Synthesis of Some *N,N'*-Disubstituted Piperazines as Potential Analgesics

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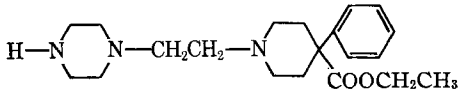
The synthesis and pharmacological screening of some *N,N'*-disubstituted piperazinonorpethidines is described. Certain members were prepared by *N*-alkylating norpethidine, while other analogs were made by condensing an appropriate *N*-monosubstituted piperazine with *N*-(2-chloroethyl)-norpethidine. Two compounds possessed significant analgesic activity although of a lower order than pethidine.

RECENT INVESTIGATIONS have demonstrated that certain *N,N'*-disubstituted piperazines possessed antihypertensive, adrenolytic, and anti-inflammatory properties (1). Some bicyclic structures containing a piperazine moiety have been shown to have analgesic activity (2). It previously had been reported that the *N*-piperazinoethyl analog of norpethidine (I) had ex-



I

hibited no demonstrable analgesic activity when tested in doses of at least 50 mg./Kg. in rats. However, hetero atoms in the four position of a six membered ring analog do not necessarily lead to lowered activity, for *N*-morpholinoethylnorpethidine and *N*-1,4-thiazinoethylnorpethidine were found to be more potent than pethidine (3).

This communication deals with the synthesis of certain *N,N'*-disubstituted piperazines in an attempt to prepare suitable analgesics. The rationale for introducing some selected groups to form some of the desired analogs was drawn from the area of the phenothiazine tranquilizers. The substitution of β-acetoxyethyl and β-hydroxyethyl moieties on one nitrogen of the piperazino group in the 2-chloro-10-piperazinopropylenephenothiazines gave drugs possessing both ataractic and antiemetic properties. The incorporation of these substituents into the piperazinonorpethidines was carried out in order to determine their contributions to analgesic and other activities.

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DISCUSSION

Ethylene oxide was distilled into a solution of *N*-benzylpiperazine in methanol to yield 1-(2-hydroxyethyl)-4-benzylpiperazine, which has been reported by Baltzly (4). The synthesis of 1-(2-chloroethyl) - 4 - benzylpiperazine dihydrochloride (II) was completed by refluxing the substituted alcohol with thionyl chloride. Amination with norpethidine in dimethylformamide afforded the wanted product (XI) which was characterized as the trimaleate. All of the 1-substituted norpethidines were isolated as their trimaleates.

The preparation of 1-(3-hydroxy-*n*-propyl)-4-methylpiperazine was accomplished by following the procedure of McElvain and Bannister (5), *i.e.*, monoalkylation of piperazine with trimethylene chlorohydrin, followed by reductive formylation. Treatment of this product with 48% HBr gave the desired alkyl halide, 1-(3-bromo-*n*-propyl)-4-methylpiperazine (III). Condensing this product with norpethidine yielded *N*-(4-methyl-1-*n*-propylenepiperazino)-norpethidine (XII).

Alkylation of norpethidine with 1-(2-chloroethyl)-4-methylpiperazine[1] in dimethylsulfoxide at 100° for 18 hr. yielded *N*-(4-methyl-1-ethylenepiperazino)-norpethidine (XIII).

Some of the desired compounds were prepared *via* the condensation of β-chloroethylnorpethidine with an *N*-monosubstituted piperazine. A modification of the procedure of Anderson *et al.* (6) gave the desired β-haloamine. One of the monosubstituted piperazine intermediates, 1-(2-hydroxyethyl)-piperazine, was prepared according to the procedure of McElvain and Bannister (5), *i.e.*, by reacting piperazine with ethylene oxide.

A second *N*-substituted piperazine intermediate, 1-(2-ethoxyethyl)-piperazine, was synthesized in two steps as follows: *N*-benzylpiperazine was refluxed in benzene with an equivalent amount of β-bromoethyl ethyl ether to give 1-(2-ethoxyethyl)-4-benzylpiperazine (IV). It was obtained as an oil by fractional distillation and was analyzed as the dihydrochloride (V). Catalytic hydrogenation debenzylated the substituted piperazine yielding the dihydrochloride of 1-(2-ethoxyethyl)-piperazine (VI).

