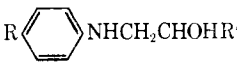
TABLE I

N-SUBSTITUTED DIAMINO-2-PROPANOLS

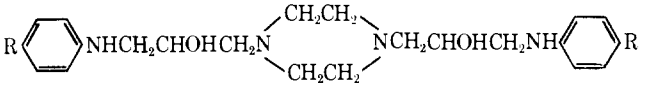


R	R'[a]	Yield, %	Mp, °C	Formula	Isolation method	Recrystn solvent	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
H	Pip	63	114	$C_{14}H_{22}N_2O$	A	Hexane	71.75	9.46	11.96	71.55	9.57	11.81
H	Pyr	69	102.3	$C_{13}H_{20}N_2O$	A	Hexane	70.87	9.15	12.72	70.91	9.22	12.65
H	Mor	74	125[b]	$C_{13}H_{20}N_2O_2$								
H	Hypip	Trace	110	$C_{14}H_{22}N_2O_2$	B	Benzene	67.16	8.86	11.19	67.28	8.74	10.98
CH_3	Pip	57	114.5	$C_{15}H_{24}N_2O$	A	Ethanol	72.54	9.74	11.28	72.47	9.61	11.05
CH_3	Pyr	91	136	$C_{14}H_{22}N_2O$	A	Benzene	71.75	9.46	11.96	71.74	9.59	11.88
CH_3	Mor	90	111–112[c]	$C_{14}H_{24}N_2O_2$								
OCH_3	Pip	54	105–107	$C_{15}H_{24}N_2O_2$	A	Hexane	68.15	9.15	10.60	68.18	9.30	10.57
OCH_3	Pyr	85	119	$C_{14}H_{22}N_2O_2$	A	Hexane	67.16	8.86	11.19	67.37	8.99	11.06
OCH_3	Mor	29	75	$C_{14}H_{22}N_2O_3$	B	Hexane	63.13	8.33	10.52	63.09	8.50	10.47
Cl	Pip	55	108	$C_{14}H_{21}ClN_2O$	A	Ethanol–water	62.55	7.88	10.42	62.68	7.84	10.24
Cl	Pyr	64	127	$C_{13}H_{19}ClN_2O$	A	Ethanol–water	61.29	7.52	11.00	61.23	7.67	11.28
Cl	Mor	67	102	$C_{13}H_{19}ClN_2O_2$	A	Benzene	57.66	7.07	10.35	57.52	6.99	10.28
Cl	Hypip	Trace	130	$C_{14}H_{21}ClN_2O_2$	B	Benzene	59.04	7.43	9.84	59.11	7.66	9.75

[a] Pip = 1-piperidyl, Pyr = 1-pyrrolidyl, Mor = 4-morpholinyl, Hypip = 1-(3-hydroxypiperidyl). [b] Lit.[1] mp 124–125°. [c] Lit.[1] mp 110–111.6°.

TABLE II

SUBSTITUTED 2-PROPANOLS DERIVED FROM PIPERAZINE



R	Yield, %	Mp, °C	Formula	Isolation method	Recrystn solvent	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
H	19	174	$C_{22}H_{32}N_4O_2$	A	C_6H_6	68.72	8.39	14.57	68.85	8.18	14.45
CH_3	25	170	$C_{24}H_{36}N_4O_2$	A	C_6H_6	69.87	8.80	13.58	69.74	8.89	13.51
Cl	56	187	$C_{22}H_{30}Cl_2N_4O_2$	A	C_6H_6	58.28	6.67	12.36	58.41	6.85	12.24
CH_3O	24	210	$C_{24}H_{36}N_4O_4$	A	C_6H_6	64.84	8.16	12.60	65.04	8.30	12.40

extracted with a mixture of bromobenzene and 1,2,4-trichlorobenzene and dried (Na_2SO_4).

