by Nodiff and Hausman.[5] Condensation of the 2-aminobenzenethiol zinc salts (Ia and Ib) with 4-chloro-2,5-dihydroxybenzoic acid (IIb) provided 8-chloro- and 8-trifluoromethyl-3-hydroxyphenothiazine-2-carboxylic acids (IVa and IVb, respectively).

An alternate approach (path B) to IVa and IVb employed the Kolbe–Schmitt reaction.[6] Using Marasse's modification,[7] the carbonation of 2-chloro- (IIIa) and 2-trifluoromethyl-7-hydroxyphenothiazines (IIIb) produced the 3-hydroxyphenothiazine-2-carboxylic acids (IVa and IVb). Although two positions *ortho* to the hydroxyl group are available for carbonation, only one isomer was isolated in each case. Physical and spectral data revealed that the products from paths A and B were identical.

Compounds IVa and IVb were tested for antiinflammatory activity in two biological assays. Preliminary data indicate that these compounds possess a low order of activity. 8-Chloro-3-hydroxyphenothiazine-2-carboxylic acid (IVa) produced a significant inhibition of granuloma growth in the carrageenin filter paper granuloma assay[7] in adrenalectomized rats subcutaneously at a dose of 80 mg/kg. At a lower dose of 20 mg/kg it was without effect. The trifluoromethyl analog (IVb) was ineffective at 40 mg/kg. Phenylbutazone was effective in this assay subcutaneously at 20 mg/kg. IVa was ineffective in the ultraviolet erythema test[8] when administered orally at a dose of 40 mg/kg. The oral ED_{50} of phenylbutazone by this method was 7.4 mg/kg.

Experimental Section[9]

2-Trifluoromethyl-7-hydroxyphenothiazine (IIIb) was prepared from the zinc salt of 2-amino-4-trifluoromethylbenzenethiol[10] (Ib) and 2-chlorohydroquinone (Aldrich Chemical Co.) (IIa) using the method described in ref 5. IIIb was obtained (77%) as tan platelets (C_6H_6), mp 211–214°. *Anal.* ($C_{13}H_8F_3NOS$) C, H.

3-Hydroxyphenothiazine-2-carboxylic Acids (IVa and IVb). Method A.—A stream of O_2 was bubbled for 1 hr through a refluxing mixture of 4-chloro-2,5-dihydroxybenzoic acid[11] (0.0186 mole), NaOH (0.0372 mole) in H_2O (7 ml), and 4-chloro-2-aminobenzenethiol zinc salt (Ia, 0.0093 mole) in EtOH (50 ml). The dark brown suspension was filtered hot, and the filtrate was treated with sodium dithionite (3.2 g) in H_2O (214 ml). The yellow mixture was then heated at 40–50° for 15 min and was decanted from a small amount of gum. Overnight the decantate deposited a yellow solid[12] which on recrystallization from AcOH gave IVa, 40%, mp 277–280° dec. *Anal.* ($C_{13}H_8ClNO_3S$) C, H. Similarly, 4-trifluoromethyl-2-aminobenzenethiol zinc salt (Ib) provided IVb, 14%, mp 253–254.5° dec. *Anal.* ($C_{14}H_8F_3NO_3S$) C, H. Absorption bands of ir spectra were as expected.

Method B.—An intimate mixture of granular anhydrous potassium carbonate (107.4 g, 0.78 mole) and 2-chloro-7-hydroxyphenothiazine[5] (35.4 g, 0.14 mole) was placed in a 250-ml Hastelloy C pressure vessel. The reactor was sealed, CO_2 gas was admitted under pressure, and the vessel was vented. This procedure was carried out several times. Finally, the reactor was pressurized with CO_2 (42.2–56.2 kg/cm²), heated to 200° during 19 hr, and maintained at 200–220° for 28 hr. The pressure vessel was cooled to room temperature and vented. After extracting the reaction cake with 2.5 l. of hot H_2O, the extract was treated with carbon. Acidification of the filtrate with HCl gave a brown precipitate which on recrystallization provided IVa (18%). The 8-trifluoromethyl derivative IVb was obtained (41%) in a similar manner. Samples of IVa and IVb prepared by methods A and B gave identical ir spectra, and mixture melting points were not depressed.