The synthesis of 1-(2-acetoxyethyl)-piperazine (IX) was carried out in a manner similar to that of

[1] Purchased as the dihydrochloride from Aldrich Chemical Co., Milwaukee, Wis.

TABLE I—*N,N'*-DISUBSTITUTED PIPERAZINES AND THEIR SALTS

Compd.	R	R'	B.p., or M.p., °C.	Salt	Formula	Anal., % Calcd.	Found
II	Benzyl	CH_2CH_2Cl	214–216	.2 HCl	$C_{13}H_{21}Cl_3N_2$	C, 51.07	51.29
						H, 6.92	6.94
III	CH_3	$CH_2CH_2CH_2Br$	253–354 dec.	.2 HBr	$C_8H_{19}Br_3N_2$	C, 25.09	25.19
						H, 5.00	5.06
IV	Benzyl	$CH_2CH_2OCH_2CH_3$	145–146 at 2.5 mm.				
V	Benzyl	$CH_2CH_2OCH_2CH_3$	234–236	.2 HCl	$C_{15}H_{26}Cl_2N_2O$	C, 56.07	56.35
						H, 8.16	8.01
VI	H	$CH_2CH_2OCH_2CH_3$	151–153	.2 HCl	$C_8H_{20}Cl_2N_2O$	C, 55.35	55.55
						H, 6.42	6.54
VII	Benzyl	$CH_2CH_2OOCCH_3$	144–147 at 0.7 mm.				
VIII	Benzyl	$CH_2CH_2OOCCH_3$	196–198	.2 $C_4H_4O_4$	$C_{23}H_{30}N_2O_{10}$	C, 55.86	56.14
						H, 6.12	6.28
IX	H	$CH_2CH_2OOCCH_3$	81–84 at 0.8 mm.				
X	H	$CH_2CH_2OOCCH_3$	136–139	.2 $C_4H_4O_4$	$C_{16}H_{24}N_2O_{10}$	C, 47.52	47.39
						H, 5.98	6.27

the ethoxyethyl analog with the exception that debenzylation by catalytic hydrogenation was done in the absence of any aqueous acid in order to prevent any possible hydrolysis of the ester.

β-Chloroethylnorpethidine was condensed with 1-(2-hydroxyethyl)-piperazine, 1-(2-ethoxyethyl)-piperazine, and 1-(2-acetoxyethyl)-piperazine to yield, respectively, products XIV, XV, and XVI.

EXPERIMENTAL

All melting points were taken with a Thomas-Hoover Uni-Melt apparatus. The melting points and the boiling points are uncorrected. With the exception of products XI, XII, and XIII, which were microanalyzed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., all of the elemental analyses were performed by the Microanalytical Laboratory, School of Chemistry, University of Minnesota, Minneapolis, Minn.

1 - (2 - Chloroethyl) - 4 - benzylpiperazine Dihydrochloride (II)—A stirred ice-cold solution of 1-(2-hydroxyethyl)-4-benzylpiperazine (4.0 Gm., 0.018 mole) in 50 ml. of benzene was treated with dropwise addition of thionyl chloride (4.6 Gm., 0.038 mole). The mixture was refluxed for 30 min., cooled, 50 ml. of dry ether added, and the tan solid filtered. After recrystallization from methanol–ether, white crystals resulted. Yield: 2.6 Gm. (46.5%). (Table I.)

1 - (3 - Bromo - n - propyl) - 4 - methylpiperazine Dihydrobromide (III)—A solution of 1-(3-hydroxypropyl)-4-methylpiperazine (3.5 Gm., 0.022 mole) in 160 ml. of 48% aqueous hydrogen bromide was slowly distilled from an all-glass apparatus until 80 ml. of distillate had been collected. After refluxing overnight, the reaction mixture was concentrated to dryness under reduced pressure, and the oily precipitate was triturated in acetone, which rapidly transformed it into a fine brownish powder. The solid was recrystallized from 95% ethanol giving white crystals. Yield: 8.0 Gm. (95.0%). (Table I.)

