An Improved Synthesis of Diaveridine, Trimethoprim, and Closely Related 2,4-Diaminopyrimidines

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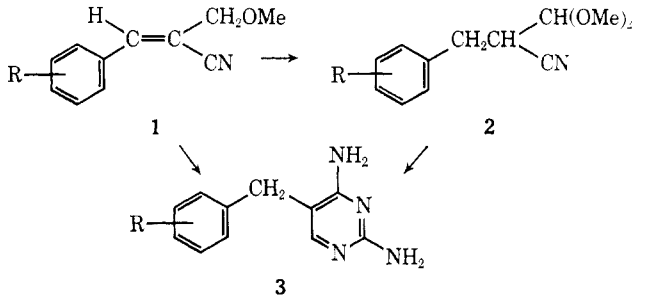
The important sulfonamide potentiators diaveridine (**3a**) and trimethoprim (**3b**)[1] have been prepared by condensation of veratraldehyde and 3,4,5-trimethoxybenzaldehyde, resp, with β-methoxypropionitrile and further reaction of the intermediate cinnamonitriles **1a** and **1b** with guanidine base in MeOH.[2]



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a, R = 3,4-(OMe)$_2$
b, R = 3,4,5-(OMe)$_3$
c, R = 2,4,5-Cl$_3$
d, R = 3,4,5-Cl$_3$
e, R = 2-Me-4,5-(OMe)$_2$

The position of the vinylogous proton in **1a** (δ 7.40) and **1b** (δ 7.46) differs considerably from the calcd values.[3] In our opinion the observed discrepancy can be explained best by a close proximity of the bulky CH_2O-Me group and the vinylogous proton, and a cis configuration (CN cis to substd Ph) for the cinnamonitriles **1a** and **1b** is therefore indicated.

We have found that the cinnamonitriles **1a**, **1b**, and **1e**, with excess alkali, methylate in MeOH under anhyd conditions to afford the dihydrocinnamaldehyde dimethyl acetals **2a**, **2b**, and **2e** (method A).[4] Since the latter upon further reaction with guanidine give the 2,4-diaminopyrimidines **3a**, **3b**, and **3e** in high yields, the preparation of these 2,4-diaminopyrimidines *via* their intermediate dimethyl acetals **2a**, **2b**, and **2e** constitutes a marked improvement[5] over the original procedure.

The condensation of 2,4,5- and 3,4,5-trichlorobenzaldehyde with β-methoxypropionitrile in MeOH in the presence of alkali methoxide affords the dimethyl acetals **2c** and **2d** directly (method B). The simultanous formation of substantial amounts of 2,4,5- and 3,4,5-trichlorobenzyl alcohol is the result of a side reaction and accounts for the lower yields of the dimethyl acetals **2c** and **2d**. Examples illustrating procedures A and B are given below. This includes a synthesis of the new sulfonamide potentiator ormetoprim (**3e**), which in combination with sulfadimethoxine[6] has found useful application as a coccidiostat–antibacterial in chickens[7,8] and turkeys.[9]

The new 2,4-diaminopyrimidines **3c–e** prepared by the improved process are listed in Table II whereas Table I gives details regarding the intermediate dimethyl acetals **2a–e**.

TABLE I

DIMETHYL ACETALS **2**

Compd	Mp, °C	Method	Yield, %	Formula	Analysis
a	50–51	A	74.5	$C_{14}H_{19}NO_4$	C, H, N
b	69–70	A	71	$C_{15}H_{21}NO_5$	C, H, N
c	77–78	B	50	$C_{12}H_{12}Cl_3NO_2$	C, H, Cl
d	85–86	B	35	$C_{12}H_{12}Cl_3NO_2$	C, H, Cl
e	60–61	A	78	$C_{15}H_{21}NO_4$	C, H, N

TABLE II

2,4-DIAMINOPYRIMIDINES **3**

Compd	Mp, °C	Yield, %	Formula	Analysis
c	247	95	$C_{11}H_9O_3N_4$	C, H, Cl
d	285–286	86	$C_{11}H_9O_3N_4$	C, H, N
e	230	86	$C_{14}H_{18}O_2N_4$	C, H, N

Experimental Section[10]

Method A. 4,5-Dimethoxy-2-methyl-2′-methoxymethylcinnamonitrile (1e).—4,5-Dimethoxy-2-methylbenzaldehyde (90 g, 0.5 mole), methoxypropionitrile (50 g, 0.59 mole), and a methanolic NaOMe soln (5.5 g of Na in 150 ml of MeOH) were refluxed with stirring for 4 hr. The soln was poured into 1 l. of H_2O and extd (PhH). The PhH layer was washed (H_2O), the solvent was evapd *in vacuo*, and the residue was distd at 200–208° (11 mm). The product, a yellowish oil, solidified upon standing, yield 103 g (83%). A sample recrystd from MeOH melted at 68–69°, $n^{25}D$ 1.5823.