Acknowledgment.—The authors are indebted to Dr. J. H. Birnie of Smith Kline and French Laboratories for the biological testing and to Miss Pauline Schwartz for her assistance with some of the experiments.

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(6) A review of this reaction and its modifications is presented by A. Lindsey and H. Jeskey, *Chem. Rev.*, **57**, 583 (1957).

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(8) C. Winder, J. Wax, V. Burc, M. Benn, and C. Rosiere, *Arch. Intern. Pharmacodyn.*, **116**, 261 (1958).

(9) Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Melting points were determined in open capillary tubes in an electrically heated Thiele-Dennis apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(10) A. Kiprianov and L. Yagupolskii, *Zh. Obshch. Khim.*, **22**, 2209 (1952); *Chem. Abstr.*, **47**, 4769 (1953).

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(12) In the case of IVb, this solid was precipitated only by the addition of AcOH.

Synthesis of 1,4-Disubstituted Piperazines. II[1]

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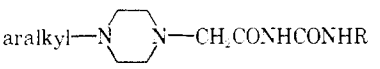
In the first paper[2] in this series, various piperazines were made having, as one substituent, an aromatic ring and, as the other, a substituted acylurea in order to obtain possible sedatives or other physiologically active compounds.

In this article, the piperazines synthesized generally contain various aralkyl groups and either acylurea substituents or substituted carbamoyl groups. Most of them are of types I and II.



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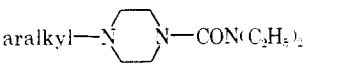


II

Biological Data.[3]—Compound **1** was active at 100 mg but inactive at 50 mg/kg ip in affording protection to mice against electroshock when administered 30 min before the stimulus. Also, when administered 30 min previous to pentylenetetrazole **1** showed antipentylenetetrazole activity (clonic convulsions) in mice at 100 mg/kg ip but was ineffective at 50 mg.

Compound **3** was a mildly acting psychomotor stimulant (photocell count method) at 300 mg/kg *po* in mice. Compound **12** showed slight psychomotor stimulation in mice at 100 mg/kg *po*. Compound **15** was a mild psychomotor depressant at 300 mg/kg *po* and a mild stimulant at 30 mg/kg *po*. Compound **15** also showed questionable activity against a *Trichomonas gallinae* vaginal infection in hamsters at 100 mg/kg *po*. Compound **19** was a feeble stimulant at 30 mg/kg *po*,

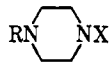
(1) Support of this work by the Sterling-Winthrop Research Institute of Rensselaer, N. Y., is acknowledged with gratitude.

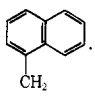
(2) M. Verderame, *J. Med. Chem.*, **9**, 153 (1966).

(3) The author is indebted to the Biological Division of the Sterling-Winthrop Research Institute for carrying out these studies.

