ethoxide was effected as described in the previous experiment. Reaction of 9.85 g. of the distillate [b.p. 160-178° (0.2 mm)] of this condensation with four equivalents of guanidine yielded, after solvent removal a thick gum. Extraction with hot tetrahydrofuran and chromatography of the tetrahydrofuran residue through a base treated silica gel column gave 1.8 g. of product in the acetone eluate, m.p. 213-215° (ethanol-ether).

Anal. Calcd. for $C_{11}H_{14}N_6O_2$: C, 50.38; H, 5.34; N, 32.06. Found: C, 50.26; H, 5.60; N, 31.84.

REFERENCES

(1) This work was supported by the U. S. Army Medicinal Research and Development Command under Contract No. DADA 17-68-C-8103. This is Contribution No. 1189 from the Army Research Program on Malaria.

(2) D. C. Martin and J. D. Arnold, *J. Am. Med. Assoc.*, **203**, 476 (1968).

(3) G. H. Hitchings and J. J. Burchall, *Advan. Enzymol.*, **27**, 417 (1965).

(4) B. R. Baker, *Acc. Chem. Res.*, **2**, 129 (1969).

(5) P. Stenbuck and R. Baltzly, *J. Org. Chem.*, **28**, 1983 (1963).

(6) D. M. Mulvey, R. D. Babson, S. Zawoiski, and M. A. Ryder, *J. Heterocyclic Chem.*, **10**, 79 (1973); M. P. L. Caton, M. S. Grant, D. L. Pain, and R. Slack, *J. Chem. Soc.*, 5467 (1965).

(7) E. Gerberg, L. T. Richard, and J. T. Poole, *Mosquito News*, **26**, 359 (1966).

(8) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

(9) D. Heinert and A. E. Martell, *Tetrahedron*, **3**, 49 (1958).

(10) M. M. Robinson, *J. Am. Chem. Soc.*, **80**, 5481 (1958).

(11) F. H. McMillan, F. Leonard, R. I. Meltzer, and J. A. King, *J. Am. Pharm. Assoc.*, **42**, 457 (1953).

(12) J. Pitha, *Collec. Czech. Chem. Commun.*, **28**, 1408 (1963).

(13) K. Zee-Cheng and C. C. Cheng, *J. Heterocyclic Chem.*, **4**, 163 (1967).