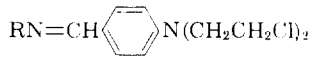
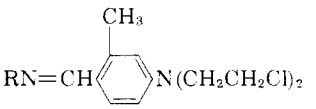
TABLE I
CONDENSATIONS OF AMINES WITH BENZALDEHYDE NITROGEN MUSTARD



Amine (RNH_2)	Mp, °C[a]	Yield, %	Formula	% calcd C	% calcd H	% calcd N	% found[b] C	% found[b] H	% found[b] N
Cyclohexanemethylamine	48	95	$C_{18}H_{26}Cl_2N_2$	64.49	6.01	8.35	63.58	7.79	8.69
3-Amino-9-ethylcarbazole	112–113	94	$C_{27}H_{29}Cl_2N_3$	69.52	6.26	9.00	68.21	5.43	9.29
1,2-Diaminopropane	125–126	93	$C_{25}H_{32}Cl_4N_4$	56.64	6.08	10.56	56.52	6.22	10.24
1,4-Diaminobutane	111–112	72	$C_{26}H_{34}Cl_4N_4$	57.36	6.47	10.29	57.43	6.47	10.24

[a] Melting points were determined on a Fisher-Johns apparatus and are uncorrected. [b] Organic microanalyses by Dr. C. Daessle, Montreal, Canada.

TABLE II
CONDENSATIONS OF AMINES WITH TOLUALDEHYDE NITROGEN MUSTARD



Amine (RNH_2)	Mp, °C	Yield, %	Formula	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N
Cyclohexanemethylamine	41–43	89	$C_{19}H_{28}Cl_2N_2$	65.33	6.46	8.02	64.76	7.98	7.98
3-Amino-9-ethylcarbazole	111	85	$C_{28}H_{27}Cl_2N_3$	69.02	6.01	9.28	68.16	6.20	9.46
Sulfanilamide	165	±90	$C_{18}H_{21}Cl_2N_3O_2S$	52.17	5.10	10.14	53.17	5.61	10.10
1,5-Dimethylhexylamine	34	77	$C_{20}H_{32}Cl_2N_2$	64.67	8.68	7.54	64.91	8.96	7.53
2-Methoxy-5-nitroaniline	133–135	47	$C_{19}H_{21}Cl_2N_3O_3$	55.61	5.15	10.24	55.82	5.63	10.06
Ethyl *p*-aminobenzoate	112–113	63	$C_{21}H_{23}Cl_2N_2O_2$	61.97	5.93	6.87	61.67	5.95	7.01
1,2-Diaminopropane	148–149	90	$C_{27}H_{38}Cl_4N_4$	58.07	6.49	10.03	58.01	6.54	9.69
1,4-Diaminobutane	132–133	94	$C_{28}H_{40}Cl_4N_4$	58.72	6.69	9.78	58.00	6.63	9.78
1,3-Diaminopropane	80	±90	$C_{27}H_{36}Cl_4N_4$	58.07	6.49	10.03	58.06	6.58	9.70

Acknowledgment.—The authors wish to thank Mssrs. B. Girard, J. Beaulé, and C. Lemay for their technical assistance. We wish to acknowledge Dr. Harry B. Wood, Jr., of the Cancer Chemotherapy National Service Center for his cooperation in obtaining the screening data.

1,3-Dimethyl-5-fluoro-6-azauracil and Some 5-Bromo-6-azauracil Derivatives[1]