TABLE I

1,4-DISUBSTITUTED PIPERAZINES



No.	R	X	Yield, %	Mp,[a] °C	Procedure[b]	Reaction time,[c] hr	Recrystn[d] solvent	Formula	Analyses
1	$(C_6H_5)_2CH$	$CH_2CHOHCH_2OH$	44	124–125	A (acet)	0.75	C–D	$C_{20}H_{26}N_2O_2$	C, H, N
2	$(C_6H_5)_2CH$	$CON(C_2H_5)_2$	33	95–96	B[e]	0.75	E	$C_{22}H_{29}N_3O$	C, H, N
3	$(C_6H_5)_2CH$	$CH_2C(Br)=CH_2\cdot 2HCl$	50	233–234 dec	A (acet)	0.25	F–H, 1:3	$C_{20}H_{25}BrCl_2N_2$	Br, N
4	$(C_6H_5)_2CH$	$CSNHC_6H_5$	69	215–217	*g*	...	H	$C_{24}H_{25}N_3S$	S, N
5	$C_6H_5CH_2$	$CH_2CONHCONHCH_3$	33	111–114	A (alc)	1.5	1st: I–J 2nd: C–D	$C_{15}H_{22}N_4O_2$	C, H, N
6	$C_6H_5CH_2$	$CH_2CONHC_6H_5$	41	105–107	A (acet)	2	E	$C_{19}H_{23}N_3O$	C, H, N
7	$H_5C_2NHCONHCOCH_2$	$CH_2CONHCONHC_2H_5$	78	225 dec	A (acet)	1.5	I–J	$C_{14}H_{26}N_6O_4$	C, H, N
8	$(C_6H_5)_2CH$	p-$SO_2C_6H_4NH_2$	60	180–182	*h*	...	K–L	$C_{23}H_{25}N_3O_2S$	S, N
9	$CH_3CHCONHCONHCH_3$	$CON(C_2H_5)_2$	67	95–97	B (acet)	3	E	$C_{14}H_{27}N_5O_3$	C, H, N
10	H	$CON(C_2H_5)_2\cdot HCl$	62	150–152	*j*	...	M	$C_9H_{20}ClN_3O$	Cl, N
11	$C_6H_5CH_2CH_2$	$CH_2CONHCONHCH_3$	43	99–102.5	A (alc)	*k*	K–D	$C_{14}H_{24}N_4O_2$	C, H, N
12	$(C_6H_5)_2CH$	$CH_2CONHCONHCH_3$	55	103.5–107	A (alc)	2	C	$C_{21}H_{26}N_4O_2$	C, H, N
13	CH_3	$CON(C_6H_5)_2$	85	94.5–96.5	B (ether)	*l*	E	$C_{18}H_{21}N_3O$	C, H, N
14	$C_6H_5CH_2$		62	256–257 dec	A (acet)	6	I	$C_{22}H_{26}Cl_2N_2\cdot 0.5H_2O$	C, H, Cl, N, H_2O
15	$C_6H_5CHC_6H_4Cl$-*o*	$CH_2CONHCONHCH_3$	30	108–110	A (alc)	2.5	E	$C_{21}H_{25}ClN_4O_2$	Cl, N
16	$CH_2CH_2N(C_2H_5)_2$	$CON(C_2H_5)_2\cdot 2H_2SO_4$	38	130–132	*m*	1	G–M	$C_{15}H_{36}N_4S_2O_8$	C, H, N, S
17	CH_3		57	39.5–40.5	B (ether)	*n*	E	$C_{12}H_{15}N_3O$	C, H, N
18	$C_6H_5CH_2$	$COC(Br)(CH_3)_2\cdot HBr$	39	188–190 dec	B (ether)	*o*	I	$C_{15}H_{22}Br_2N_2O$	Br, N
19	p-$ClC_6H_4CHC_6H_5$	$CH_2CONHCONHCH_3$	41	75–77	A (alc)	3	N	$C_{27}H_{35}ClN_4O_2$	Cl, N
20	$(C_6H_5)_2CH$	$CH_3CHCONHCONHCH_3$	34	107–109	B (acet)	12	E	$C_{22}H_{28}N_4O_2$	C, H, N

[a] Melting points are uncorrected and were taken with a Fisher-Johns apparatus. [b] These procedures are described in Experimental Section. The acet and alc refer to the acetone or alcohol solvents used in the reaction mixture. [c] Unless otherwise specified, the reactions were conducted at reflux temperatures. [d] C, ethyl acetate; D, petroleum ether (bp 30–80°); E, petroleum ether (bp 65–110°); F, absolute methyl alcohol; H, dioxane; I, ethyl alcohol; J, water; K, benzene; L, carbon tetrachloride; M, acetone; N, hexane. [e] Prepared from 10% molar excess of benzhydryl chloride plus N,N-diethylcarbamoylpiperazine; temperature kept under 90°. [f] The crude product precipitated out as a dihydrochloride salt when it was dissolved in 10% hydrochloric acid solution. [g] Prepared from equimolar amounts of 1-(diphenylmethyl)piperazine plus phenyl isothiocyanate in anhydrous ether at room temperature. [h] See Experimental Section for synthesis. [i] New compound. Made by mixing equimolar amounts of 2-chloropropionyl chloride plus methylurea. Product recrystallized from EtOH; yield 40%, mp 139–141°. *Anal.* Calcd for $C_5H_9ClN_2O_2$: N, 17.02; Cl, 21.54. Found: N, 17.11; Cl, 20.59. [j] Isolated from the same reaction mixture from which **9** was made. [k] 5 hr at 35° plus 2 hr at 50°. [l] Immediate reaction, but left standing overnight at room temperature. [m] See Experimental Section for preparation. [n] Dropwise addition of ethereal solution of 2-chlorobenzoxazole to methylpiperazine in ether at room temperature. [o] Reaction run in ice bath; 2-bromoisobutyryl bromide added dropwise to benzylpiperazine.