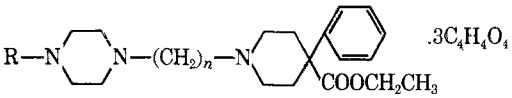
1 - (2 - Ethoxyethyl) - piperazine Dihydrochloride (VI)—1-(2-Ethoxyethyl)-4-benzylpiperazine (IV) (5.0 Gm., 0.02 mole) was dissolved in a mixture of 15 ml. of 10% aqueous HCl and 45 ml. of 95% ethanol and to it was added 1 Gm. of 10% palladium on charcoal. The mixture then was hydrogenated at 40 p.s.i. for 24 hr. The reaction mixture was filtered through a diatomaceous earth[2] filter bed, and the filtrate was concentrated to dryness *in vacuo*. The resulting white powder was crystallized from a mixture of absolute ethanol and ether. Yield: 2.25 Gm. (48.5%). (Table I.)

1 - (2 - Acetoxyethyl) - 4 - benzylpiperazine Dimaleate (VIII)—To 20 ml. of dimethylformamide was added *N*-benzylpiperazine (10 Gm., 0.057 mole) and β-chloroethyl acetate (7.0 Gm., 0.057 mole). Five grams of anhydrous sodium carbonate was added and the mixture was stirred at 100° for 16 hr. After cooling, 50 ml. of water was added, and the aqueous mixture was extracted three times with ether. The ethereal extracts were dried over anhydrous sodium sulfate, the solvent removed on a rotating evaporator, and the residue fractionally distilled. Yield: 10.0 Gm. (67.5%) (VII). (Table I.) The dimaleate salt was prepared by dissolving the product (0.5 Gm., 0.0019 mole) in 5 ml. of absolute ethanol and adding it to a solution of maleic acid (0.44 Gm., 0.0038 mole) in 5 ml. of absolute ethanol. The white crystals that formed on standing were recrystallized from 85% ethanol. Yield: 0.5 Gm. (53%). (Table I.)

1 - (2 - Acetoxyethyl) - piperazine Dimaleate (X)—1 - (2 - Acetoxyethyl) - 4 - benzylpiperazine (VII) (7.0 Gm., 0.019 mole) was dissolved in 50 ml. of absolute ethanol and to it was added 1 Gm. of 10% palladium on charcoal. The mixture was hydrogenated in a Parr hydrogenating apparatus at 40 p.s.i. for 24 hr. The reaction mixture was filtered through a diatomaceous earth filter bed, and the ethanol removed on a rotating evaporator. The residual oil was fractionally distilled under reduced pressure. Yield: 3.0 Gm., (65.2%) (IX). (Table I.) A portion of the oil (0.5 Gm., 0.0029 mole) was dissolved in 5 ml. of absolute ethanol and added to a solution of maleic acid (0.68 Gm., 0.006 mole) in 5 ml. of absolute ethanol. The white crystals that resulted upon cooling were recrystallized from absolute ethanol–ether. (Table I.)

[2] Marketed as Celite by Johns Manville, New York, N. Y.

TABLE II—TRIMALEATE SALTS OF *N*-SUBSTITUTED PIPERAZINONORPETHIDINES



Compd.	R	*n*	M.p., °C.	Formula	Anal., % Calcd.	Found	ED_{50}, mg./Kg.[a]
XI	Benzyl	2	205–207	$C_{39}H_{49}N_3O_{14}$	C, 59.76	59.47	34.8 ± 4.1
					H, 6.30	6.21	
XII	CH_3	3	198–200	$C_{34}H_{47}N_3O_{14}$	C, 56.58	56.95	NA
					H, 6.56	6.52	
XIII	CH_3	2	195–197	$C_{33}H_{45}N_3O_{14}$	C, 56.10	55.69	14.5 ± 2.4
					H, 6.35	6.49	
					N, 5.94	5.95	
XIV	CH_2CH_2OH	2	192–195	$C_{34}H_{47}N_3O_{15}$	C, 55.35	55.55	NA
					H, 6.42	6.54	
					N, 5.70	5.98	
XV	$CH_2CH_2OCH_2CH_3$	2	187–189	$C_{36}H_{51}N_3O_{15}$	C, 56.46	56.75	NA
					H, 6.71	6.95	
					N, 5.49	5.45	
XVI	$CH_2CH_2OOCCH_3$	2	180–182	$C_{36}H_{49}N_3O_{16}$	C, 55.45	55.17	NA
					H, 6.33	6.63	

[a] Calculated as the free base; NA, no activity at 50 mg./Kg.

