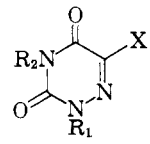
TABLE I



No.	R_1	R_2	X	Mp, °C	Yield, %	Formula	Calcd, % C	H	N	X	Found, % C	H	N	X
I	H	CH_3	Br	190–191	85	$C_4H_4BrN_3O_2$	23.32	1.96	20.40	38.79	23.24	2.04	20.70	28.70
II	CH_3CO	CH_3	Br	111.5–113[a]	87	$C_6H_6BrN_3O_3$	29.05	2.44	16.94	32.22	29.17	2.65	17.07	32.02
III	CF_3CO	CH_3	Br	135–136[b]	83	$C_6H_3BrF_3N_3O_3$	23.86	1.00	13.91		23.73	1.26	14.15	
IV	CH_3	CH_3	Br	105–106	88	$C_5H_6BrN_3O_2$	27.29	2.75	19.10	36.32	27.19	3.00	18.80	36.24
V	CH_3	CH_3	F	130–131[c]	34[d]	$C_5H_6FN_3O_2$	37.74	3.80	26.41	11.94	37.82	3.84	26.14	11.93
VI	$(C_6H_5)_2CH$	$(C_6H_5)_2CH$	Br	183–185[e]	60[f]	$C_{29}H_{22}BrN_3O_2$	66.42	4.23	8.01	15.24	66.65	4.35	7.74	15.05

[a] Crystallized from C_6H_6–CCl_4. [b] Recrystallizing and remelting at 183°. [c] Recrystallizing and remelting at 138°. Purified by sublimation. [d] Crude product. [e] Crystallized from absolute ethanol. [f] Crude product, mp 176–178°.

dry dioxane was treated with 4.6 g (25 mmoles) of diphenyldiazomethane[8] in 20 ml of dry dioxane and stirred overnight at 90°.[9] After evaporation of this mixture to dryness, the crude product (VI) was obtained.

(8) J. H. Ford, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 35.

(9) Methodology of M. Prystas and F. Šorm, *Collection Czech. Chem. Commun.*, **27**, 1578 (1962).

cis-1-(3-Dimethylaminopropyl)-2,3-pentamethylenetetrahydroquinoline

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The useful antidepressant clinical activity of imipramine suggested the synthesis of the title compound as a variation on the basic heterocyclic system. However, the only activity of note uncovered was the antagonism of ethanol depression and death in mice.

Experimental Section[1]

2,3-Pentamethylenecinchoninic acid:[2] mp 302–303° (lit.[2] mp 291–292°); 95% yield; λ_{max}^{Nujol} 2.95, 3.75, 4.30, 4.97, 6.29 μ.

2,3-Pentamethylenequinoline:[2] mp 91–92.5° (lit.[2] mp 93.5°); 93% yield; λ_{max}^{Nujol} 6.25, 6.43, 6.72 μ.

***cis*-Tetrahydro-2,3-pentamethylenequinoline.**[3]—2,3-Pentamethylenequinoline was reduced with tin and HCl or catalytically (PtO_2, H_2) to give, in either case, an oil which was shown by tlc to consist of starting material and a new component. The oil was treated with benzoyl chloride under Schotten–Baumann conditions to give *cis*-1-benzoyl-2,3-pentamethylenetetrahydroquinoline, mp 142–146° (33% yield based on the quinoline). A recrystallized sample melted at 145–146.5° (lit. mp 145–146°,[3a] 146.5°[3b]); $\lambda_{max}^{CHCl_3}$ 6.16, 6.37, 6.72, 7.19, 7.37 μ. The benzamide was hydrolyzed by refluxing it in a mixture of KOH, ethanol, and water for 45 hr. Work-up afforded a 94% yield of a clear oil which showed one spot on tlc, and was used as such; $\lambda_{max}^{CHCl_3}$ 2.92, 6.30, 6.38, 6.78, 6.94 μ. A portion of the base was converted to the hydrochloride, mp 141–144° (lit.[3] mp 143–145°).

