

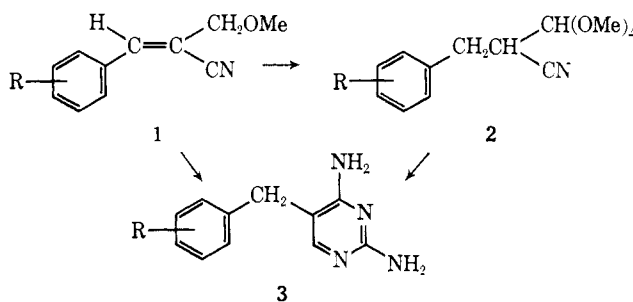
An Improved Synthesis of Diaveridine, Trimethoprim, and Closely Related 2,4-Diaminopyrimidines

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Received October 27, 1970

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 cinnamitriles **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-Cl₃
 - d. R = 3,4,5-Cl₃
 - 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 CH₂OMe group and the vinylogous proton, and a cis configuration (CN cis to substd Ph) for the cinnamitriles **1a** and **1b** is therefore indicated.

We have found that the cinnamitriles **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 improvement⁵ 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 simultaneous 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 sul-

fonamide potentiator ormetoprim (**3e**), which in combination with sulfadimethoxine⁶ 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 ₁₃ NO ₄	C, H, N
b	69-70	A	71	C ₁₃ H ₂₁ NO ₅	C, H, N
c	77-78	B	50	C ₁₂ H ₁₂ Cl ₃ NO ₂	C, H, Cl
d	85-86	B	35	C ₁₂ H ₁₂ Cl ₃ NO ₂	C, H, Cl
e	60-61	A	78	C ₁₃ 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 ₉ O ₃ N ₄	C, H, Cl
d	285-286	86	C ₁₁ H ₉ O ₃ N ₄	C, H, N
e	230	86	C ₁₄ H ₁₃ O ₂ N ₄	C, H, N

Experimental Section¹⁰

Method A. 4,5-Dimethoxy-2-methyl-2'-methoxymethyl-cinnamitrile (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 H₂O and extd (PhH). The PhH layer was washed (H₂O), 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*_D²⁰ 1.5823.

4,5-Dimethoxy-2-methyl-2'-cyanodihydrocinnamaldehyde Dimethyl Acetal (2e).—4,5-Dimethoxy-2-methyl-2-methoxymethyl-cinnamitrile (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 H₂O, and the pptd oil extd (PhH). The PhH layer was washed repeatedly with H₂O 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*_D²⁰ 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 H₂O (100 ml), filtered by suction, and washed with a little ice-cold EtOH and Et₂O, 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 H₂O, and the pptd oil extd with Et₂O.

(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 $\pm 0.4\%$. The nmr spectra were taken with a Varian A-60 instrument using DMF-*d*₇ as solvent and TMS as internal standard.

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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).

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)
<i>Streptococcus pyogenes</i>	4	2.1	3.8	2.6	6.2	1.7
<i>Diplococcus pneumoniae</i>	6301		2.1	2.1		3.8
<i>Staphylococcus aureus</i>	Smith	>5.0	4.0 ^b	>3.5	2.5	>11.0
<i>E. coli</i>	257	2.0	5.7 ^b	4.7	2.5	>8.9
<i>Klebsiella pneumoniae</i>	KA		3.1	1.7		4.1
<i>Proteus vulgaris</i>	190	2.3	2.6 ^b	11.1		9.2
<i>Pseudomonas aeruginosa</i>	B	1.1	1.4	>1.2	0.6	0.8
<i>Salmonella typhosa</i>	P58a		11.0			4.0
<i>Salmonella schottmuelleri</i>			5.4	1.9		1.4

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

After evapn of Et₂O, 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 H₂O 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.

Acknowledgment.—The microanalyses were obtained by Dr. F. Scheidl and his associates of our Microanalytical Laboratory. The nmr spectra were obtained by Dr. T. Williams of our Physical Chemistry

Department. We gratefully acknowledge the technical assistance of Mr. Sam Gruenman.

Seeds as Sources of L-Dopa¹

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Received October 1, 1970

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 issued⁴ 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 lathyris*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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