[CONTRIBUTION FROM MCNEIL LABORATORIES, INC.]

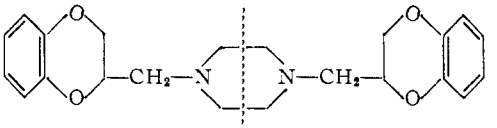
Adrenergic Blocking Agents. II. Piperazines[1]

BY ANSEL P. SWAIN AND SARA K. NAEGELE

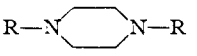
RECEIVED MAY 3, 1954

The synthesis of symmetrical 1,4-substituted piperazines in which the substituents are 1,4-benzodioxan-2-ylmethyl, 2-phenoxyethyl, 3-phenoxypropyl, tetrahydropyran-2-ylmethyl, tetrahydrofurfuryl or 2-ethoxyethyl groups is reported. In addition, the synthesis of several unsymmetrical 1,4-substituted piperazines in which the substituents are carbethoxy, phenyl, 2-phenoxyethyl or 1,4-benzodioxan-2-ylmethyl groups in various combinations is described, as well as that of the 1,4-bis- and 1-(1,4-benzodioxan-2-ylmethyl) derivatives of *trans*-2,5-dimethylpiperazine. Some of these compounds are potent, long-acting sympatholytic and adrenolytic agents by both oral and parenteral routes of administration. Clinical evaluation is in progress.

The synthesis of N,N'-disubstituted ethylenediamines possessing adrenergic blocking activity was described in paper I.[2] This paper reports the synthesis of similarly substituted piperazines (I–IV).

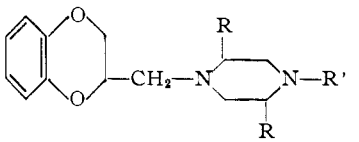


I 1,4-Bis-(1,4-benzodioxan-2-ylmethyl)-piperazine



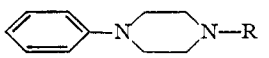
II

R = tetrahydropyran-2-ylmethyl, tetrahydrofurfuryl, 2-phenoxyethyl, 3-phenoxypropyl or 2-ethoxyethyl



III

R = H, R' = H, carbethoxy, phenyl or 2-phenoxyethyl
R = CH_3, R' = H or 1,4-benzodioxan-2-ylmethyl

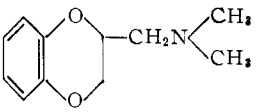


IV

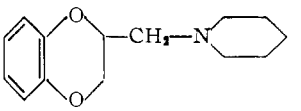
R = 2-phenoxyethyl or 1,4-benzodioxan-2-ylmethyl

The compound of formula I can be thought of as being composed of identical halves[3] derived from a known adrenergic blocking agent (V).[4] The related piperoxan[4] (933F, VI) is a potent adrenolytic substance when administered parenterally but has little sympatholytic activity and is not orally active. 1-Phenylpiperazine (IV, R = H) and its 4-methyl derivative (IV, R = CH_3) are moderately active adrenolytic agents, but this activity coexists with other pharmacological actions which tend to raise instead of lower the blood pressure.[5]

Symmetrical piperazines were obtained by reaction of two molecular equivalents of a haloalkyl compound with one of piperazine in refluxing alkaline solution. Reaction of 1-phenylpiperazine with



V



VI

haloalkyl compounds led to the corresponding 4-substituted phenylpiperazines. To obtain 1-(1,4-benzodioxan-2-ylmethyl)-4-(2-phenoxyethyl)-piperazine (III, R = H, R' = $C_6H_5OCH_2CH_2$), 1-carbethoxypiperazine was alkylated with 2-chloromethyl-1,4-benzodioxan, the resulting carbethoxy derivative was hydrolyzed, and the hydrolysis product (III, R = R' = H) was treated with 2-phenoxyethyl bromide. Pertinent data appear in the tables.

Separation of the stereoisomers of 1,4-bis-(1,4-benzodioxan-2-ylmethyl)-piperazine (I) was accomplished by fractional crystallization of the bis-(*d*-camphorsulfonates).