***cis*-1-(3-Dimethylaminopropyl)-2,3-pentamethylenetetrahydroquinoline Hydrochloride.**—To a suspension of 1.75 g (0.076 mole) of sodamide in 175 ml of liquid NH_3 was added 12.5 g (0.062 mole) of *cis*-tetrahydro-2,3-pentamethylenequinoline in 25 ml of ether. After allowing this mixture to stir for 1 hr, there was added a solution of 3-dimethylaminopropyl chloride (liberated from 23.5 g, 0.15 mole, of the corresponding hydrochloride) in 10 ml of ether over a 15-min period. The resultant mixture was stirred for 1.5 hr and then allowed to stand overnight, whereby NH_3 evaporated. Water was then added, the layers were separated, and the aqueous phase was extracted several times with ether. The combined organic portions were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residual oil was distilled, and the main fraction [bp 155–160° (0.2 mm)] amounted to 9.0 g (51%). This yellow oil showed one component (not the starting material) on tlc; $\lambda_{max}^{CHCl_3}$ 6.28, 6.70, 6.90 μ. The oil was converted to the hydrochloride to give 7.1 g of crude solid. Recrystallization from ethanol–ether gave 4.3 g, mp 155–157° dec, and 0.8 g, mp 153.5–156° dec. An analytical sample, prepared from this latter material, melted at 155.5–157.5° dec; λ_{max}^{KBr} 3.79, 4.10, 6.26, 6.68, 7.34, 7.82 μ; λ_{max}^{EtOH} 258, 311 mμ ($\epsilon \times 10^{-3}$ 17.6, 3.35).

Anal. Calcd for $C_{19}H_{31}ClN_2$: C, 70.67; H, 9.68; N, 8.68. Found: C, 70.84; H, 9.66; N, 8.83.

Acknowledgment.—We wish to express our appreciation to the S. E. Massengill Co., Bristol, Tenn., for instituting and supporting this work.

(1) Melting points were determined on a Thomas–Hoover capillary apparatus and are corrected.

(2) W. Borsche, *Ann.*, **377**, 122 (1910).

(3) (a) T. Masamune, *J. Am. Chem. Soc.*, **79**, 4418 (1957); (b) S. G. P. Plant and R. J. Rosser, *J. Chem. Soc.*, 1840 (1930).

Preparation of Substituted Diaminopropanols

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In a search for compounds that might be useful hypotensive agents a series of N-substituted diamino-2-propanols have been prepared[1] (Tables I and II).

Experimental Section

Analysis of Reactions and Compounds by Means of Thin Layer Chromatography (Tlc).—Aluminum oxide was used as an adsorbent.[2] The spotted plates were developed by means of an acetone–hexane mixture (2:5 v/v), and the plates were exposed to HNO_3 fumes.

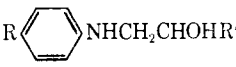
Synthesis of Substituted Diaminopropanols.—Substituted 1-anilino-3-chloropropanols were prepared from aromatic primary amines and epichlorohydrin by procedures previously reported.[3] These were usually isolated as picrates and regenerated by means of saturated LiOH. The halo compound was immediately

(1) *Cf.* B. J. Ludwig, W. A. West, and D. W. Farnsworth, *J. Am. Chem. Soc.*, **76**, 2893 (1954).

(2) Camag, Arthur H. Thomas Co., Philadelphia, Pa.

TABLE I

N-SUBSTITUTED DIAMINO-2-PROPANOLS

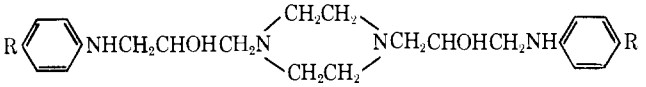


R	R'[a]	Yield, %	Mp, °C	Formula	Isolation method	Recrystn solvent	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
H	Pip	63	114	$C_{14}H_{22}N_2O$	A	Hexane	71.75	9.46	11.96	71.55	9.57	11.81
H	Pyr	69	102.3	$C_{13}H_{20}N_2O$	A	Hexane	70.87	9.15	12.72	70.91	9.22	12.65
H	Mor	74	125[b]	$C_{13}H_{20}N_2O_2$								
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]	$C_{14}H_{22}N_2O_2$								
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 O. 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]

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We would like to report the synthesis and antimicrobial 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).