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The anticancer activity of 6-azauracil is well known.[2] The syntheses of the following 6-azauracil analogs are here described: 5-bromo-3-methyl 6-azauracil [6-bromo-4-methyl-*as*-triazine-3,5(2H,4H)-dione] (I), 1-acetyl-5-bromo-3-methyl-6-azauracil [2-acetyl-6-bromo-4-methyl-*as*-triazine-3,5(2H,4H)-dione] (II), 5-bromo-3-methyl-1-trifluoroacetyl-6-azauracil [6-bromo-4-methyl-2-trifluoroacetyl-*as*-triazine-3,5(2H,4H)-dione] (III), 5-bromo-1,3-dimethyl-6-azauracil [6-bromo-2,4-dimethyl-*as*-triazine-3,5-(2H,4H)-dione] (IV), 1,3-dimethyl-5-fluoro-6-azauracil [2,4-dimethyl-6-fluoro-*as*-triazine-3,5(2H,4H)-dione] (V), and 5-bromo-1,3-bis(diphenylmethyl)-6-azauracil [6-bromo-2,4-bis(diphenylmethyl)-*as*-triazine-3,5(2H,4H)-dione] (VI) (Table I). Attempts to prepare 5-fluoro-6-azauracil failed.

(1) Supported largely by the Research Grant CA 08095 from the National Cancer Institute, Public Health Service.

(2) J. Skoda, *Progr. Nucleic Acid Res.*, **3**, 197 (1963); G. B. Elion and G. H. Hitchings, *Advan. Chemotherapy*, **2**, 91 (1965).

Experimental Section[3]

5-Bromo-3-methyl-6-azauracil (I).—On stirring a mixture of 508 mg (4 mmoles) of 3-methyl-6-azauracil,[4] 10 ml of water, and 1.44 g (9 mmoles) of bromine over night, I crystallized from solution.

1-Acetyl-5-bromo-3-methyl-6-azauracil (II).—A mixture of 412 mg (2 mmoles) of I and 5 ml of acetic anhydride was refluxed for 30 min,[5] at which time it was filtered to remove a small amount of insoluble material. Evaporation of the filtrate, *in vacuo*, gave II as an oil. The crystallization solvent is recorded in Table I.

5-Bromo-3-methyl-1-trifluoroacetyl-6-azauracil (III).—A mixture of 550 mg (2.66 mmoles) of I and 5 ml of trifluoroacetic anhydride was refluxed overnight. On cooling in an ice bath III crystallized as needles.

5-Bromo-1,3-dimethyl-6-azauracil (IV).[6]—A mixture of 2.1 g (15 mmoles) of 1,3-dimethyl-6-azauracil,[4] 30 ml of water, and 2.0 ml (30 mmoles) of bromine was stirred overnight at room temperature and cooled, and the product (IV) was removed by filtration.

1,3-Dimethyl-5-fluoro-6-azauracil (V).—A mixture of 440 mg (2 mmoles) of IV, 440 mg of anhydrous KF, and 1 ml of dry dimethyl sulfoxide was stirred at 125° for 7 days. On cooling to −10°, 60 mg of V crystallized and was removed by filtration. The filtrate was diluted with 12 ml of water and extracted with chloroform. After drying, the chloroform layer was evaporated to dryness, yielding an additional 50 mg of V.

5-Bromo-1,3-bis(diphenylmethyl)-6-azauracil (VI).—A mixture of 1.8 g (9.4 mmoles) of 5-bromo-6-azauracil[7] in 20 ml of

(3) Melting points were determined using a Kofler hot stage. Analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

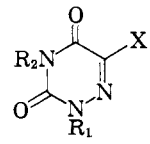
(4) K. Y. Zee-Cheng and C. C. Cheng, *J. Org. Chem.*, **27**, 976 (1962); J. Gut, M. Prystas, J. Jonas, and F. Šorm, *Collection Czech. Chem. Commun.*, **26**, 974 (1961).

(5) The acylation of 6-azauracil is described by A. Novacek, D. Hesoun, and J. Gut, *ibid.*, **30**, 1890 (1965).

(6) The synthesis of this compound by the methylation of 5-bromo-6-azauracil is given by M. Horak and J. Gut, *ibid.*, **28**, 3392 (1963).

(7) P. K. Chang and T. L. V. Ulbricht, *J. Am. Chem. Soc.*, **80**, 976 (1958).

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.**—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.