The results of pharmacological studies of some of the new compounds have been reported.[6-8] Representative data are included in Table I. 1,4-Bis-(1,4-benzodioxan-2-ylmethyl)-piperazine (I, McN-181, Dibozane[9]) produces typical sympatholytic and adrenolytic responses in dogs at 0.2–0.3 mg./kg. and 0.05–0.1 mg./kg., respectively. Comparable effects after oral administration are obtained at 0.6 and 0.3 mg./kg.

The effect of single intravenous and oral doses of I upon the blood pressure of human hypertensive subjects has been studied.[10] Further animal and clinical studies using the separated *meso*, *d* and *l* isomers as well as the mixture of isomers obtained synthetically are in progress.

Experimental[11]

Preparation of Symmetrical 1,4-Bis-substituted Piperazines. General Procedures.—The reaction of phenoxyalkyl bromides with piperazine proceeded smoothly in an alkaline aqueous medium. No difficulty was experienced in obtaining the tetrahydropyran-2-ylmethyl, tetrahydrofurfuryl and ethoxyethyl derivatives by reaction of the halides with piperazine, although yields were low with 2-chloromethyltetrahydropyran.[12] The reaction of piperazines with 2-chloromethylbenzodioxan required long refluxing with 40% aqueous sodium hydroxide.

(1) Presented before the Division of Medicinal Chemistry at the 124th Meeting of the American Chemical Society, Chicago, Ill., September 9, 1953.

(2) A. P. Swain and S. K. Naegele, THIS JOURNAL, **76**, 5089 (1954).

(3) Dotted line in formula I. Compare the work of D. E. Adelson, L. G. MacDowell and C. B. Pollard, *ibid.*, **57**, 1988 (1935), who synthesized a piperazine derivative which resembles a doubled procaine molecule.

(4) D. Bovet and A. Simon, *Arch. intern. pharmacodynamie*, **55**, 15 (1937).

(5) D. Bovet and F. Bovet-Nitti, "Médicaments du Système Nerveux Végétatif," S. Karger, Basel, 1948, p. 247.

(6) J. F. O'Leary, *Federation Proc.*, **12**, 355 (1953).

(7) D. F. Marsh and J. F. O'Leary, *ibid.*, **12**, 348 (1953).

(8) J. F. O'Leary, *Am. J. Med. Sci.*, **226**, 111 (1953).

(9) Trade-mark.

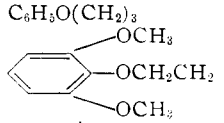
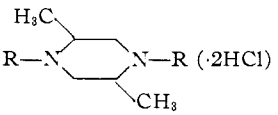
(10) W. H. Rosenblatt, T. A. Haymond, S. Bellet and G. B. Koelle, *Am. J. Med. Sci.*, **227**, 179 (1954).

(11) Melting points are uncorrected.

(12) B.p. 39–40° (1.5 mm.). Prepared from commercial 2-hydroxymethyltetrahydropyran and thionyl chloride.

TABLE I

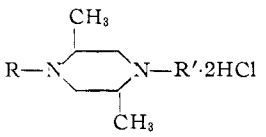
SYMMETRICAL PIPERAZINES AND PIPERAZINE DIHYDROCHLORIDES R—N⟨⟩N—R (·2HCl)