4,5-Dimethoxy-2-methyl-2′-cyanodihydrocinnamaldehyde Dimethyl Acetal (2e).—4,5-Dimethoxy-2-methyl-2-methoxymethylcinnamonitrile (283 g, 1.145 moles) was refluxed with a methanolic NaOMe soln (53 g, 2.29 g-atoms of Na in 800 ml of abs MeOH) for 24 hr. The brown soln was poured into 1.5 l. of H_2O, and the pptd oil extd (PhH). The PhH layer was washed repeatedly with H_2O containing a small amount of AcOH. The solvent was evapd under vacuum and the residue distd at 205–211° (11 mm). The colorless dist solidified upon standing, yield 250 g (78%). A sample recrystd from MeOH melted at 60–61°, $n^{25}D$ 1.6228.

2,4-Diamino-5-(3,4-dimethoxy-2-methylbenzyl)pyrimidine (3e).—4,5-Dimethoxy-2-methyl-2′-cyanocinnamaldehyde dimethyl acetal (55.8 g, 0.2 mole) was refluxed with a methanolic guanidine soln (250 ml, 1 *M*) for 2 hr, and then the solvent was distd completely from an oil bath at 140°. The cryst residue was slurried with H_2O (100 ml), filtered by suction, and washed with a little ice-cold EtOH and Et_2O, yield 47 g (86%). The material melted at 230°. Recrystd from EtOH (1 g from 30 ml), the mp remained unchanged.

Method B. 3,4,5-Trichloro-2′-cyanodihydrocinnamaldehyde Dimethyl Acetal (2d).—3,4,5-Trichlorobenzaldehyde (40 g, 0.191 mole), β-methoxypropionaldehyde (34 g, 0.4 mole), and a soln of NaOMe (4.4 g, 0.19 g-atom, of Na in 100 ml of MeOH) were mixed and refluxed with stirring for 4 hr. The brownish soln was dild with 200 ml of H_2O, and the pptd oil extd with Et_2O.

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(4) Aromatic OMe groups exchange easily.[2] It is indicated, therefore, to use MeOH as solvent and alkali methoxide as a catalyst.

(5) Hoffmann-La Roche, U. S. Patent 3,341,541 (1967).

(6) Rofenaid is a coccidiostat and antibacterial containing 5 parts of sulfadimethoxine and 3 parts of ormetoprim.

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(10) All melting points are uncorrected and were taken with a Thomas-Hoover melting point apparatus. The new compds analyzed for the indicated elements within ±0.4%. The nmr spectra were taken with a Varian A-60 instrument using DMF-d_7 as solvent and TMS as internal standard.

TABLE III
POTENTIATING EFFECT OF 2,4-DIAMINOPYRIMIDINES IN COMBINATION WITH SULFISOXAZOLE (SI) AGAINST BACTERIAL INFECTIONS IN MICE

Organism	Strain	CD_{50}, mg/kg per os: SI + 3a[a] potentiation (-fold)	SI + 3b[a] potentiation (-fold)	SI + 3c[a] potentiation (-fold)	SI + 3d[a] potentiation (-fold)	SI + 3e[a] potentiation (-fold)
Streptococcus pyogenes	4	2.1	3.8	2.6	6.2	1.7
Diplococcus pneumoniae	6301		2.1	2.1		3.8
Staphylococcus aureus	Smith	>5.0	4.0[b]	>3.5	2.5	>11.0
E. coli	257	2.0	5.7[b]	4.7	2.5	>8.9
Klebsiella pneumoniae	KA		3.1	1.7		4.1
Proteus vulgaris	190	2.3	2.6[b]	11.1		9.2
Pseudomonas aeruginosa	B	1.1	1.4	>1.2	0.6	0.8
Salmonella typhosa	P58a		11.0			4.0
Salmonella schottmuelleri			5.4	1.9		1.4

[a] Pyrimidine dose, 50 mg/kg, except [b] 10 mg/kg.