A solution of the substituted 1-anilino-3-chloropropanol (0.025 mole) in a mixture of bromobenzene (8.0 ml) and trichlorobenzene (50 ml) was heated under reflux with a cyclic secondary aliphatic amine (0.025 mole) in a wax bath (205°), usually for about 3 hr. The reaction was followed by means of tlc. The unreacted halo compound had the greatest R_f. When tlc showed that the reaction was complete, the reaction mixture was cooled. Frequently, a solid product precipitated which was filtered, suspended in distilled water, and warmed to dissolve the hydrochloride salts. The cooled solution was neutralized ($NaHCO_3$) and the substituted diamino-2-propanol was filtered and recrystallized.

To extract the product from oily precipitates and mother liquors either isolation procedure A or B was followed. Method A: The product was extracted with 10% HCl and precipitated by neutralization with 10% NaOH. Solid precipitates were filtered and recrystallized from an appropriate solvent. Method B: Oily precipitates were extracted with benzene. The extract was dried (Na_2SO_4) and concentrated *in vacuo*. The concentrated solution was chromatographed on an alumina column and eluted with benzene, ether–benzene, ether, acetone–ether, and acetone. The eluents were collected and the solvents were allowed to evaporate. Solid products were collected and recrystallized.

Acknowledgment.—This work was supported by a National Science Foundation Undergraduate Research Participation Grant and a Du Pont Grant for Advancing Teaching.

(3) F. C. Pennington, G. L. Tritle, S. D. Boyd, W. Bowersox, and D. Aniline, *J. Org. Chem.*, **30**, 2801 (1965); F. C. Pennington, L. J. Martin, R. E. Reid, and T. W. Lapp, *ibid.*, **24**, 2030 (1959).

Orotic Acid Analogs. 2,5-Disubstituted 6-Hydroxy-4-carboxypyrimidines[1]

SAUL BORODKIN, SIGURDUR JONSSON,[2] GEORGE H. COCOLAS, AND ROBERT L. MCKEE

School of Pharmacy and Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina

Received September 2, 1966

We would like to report the synthesis and antimicrobical testing of a series of 2-alkylmercapto-, 2-amino-, and 2-hydroxy-5-substituted 4-carboxypyrimidines (Table I). Reports of biochemical antagonism by 5-fluorouracil[3] prompted the synthesis of these analogs as potential antimetabolites of orotic acid. The synthesis of unsubstituted orotic acids has been reported by Daves, *et al.*,[4] who prepared the nine possible combinations of 4-carboxypyrimidine if hydroxyl, amine, and thiol groups are interchanged on the 2 and 6 positions of 4-carboxypyrimidine. Compounds **1, 5, 6, 8, 12–14, 16, 18,** and **20** were tested *in vitro* at concentrations up to 200 μg/ml against *Staphylococcus aureus* (resistant

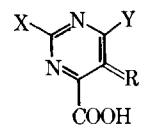
(1) Supported by a research grant from Smith Kline and French Laboratories, Philadelphia, Pa. For preceding paper see S. Borodkin, S. Jonsson, G. H. Cocolas, and R. L. McKee, *J. Med. Chem.*, **10**, 248 (1967).

(2) Deceased.

(3) (a) W. Munyon and N. P. Salzman, *Virology*, **18**, 95 (1962); (b) L. Cheong, M. A. Rich, and M. L. Eidenoff, *Cancer Res.*, **20**, 1602 (1960); (c) M. L. Eidinoff, J. E. Knoll, B. J. Marano, and D. Klein, *ibid.*, **21**, 1377 (1961).

(4) G. D. Daves, F. Baiocchi, R. K. Robbins, and C. C. Cheng, *J. Org. Chem.*, **26**, 2755 (1961).