N - (4 - Methyl - 1 - n - propylenepiperazino)-norpethidine Trimaleate (XII)—Norpethidine[3] (0.5 Gm., 0.002 mole) was dissolved in 10 ml. of dimethylformamide and to it was added 1-(3-bromo-*n*-propyl)-4-methylpiperazine dihydrobromide (III) (0.83 Gm., 0.0022 mole) dissolved in 1 ml. of 20% aqueous sodium hydroxide. The mixture was dried over anhydrous sodium sulfate, anhydrous sodium carbonate (0.39 Gm., 0.003 mole) was added, and the mixture was stirred at 100° for 18 hr. After filtration, the solvent was removed *in vacuo*. The residue, dissolved in 10 ml. of absolute ethanol, was added to maleic acid (0.75 Gm., 0.006 mole) in 5 ml. of absolute ethanol. The white crystals which separated were recrystallized from 95% ethanol. Yield: 0.45 Gm. (31%). (Table II.)

N - [4 - (2 - Ethoxyethyl) - 1 - ethylenepiperazino] - norpethidine Trimaleate (XV)—*N* - (2-Chloroethyl)-norpethidine hydrochloride (0.5 Gm., 0.0015 mole) and 1-(2-ethoxyethyl)-piperazine dihydrochloride (VI) (0.35 Gm., 0.0015 mole) were dissolved in 3 ml. of water and the solution was basified with 5% aqueous sodium hydroxide. Dimethylformamide (10 ml.) was added along with anhydrous sodium carbonate (2.0 Gm.) and the mixture was stirred at 100° for 18 hr. After filtration of the solid, the filtrate was concentrated on a rotating evaporator to an oily residue. The oil was dissolved in 10 ml. of absolute ethanol and added to maleic acid (0.52 Gm., 0.0045 mole) dissolved in 5 ml. of absolute ethanol. The white solid was filtered and recrystallized from 85% ethanol. The yield of white microcrystals was 0.45 Gm. (39%). (Table II.)

[3] Prepared according to the procedure of Thorp, R., and Walton, E., *J. Chem. Soc.*, **1948**, 559.

BIOLOGICAL DATA

Preliminary screening for analgesic activity was carried out using a modification of the procedure described by Eddy and Leimbach (7). Mixed white mice were placed on a metal plate kept at 53° by floating it on top of a circulating hot water bath. Those animals whose reaction time increased to at least twice the mean reaction time for the control animals were assumed to show significant pain relief. The reaction time was the interval from the time the animal was placed on the plate to the time it licked its hind feet or attempted to jump off the container. The test was conducted 30 min. after the required dose was given subcutaneously. The test animals were kept on the plate for a maximal period of 60 sec. The ED_{50} levels were calculated according to the method of Miller and Tainter (8). Pethidine, according to this method, had an ED_{50} of 9 mg./Kg.

REFERENCES

(1) Mull, R., Tannenbaum, C., Dapero, M., Bernier, M., Yost, W., and de Stevens, C., *J. Med. Chem.*, **8**, 332(1965).
(2) Cignarella, G., Occelli, E., and Testa, E., *ibid.*, **8**, 326 (1965).
(3) Millar, R., and Stephenson, R., *Brit. J. Pharmacol.*, **11**, 27(1956).
(4) Baltzly, R., Buck, J. S., Lorz, E., and Schön, W., *J. Am. Chem. Soc.*, **66**, 263(1944).
(5) McElvain, S., and Bannister, L., *ibid.*, **76**, 1126(1954).
(6) Anderson, R., Frearson, P., and Stearn, E., *J. Chem. Soc.*, **1956**, 4088.
(7) Eddy, N., and Leimbach, D., *J. Pharmacol. Exptl. Therap.*, **107**, 385(1953).
(8) Miller, L., and Tainter, M., *Proc. Soc. Exptl. Biol. Med.*, **57**, 261(1944).