showed maximum stimulation at 256 (128% difference from control group), but was lethal at 300 mg/kg *po*. Compound **20** was a feeble psychomotor stimulant in mice at 300 mg/kg *po*. These compounds were also tested for such other physiological responses or possible uses as hexobarbital potentiation, anthelmintic, schistosomacidal, antibacterial, analgetic, antiinflammatory, and antihypertensive activities.

Experimental Section[4]

The chemicals were purchased either from Eastman or Aldrich Chemical Co. Microanalyses were run at the Sterling-Winthrop Research Institute. The compounds of types I and II were prepared by first making the 1-aralkylpiperazines or 1-diethylcarbamoylpiperazines and then alkylating them according to the procedures described below.

The following compounds were made by literature methods: α-chloroacetanilide,[5] 1-methyl-3-chloroacetylurea,[6] 1-(4-chlorodiphenylmethyl)piperazine,[7] 1-(2-chlorodiphenylmethyl)piperazine,[8] 1-phenethylpiperazine dihydrochloride,[9] 1-N,N-diethylcarbamoylpiperazine,[10] 1-benzylpiperazine dihydrochloride,[11] and 1-diphenylmethylpiperazine.[12]

1,4-Disubstituted Piperazines (Table I). Procedure A.—The stirred reaction mixture, which contained the alkyl halide in 10% molar excess to the monoalkylpiperazine or its hydrochloride, plus H_2O, Me_2CO, or EtOH, and sufficient $NaHCO_3$, was heated in the period of time indicated in Table I. The solvent was then removed by reduced pressure distillation, and the residue was dissolved in dilute HCl, filtered and made alkaline (NaOH). The products were collected and recrystallized from the solvents shown in Table I.

Procedure B.—Two parts of the appropriate monosubstituted piperazine was treated with one part of either the appropriate alkyl chloride or acid halide in the indicated solvent shown in the procedure column of the table. When the reaction was ended,

(4) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for these elements or functions were within ±0.4% of the theoretical values.

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the solvent was removed under reduced pressure, and the products were recrystallized from the listed solvents.

1-Diphenylmethyl-4-sulfanilylpiperazine.—A mixture of 8.6 g (0.037 mole) of *p*-acetaminobenzenesulfonyl chloride, 10.7 g (0.037 mole) of 1-(diphenylmethyl)piperazine hydrochloride, 7.5 g (0.09 mole) of $NaHCO_3$, 250 ml of ether, 30 ml of $CHCl_3$, plus 80 ml of H_2O was vigorously agitated and refluxed for 1 hr. The mixture was chilled, and the precipitate was collected and hydrolyzed without further purification with 50 ml of concentrated HCl, 150 ml of H_2O, and 100 ml of EtOH by refluxing for 45 min. After chilling, a brownish precipitate was discarded. The filtrate, made alkaline and distilled under reduced pressure, yielded a light brown solid which was partially purified by dissolving it with heat in 250 ml of dilute HCl containing charcoal. The chilled filtrate, made alkaline, yielded a white precipitate. Table I gives additional data.