TABLE I
OROTIC ACID ANALOGS



No.	X	Y	R	Method used	% yield	Mp, °C[a]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Sulfur, % Calcd	Sulfur, % Found	Ultraviolet spectra[b] λ, mμ (ε) Max	Min
1	CH_3S	OH	CH_3	A	34	234–235	$C_7H_8N_2O_3S$	42.00	41.75	4.03	3.88	14.00	13.85	15.99	15.90	244 (9000), 293 (7500)	266 (5000)
2	CH_3S	OH	C_2H_5	A	30	232–233	$C_8H_{10}N_2O_3S$	44.86	45.29	4.71	4.66	13.08	12.98	14.96	14.87	244 (9000), 293 (8000)	265 (5000)
3	CH_3S	OH	n-C_3H_7	A	35	219–220	$C_9H_{12}N_2O_3S$	47.36	47.35	5.30	5.24	12.28	12.01	14.02	14.05	245 (9500), 294 (8500)	266 (5000)
4	CH_3S	OH	n-C_4H_9	A	24	181–182	$C_{10}H_{14}N_2O_3S$	49.54	49.27	5.82	5.82	11.56	11.53	13.23	13.16	245 (9000), 294 (8000)	266 (5000)
5	CH_3S	OH	$C_6H_5CH_2$	A	26	227–228	$C_{13}H_{12}N_2O_3S$	56.52	56.69	4.38	4.59	10.14	10.06	11.60	11.53	244 (9500), 296 (8500)	266 (5000)
6	C_2H_5S	OH	C_2H_5	A	37	208–209	$C_9H_{12}N_2O_3S \cdot 0.5H_2O$	45.55	45.35	5.52	5.02	11.81	12.01	13.51	13.63	245 (9000), 293 (8000)	266 (5000)
7	C_2H_5S	OH	i-C_3H_7	A	23	206–207	$C_{10}H_{14}N_2O_3S$	49.54	49.35	5.82	6.52	11.57	11.68	13.21	13.27	245 (9000), 293 (8000)	266 (5000)
8	$C_6H_5CH_2S$	OH	CH_3	A	28	227–228	$C_{13}H_{12}N_2O_3S$	56.52	56.88	4.38	4.41	10.14	10.10	11.58	11.65	245 (8500), 296 (8000)	269 (5500)
9	NH_2	OH	CH_3	B	89	300–301[c]	$C_6H_7N_3O_3$									283 (6500)	252 (3000)
10	NH_2	OH	C_2H_5	B	78	275–276	$C_7H_9N_3O_3$	45.90	46.19	4.95	4.95	22.95	23.45			283 (6500)	252 (3000)
11	NH_2	OH	n-C_3H_7	B	76	278–279	$C_8H_{11}N_3O_3$	48.72	48.52	5.62	6.18	21.31	21.13			282 (5500)	252 (3000)
12	NH_2	OH	n-C_4H_9	B	85	271–272	$C_9H_{13}N_3O_3$	51.18	50.78	6.20	6.95	19.90	19.85			279 (6500)	249 (3000)
13	NH_2	OH	i-C_3H_7	B	85	241–242	$C_8H_{11}N_3O_3 \cdot 0.5H_2O$	46.59	46.49	5.87	5.75	20.38	20.17			279 (7000)	251 (3500)
14	NH_2	OH	$C_6H_5CH_2$	B	80	272–273	$C_{12}H_{11}N_3O_3$	58.77	58.81	4.52	4.58	17.14	17.28			281 (7000)	251 (3500)
15	OH	OH	CH_3	C	96	325–237[d]	$C_6H_6N_2O_4$									274 (7000)	238 (1500)
16	OH	OH	C_2H_5	C	95	311–313	$C_7H_8N_2O_4$	45.65	45.69	4.38	4.19	15.22	15.18			273 (8000)	238 (2000)
17	OH	OH	n-C_3H_7	C	90	302–303	$C_8H_{10}N_2O_4$	48.48	48.34	5.09	4.96	14.14	14.51			274 (8000)	239 (2000)
18	OH	OH	i-C_3H_7	C	77	282–283	$C_8H_{10}N_2O_4$	48.48	48.56	5.09	5.33	14.14	14.10			273 (8500)	238 (2000)
19	OH	OH	n-C_4H_9	C	81	297–298	$C_9H_{12}N_2O_4$	51.41	50.91	5.70	5.92	13.20	13.25			275 (8000)	240 (2000)
20	OH	OH	$C_6H_5CH_2$	C	90	308–309	$C_{12}H_{10}N_2O_4$	58.54	58.59	4.09	4.03	11.38	11.14			275 (8000)	240 (2500)