After evapn of Et_2O, the residue was fractioned under vacuum. 3,4,5-Trichlorobenzyl alcohol distilled at 155–170° (11 mm) (10 g, 25%), solidified in the receiver, and melted at 111–112°. 3,4,5-Trichloro-2′-cyanodihydrocinnamaldehyde dimethyl acetal followed at 195–208° (11 mm) (20 g, 35%) and crystd upon standing, mp 85–86°.

2,4-Diamino-5-(3,4,5-trichlorobenzyl)pyrimidine (3d).—3,4,5-Trichloro-2′-cyanodihydrocinnamaldehyde dimethyl acetal (15 g, 0.04 mole) was refluxed with methanolic guanidine (100 ml, 1 *M*) for 2 hr and subsequently the solvent was distilled from an oil bath at 140°. The remaining solid was slurried with H_2O filtered by suction and purified *via* the acetate. The base melted at 285–286°. The compd formed a monohydrate, which was dehydrated upon drying at 100°.

Biological Results.[11]—The *in vivo* antibacterial activities of **3a–e** were tested in mice infected with 100–1000 MLD's of representative Gram-positive and Gram-negative bacteria and treated by oral administration of the respective substances. Compd **3b** protected 50% of the animals infected with *Staphylococcus aureus* Smith, *Escherichia coli* 257, *Klebsiella pneumoniae* KA, *Proteus vulgaris* 190, and *Salmonella typhosa* P58a at doses of 140, 841, 698, 19, and 268 mg/kg, respectively, but was inactive at doses of 1000 to 2000 mg/kg against *Streptococcus pyogenes* 4, *Diplococcus pneumoniae* 6301, *Pseudomonas aeruginosa* B, and *Salmonella schottmuelleri*. Compound **3a** protected 50% of the animals infected with *S. typhosa* P58a at a dose of 177 mg/kg but was inactive at 500–1000 mg/kg against the other organisms tested. No protective effect was detected when **3c–e** were tested at doses of 250–500, 50, and 100 mg/kg, respectively, against any of the 9 bacterial infections.

When the compds were tested *in vivo* at a fixed concn orally of 50 mg/kg (except that **3b** was administered at 10 mg/kg against *S. aureus* Smith, *E. coli* 257, and *P. vulgaris* 190) in combination with graded doses of sulfisoxazole against the bacterial infections, various degrees of potentiation of sulfisoxazole were observed. There was a two-fold or greater increase in the activity of sulfisoxazole against *S. pyogenes* 4 in combination with **3a–d** (2.1-, 3.8-, 2.6-, and 6.2-fold, respectively); against *D. pneumoniae* 6301 in combination with **3b,c,e** (2.1-, 2.1-, and 3.8-fold, respectively); against *S. aureus* 209 in combination with **3a–e** (>5.0-, 4.0-, >3.5-, 2.5-, and >11.0-fold, respectively); against *E. coli* 257 in combination with **3a–e** (2.0-, 5.7-, 4.7-, 2.5-, and >8.9-fold, respectively); against *K. pneumoniae* KA in combination with **3b** and **3e** (3.1-, and 4.1-fold, respectively); against *P. vulgaris* 190 in combination with **3a,b,c,e** (2.3-, 2.6-, 11.1-, and 9.2-fold, respectively); in combination with **3b** and **3e** against *S. typhosa* P58a (11.0- and 4.0-fold, respectively) and in combination with **3b** against *S. schottmuelleri* (5.4-fold). No potentiation of sulfisoxazole was observed with any compound against *P. aeruginosa*. These results are summarized in Table III.

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(11) The *in vivo* test methodologies may be found in E. Grunberg and W. F. DeLorenzo, *Antimicrob. Ag. Chemother.*, **1966**, 430 (1967).

Seeds as Sources of L-Dopa[1]

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The L isomer of dopa [3-(3,4-dihydroxyphenyl)alanine] is being used for symptomatic relief of Parkinson's disease.[2] It is presently obtained by synthesis or by processing fish flour.[3] A patent has been issued[4] for its preparation from velvet bean seed. Since the isolation of dopa from *Vicia faba* in 1913,[5] the compound has been reported in plant parts of species of the legumes *Baptisia, Lupinus, Mucuna* (including *Stizolobium*), and *Vicia* at levels up to 1.9%.[4,6–8] The compound has also been reported in the *Euphorbiaceae* as 1.7% of the fresh weight of the latex of *Euphorbia lathyrus*[9] and in the latex from *Euphorbia dendroides*.[10]

In the course of a survey in which amino acids in seed meals were determined by ion-exchange chromatography of acid hydrolysates, an unidentified peak eluting after leucine[11,12] was observed. The elution position of

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