McN-	R	*S*, %[a]	*A*, %[b]	*L*, %[c]	M.p., °C.[d]	Formula	Nitrogen, %[e] Calcd.	Found
181	$C_9H_9O_2$[f]	100	100	100	164–165	$C_{22}H_{26}N_2O_4$	7.3	7.2
	$C_9H_9O_2$[f]	..	..	..	287 dec.	$C_{22}H_{26}N_2O_4\cdot 2HCl$	6.2	6.1
265	$C_6H_5OCH_2CH_2$	50	100	175	88–89	$C_{20}H_{26}N_2O_2$	8.6	8.5
	$C_6H_5OCH_2CH_2$	..	..	..	255	$C_{20}H_{26}N_2O_2\cdot 2HCl$	7.0	6.9
266	$C_6H_5O(CH_2)_3$	15	5	500	88–89	$C_{22}H_{30}N_2O_2$	7.9	7.9
	$C_6H_5O(CH_2)_3$	..	..	..	251	$C_{22}H_{30}N_2O_2\cdot 2HCl$	6.5	6.5
420		5	5	325	200–201	$C_{24}H_{34}N_2O_6\cdot 2HCl$	5.4	5.4
291	$C_8H_{11}O$[h]	..[g]	..	60	271–273 dec.	$C_{16}H_{30}N_2O_2\cdot 2HCl$	7.9	7.9
303	C_5H_9O[i]	..[g]	..	50	311 dec.	$C_{14}H_{26}N_2O_2\cdot 2HCl$	8.6	8.7
302	$C_2H_5OCH_2CH_2$	..[g]	..	25	207	$C_{12}H_{26}N_2O_2\cdot 2HCl$	9.2	9.1
X-64	$C_6H_5CH_2$	2	5	200	92–93[j]	$C_{18}H_{22}N_2$	..	..
								
269	$C_9H_9O_2$[f]	1	2	700	128–129	$C_{24}H_{30}N_2O_4$	6.8	6.7
	$C_9H_9O_2$[f]	..	..	..	261 dec.	$C_{24}H_{30}N_2O_4\cdot 2HCl$	5.8	5.8

[a] Relative sympatholytic activity, McN-181 = 100. The i.v. dose of McN-181 required to prevent 50% of the pressor rise resulting from bilateral carotid occlusion in the α-chloralose-anesthetized dog is 0.2–0.3 mg./kg. [b] Relative adrenolytic activity, McN-181 = 100. The i.v. dose required to prevent 50% of the pressor rise (30–60 mm.) produced by small doses of epinephrine is 0.05–0.1 mg./kg. of McN-181. [c] Relative toxicity (LD_{50}), McN-181 = 100. LD_{50} for McN-181 is 260 mg./kg. following intraperitoneal injection in white mice. [d] Uncorrected. [e] Semimicro Kjeldahl. [f] 1,4-Benzodioxan-2-ylmethyl. M.p. is that of a mixture of isomers. [g] Less than 1% as active as McN-181 in both *S* and *A*. [h] Tetrahydropyran-2-ylmethyl. [i] Tetrahydrofurfuryl. [j] Reported m.p. 92°, S. Gabriel and R. Stelzner, *Ber.*, **29**, 2384 (1896).

TABLE II

UNSYMMETRICAL PIPERAZINES R—N⟨⟩N—R′

McN-	R	R′	*S*, %[a]	*A*, %[b]	*L*, %[c]	M.p., °C.[d]	Formula	Nitrogen, %[e] Calcd.	Found
179	$C_9H_9O_2$[f]	H	3	1	500	197[g]	$C_{13}H_{18}N_2O_2\cdot HCl$	10.3	10.3
212	$C_9H_9O_2$[f]	$COOC_2H_5$	10	6	200	235 dec.	$C_{16}H_{22}N_2O_4\cdot HCl$	8.2	8.2
261	$C_9H_9O_2$[f]	C_6H_5	13	13	40	81.5–82	$C_{19}H_{22}N_2O_2$	9.0	8.8
324	$C_9H_9O_2$[f]	$PhOCH_2CH_2$	10	50	175	235–239 dec.	$C_{21}H_{26}N_2O_3\cdot 2HCl$	6.6	6.5
325	C_6H_5	$PhOCH_2CH_2$	10	15	100	80–81	$C_{18}H_{22}N_2O\cdot H_2O$	9.3	9.2
X-49	C_6H_5	H	10	10	500	...[h]	$C_{10}H_{14}N_2$	17.3	17.2
									