[a] All 4-carboxypyrimidines melted with decomposition. [b] Determined on a Beckman Model DU spectrophotometer using 10^{-4} M aqueous solutions and scanned from 200–400 mμ. The molar absorptivity values are rounded to the nearest 500 units. [c] C. Mentzer and D. Billet [*Compt. Rend.*, **228**, 402 (1949)] reported mp 302°. [d] P. H. Laursen, W. A. Thews, and B. E. Christensen [*J. Org. Chem.*, **22**, 274 (1957)] reported mp 327°.

strain), *Klebsiella pneumoniae*, *Candida albicans*, *Trichomonas foetus*, and *Trychophyton mentagrophytes*. All were inactive.

Experimental Section[5]

Method A. 5-Substituted 2-Alkylmercapto-6-hydroxy-4-carboxypyrimidines.—To an S-alkylpseudothiourea sulfate (0.425 mole) dissolved in 1 l. of water was added 0.85 mole of the ethyl ester of the corresponding α-substituted ethoxalylacetate[6] followed by 168 g (2.55 moles) of KOH dissolved in 300 ml of water. The resulting solution was allowed to stand at room temperature for 2 days. The reaction mixture was extracted with ether and treated with charcoal and then made strongly acidic with HCl. The product precipitated as a white precipitate. It was washed liberally with water and recrystallized by dissolving it in 1% NaOH solution, filtering through charcoal, and acidifying the hot solution with HCl.

Method B. 5-Substituted 2-Amino-6-hydroxy-4-carboxypyrimidine.—5-Substituted 2-methylmercapto-6-hydroxy-4-carboxypyrimidine (10 g) was dissolved in 100 ml of 30% NH_4OH solution and the mixture was heated in a bomb at 120° for 16 hr. The reaction mixture was cooled and slowly acidified with HCl. The white precipitate was washed with water and purified as described in the above procedure.

Method C. 5-Substituted 2,6-Dihydroxy-4-carboxypyrimidine.—Substituted 6-hydroxy-2-methylmercapto-4-carboxypyrimidine (10 g) was refluxed 6 hr with 250 ml of concentrated HCl solution. After cooling, the mixture was diluted with 250 ml of water, and the precipitate was collected and washed with water and acetone. The product was purified as described in the above procedure.

(5) Melting points were taken in open capillary tubes on a Mel-Temp apparatus and are corrected. Analyses are by Alfred Bernhardt Microanalytical Laboratories, Mulheim, Germany.

(6) R. F. B. Cox and S. M. McElvain, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 272.

Routes to Unsymmetrical N,N′-Diarylethylenediamines

C. H. YODER AND J. J. ZUCKERMAN

Baker Laboratory, Cornell University, Ithaca, New York

Received July 11, 1966

Unsymmetrical diarylethylenediamines are of value both as precursors to imidazolidines and piperazines and as chelating ligands for transition metals. Two routes for the preparation are offered.

Experimental Section

Procedure I.—The first route, of general utility, requires the preparation of a 2-anilinoethanol by the action of an arylamine on 2-chloroethanol, conversion of the alcohol to a bromide with HBr, and, finally, amination of the resulting bromide with a second arylamine. The preparation of 2-(*p*-dimethylaminoanilino)- and 2-(*p*-methoxyanilino)ethanol followed that of Jacobs and Heidelberg,[1] while the procedure for the synthesis of the corresponding bromides was that of Pearlman.[2] The crude hydrobromide (0.1 mole) was heated with the appropriate arylamine (0.4 mole) at 100° for 6–10 hr with stirring, and the mixture was poured while hot and fluid into cold, swirling water (300 ml). After thorough homogenization of the precipitate, the solution was neutralized with aqueous NaOH, and the precipitate was filtered and washed with water. The precipitate was then thoroughly extracted with 1:1 methanol–water (300 ml), collected, and washed with methanol–water. Recrystallization was from ethanol or ethanol–water.