N,N-Diethyl-1-(2-N,N-diethylaminoethyl)-4-piperazinecarboxamide Sulfate.—The base corresponding to 7.0 g (0.041 mole) of 2-chlorotriethylamine hydrochloride was obtained by dissolving the latter in a minimum amount of H_2O, adding concentrated NaOH, extracting the solution several times with ether, and thoroughly drying the latter. To this filtered solution was added 13.8 g (0.074 mole) of N,N-diethylcarbamoylpiperazine and the mixture was heated on a water bath to remove the ether. The residue, dissolved in toluene, was then refluxed for 1 hr. The hydrochloride of N,N-diethylcarbamoylpiperazine (**10**) appeared on chilling. The residue obtained after removing the toluene under reduced pressure was dissolved in 100 ml of dry acetone and, while stirring, a chilled solution of H_2SO_4 in Me_2CO was added dropwise. The gummy product was subjected to preliminary purification by washing (Me_2CO, dry Et_2O). Table I gives additional information.

A New Class of Analgetic–Antiinflammatory Agents. 2-Substituted 4,5-Diphenyloxazoles

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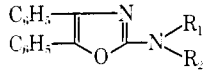
Recently, a number of five-membered heterocyclic amines, including oxadiazole,[2] indazole,[3] isoxazole,[4] and triazole[5] ring systems, have been shown to possess antiinflammatory and analgetic properties. We now wish to report the synthesis and some preliminary pharmacological results of a new series of substituted 2-aminooxazoles of general formula **1**, some of which show interesting analgetic and antiinflammatory properties associated with a low acute and chronic toxicity.



1

Chemistry.—The new aminooxazoles are listed in Table I, together with their analytical and physical data. All the compounds have been prepared in good yields by a conventional method, namely the reaction between the known 2-chloro-4,5-diphenyloxazole and the appropriate amine or amino alcohol; compound **7** has been synthetized also through the cyclization of the N-desyl-N-diethylurea, easily obtained by treating desyl bromide with N,N-diethylurea.

Pharmacological Results.—Some of the results have been summarized in Table I. Most of the new oxazole amines are characterized by a very low toxicity. Secondary amines are practically devoid of any antiinflammatory and analgetic activity, while most of the tertiary amines and amino alcohols possess such activities to a degree, which competes favorably with that of equal doses of phenylbutazone and aminopyrine, respectively. A noticeable exception is represented by the piperidine derivative **9**, which shows only a weak antiinflammatory activity and is practically devoid of analgetic properties.

Among tertiary amines maximum activity has been found with the pyrrolidine derivative (**8**), while in the amino alcohol series the diethanolamine (**18**) and the diisopropanolamine (**19**) derivatives, respectively, appear to be the most active compounds. It is interesting to note that among the diamino derivatives (**20**–**27**) some still retain the antiinflammatory activity, which is characteristic of the above tertiary amines, while they are all devoid of any analgetic properties.

The most interesting compound of the series appeared to be the diethanolamine derivative **18**, which has been selected for a more extensive pharmacological and toxicological evaluation. Its antiinflammatory activity was confirmed by the results obtained in the inhibition of edema induced by dextran, formalin, and serotonin; in the first test, 400 mg/kg *po* of **18** proved to be equipotent with an equal dose of aminopyrine, while in the two other tests 90 mg/kg *po* showed the same activity of an equal dose of phenylbutazone.

In addition, in the range between 30–90 mg/kg *po* **18** was equally active as phenylbutazone in inhibiting the cotton pellet induced granuloma. In the range between 300–400 mg/kg *po*, in the Randall and Selitto[6] and in the tail pinching tests,[7] the analgetic activity of **18** practically equalled the response obtained with the same dose of aminopyrine, while in the phenylquinone writhing test[8] **18** appeared to be less active than aminopyrine itself. In view of its interesting pharmacological activities, and low acute and chronic toxicity, **18** has been selected for clinical trial.

None of the compounds listed in Table I showed antipyretic activity.

Experimental Section

All melting points were taken on a W. Büchi melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values.

Synthesis. General Method for the 2-Amino-4,5-diphenyloxazoles.—The reactions between 2-chloro-4,5-diphenyloxazoles[9] and the various amines were carried out in boiling C_6H_6 using a 3-mole excess of the basic compound. The reactions with low-boiling amines were carried out in a sealed tube; in the case of amino alcohols, EtOH was used as the solvent. The reaction time was usually 4–6 hr. The final reaction mixture was treated

(1) Institute of Industrial Chemistry, University of Milan.

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