264	$C_9H_9O_2$[f]	H	3	0	500	271	$C_{15}H_{22}N_2O_2\cdot 2HCl$	8.4	8.2

[a] Relative sympatholytic activity, McN-181 (Table I) = 100. [b] Relative adrenolytic activity, McN-181 = 100. [c] Relative toxicity (LD_{50}), McN-181 = 100. [d] Uncorrected. [e] Semimicro Kjeldahl. [f] 1,4-Benzodioxan-2-ylmethyl. [g] Reported m.p. 180°.[15] [h] B.p. 111–114° (2 mm.).[14]

2-(2,6-Dimethoxyphenoxy)-ethyl Bromide. (McN-421).—A procedure like that of Leonard and Wildman[13] was used. To a mixture of 30.8 g. (0.2 mole) of 2,6-dimethoxyphenol and 160 g. (74 ml., 0.85 mole) of ethylene bromide was added, while stirring and refluxing, a solution of 12 g. of potassium hydroxide (85% reagent) in 140 ml. of methanol over about an hour. The hot mixture was filtered through a cotton plug to remove precipitated potassium bromide, and the combined filtrate and washings (50 ml. of methanol and 20 ml. of ethylene bromide) were refluxed for 9 hours. The cooled mixture was treated with a little water, and the organic layer was washed with a 5% aqueous sodium hydroxide solution and then with water. After drying over anhydrous sodium sulfate, the solvents were removed, and the residue was fractionated with a 3-foot, ½ inch outside diameter column packed with glass helices; yield 29 g. (53%), b.p. 132–133° (1 mm.). A portion (5.3 g.) was crystallized twice from aqueous methanol to give 4.6 g. of m.p. 30–32°.

Anal. Calcd. for $C_{10}H_{13}BrO_3$: C, 45.99; H, 5.02; Br, 30.61. Found: C, 46.39; H, 4.89; Br, 30.92.

1,4-Bis-[2-(2,6-dimethoxyphenoxy)-ethyl]-piperazine Dihydrochloride. (McN-420).—A mixture of 13.8 g. (0.053 mole) of 2-(2,6-dimethoxyphenoxy)-ethyl bromide, 4.8 g. (0.025 mole) of piperazine hexahydrate, 2.12 g. (0.053 mole) of sodium hydroxide and 6 ml. of water was refluxed for 16 hours. The cooled mixture was treated with 75 ml. of water, and the aqueous layer was separated by decanting. After three more water washes, the residual gummy material was taken up in ether, and the ether solution was

(13) N. J. Leonard and W. C. Wildman, THIS JOURNAL, **71**, 3089 (1949).

treated with dilute aqueous hydrochloric acid (20 ml.). The precipitate which formed was separated by filtration; weight 8.5 g. dried (66%). Crystallization from a mixture of 200 ml. of methanol and 25 ml. of acetone gave 8 g., m.p. 200–201°.

Anal. Calcd. for $C_{24}H_{34}N_2O_6 \cdot 2HCl$: N, 5.4. Found: N, 5.4.

1,4-Bis-(1,4-benzodioxan-2-ylmethyl)-piperazine. (McN-181).—A mixture of 38.8 g. (0.2 mole) of piperazine hexahydrate, 81.4 g. (0.44 mole) of 2-chloromethylbenzodioxan and 16 g. (0.4 mole) of sodium hydroxide in 16 ml. of water was refluxed for 48 hours. The solid which separated on cooling was collected and crystallized from aqueous acetone; yield 45.2 g. (59%), m.p. 164–165°. This is the melting point of a mixture of the *dl* and *meso* forms.

Anal. Calcd. for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.3. Found: C, 69.03; H, 6.94; N, 7.2.