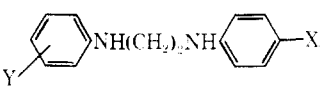
Procedure II.—The second procedure is for the special case where one aryl group carries a strongly electron-attracting substituent such as a nitro group. A mixture of *p*-nitroaniline (0.31 mole, technical grade), Na_2CO_3 (0.14 mole), and 1-bromo-2-chloroethane (70 ml) was heated at gentle reflux for 40 hr with stirring. After cooling, the mixture was suction filtered and the precipitate was washed with 1-bromo-2-chloroethane (*ca.* 20 ml). The filtrate was evaporated to one-half volume *in vacuo* and cooled. Crude product was obtained in 30% yield (20 g). Four recrystallizations from ethanol–water produced material melting at 87.0–88.3°. The product of this reaction appears to be a mixture of 2-(nitroanilino)ethyl halides as evidenced by elemental analyses of various samples of short melting point range and the rather complex nmr spectrum.

Addition of chlorobromoethane to the molten amine (equimolar quantities) and Na_2CO_3 at 150° and continued heating at this temperature for 20 hr gave N,N′-bis(*p*-nitrophenyl)ethylenediamine. The same procedure sufficed for *m*-nitroaniline where the product (yield 18%) was recrystallized once from ether and twice from CCl_4.

The crude halide (*ca.* 0.05 mole) was then mixed with the appropriate aryl amine (0.2 mole) and heated to 100° for 12–16 hr (magnetic stirring). After cooling, this mixture was stirred with 95% ethanol (150 ml) for several hours and filtered. In only two cases, N-(*p*-dimethylaminophenyl)-N′-(*p*-nitrophenyl)ethylenediamine and N-(*p*-dimethylaminophenyl)-N′-(*m*-nitrophenyl)-ethylenediamine, was solution effected. In these instances water (75–100 ml) was added to the ethanol filtrate to induce precipitation. Recrystallization was from ethanol or ethanol–water. Results are summarized in Table I.

Acknowledgments.—This investigation was supported by Public Health Service Research Grant CA-07064-03 from the National Cancer Institute and by National Science Foundation Grant GP-5025. We are indebted to the National Science Foundation for a Predoctoral Fellowship to C. H. Yoder.

TABLE I[a]
UNSYMMETRICAL ETHYLENEDIAMINES



Y	X	Method of prepn	Crude yield, % (final step)	Mp, °C[b]	Color	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
p-$(CH_3)_2N$	*p*-OCH_3	I[c]	50	94–96	White	71.55	71.50	8.12	7.98		
p-NO_2	*p*-$(CH_3)_2N$	II[d]	65	161.5–163.0	Red-brown	63.98	64.07	6.71	6.84		
p-NO_2	*p*-CH_3O	II[e]	50	151.5–152.0	Red-purple	62.69	62.55	5.97	6.15		
p-NO_2	*p*-CH_3	II[e]	65	161.5–162.5	Gold-orange	66.40	66.11	6.32	6.47	15.49	15.76
m-NO_2	*p*-$(CH_3)_2N$	II[e]	40	117.5–119	Yellow-orange	63.98	63.67	6.71	6.65		
m-NO_2	*p*-CH_3O	II[c]	85	109.0–109.5	Red-orange	62.69	62.58	5.97	5.90	14.63	14.82

[a] Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory. [b] Recorded (uncorrected) on a Townson and Mercer type 5, melting point block. [c] Amine used in the final step was *p*-anisidine. [d] Amine used in the final step was N,N-dimethyl-*p*-phenylenediamine. [e] Amine used in the final step was *p*-toluidine.

(1) W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 403 (1915).

(2) W. M. Pearlman, *J. Am. Chem. Soc.*, **70**, 870 (1948).