The three isomers of this compound were separated by forming the bis-(*d*-camphorsulfonates) in methanolic solution (1 mole of the salts per 2800 ml. of methanol). Upon allowing the hot solution to cool to room temperature, about half of the salt crystallized. The solid was separated by filtration and crystallized repeatedly from methanol to give a product with m.p. 259.5–260° and $[\alpha]^{26}D$ +28.5 ± 0.5° (*c* 2, dimethylformamide), unchanged by further crystallization. This is the salt of the *meso* base, m.p. 173–174°, $[\alpha]^{26}D$ 0.0 ± 0.5° (*c* 2, dioxane). When the filtrate from the salt of the *meso* compound was chilled in a refrigerator, another crop of crystals was obtained, and upon further crystallization from methanol yielded a salt with m.p. 240–241°, $[\alpha]^{26}D$ −8.2 ± 0.5° (*c* 2, dimethylformamide); the regenerated base had m.p. 156–157°, $[\alpha]^{26}D$ −36.3 ± 0.5° (*c* 1, dioxane). The mother liquor from this salt, upon evaporation to dryness and crystallization of the residue from a mixture of methanol and ether and finally from dimethylformamide, yielded a salt with m.p. 255–256°, $[\alpha]^{26}D$ +65.0 ± 0.5° (*c* 2, dimethylformamide), unchanged after several further crystallizations. Regeneration gave the *d*-base, m.p. 156–157°, $[\alpha]^{26}D$ +36.0 ± 0.5° (*c* 2, dioxane).

Preparation of Unsymmetrical Piperazines. General Procedures.—The preparation of 1-phenylpiperazine[14] and its reaction with haloalkyl compounds presented no difficulties. The preparation of 1-(1,4-benzodioxan-2-ylmethyl)-4-(2-phenoxyethyl)-piperazine was accomplished by reaction of 2-phenoxyethyl bromide with 1-(1,4-benzodioxan-2-ylmethyl)-piperazine (III, R = R′ = H). The latter compound has been obtained by direct reaction of piperazine with 2-chloromethyl-1,4-benzodioxan.[15] We obtained it in 10% yield when this reaction was carried out in refluxing methanol. Better yields resulted by the method illustrated, reaction of 2-chloromethylbenzodioxan with 1-carbethoxypiperazine and hydrolysis of the resulting product.

1-(1,4-Benzodioxan-2-ylmethyl)-4-carbethoxypiperazine Hydrochloride. (McN-212).—A mixture of 13.4 g. (0.085 mole) of 1-carbethoxypiperazine[16] and 7.8 g. (0.043 mole) of 2-chloromethyl-1,4-benzodioxan was heated at 100° for 32 hours. The mixture was cooled, treated with ether, and the tan solid which remained undissolved was removed by filtration. Addition of hydrogen chloride to the dried ether filtrate precipitated 13.8 g. (94%) of a solid, m.p. 233° dec. Crystallization from a mixture of methanol and ether raised the m.p. to 235°.

Anal. Calcd. for $C_{16}H_{22}N_2O_4 \cdot HCl$: N, 8.2; Cl, 10.4. Found: N, 8.2; Cl, 10.5.

1-(1,4-Benzodioxan-2-ylmethyl)-piperazine Hydrochloride. (McN-179).—A solution of 1-(1,4-benzodioxan-2-ylmethyl)-4-carbethoxypiperazine was prepared by dissolving 8.5 g. (0.025 mole) of the hydrochloride in 125 ml. of methanol and adding 1.4 g. (0.025 mole) of potassium hydroxide. The precipitate was removed by filtration, and the filtrate was treated with 11.2 g. (0.2 mole) of potassium hydroxide. The resulting solution was refluxed for 22 hours. Removal of the solvent, extraction of the residue with ether and addition of hydrogen chloride to the dried extract gave 5.4 g. (80%) of a hydrochloride. Crystallization from a mixture of acetone and ether gave 1.0 g., m.p. 197°.

Anal. Calcd. for $C_{13}H_{18}N_2O_2 \cdot HCl$: N, 10.3; Cl, 13.1. Found: N, 10.3; Cl, 13.4.

1-(1,4-Benzodioxan-2-ylmethyl)-4-(2-phenoxyethyl)-piperazine Dihydrochloride. (McN-324).—A mixture of 2.7 g. (0.01 mole) of 1-(1,4-benzodioxan-2-ylmethyl)-piperazine hydrochloride, 2 g. (0.01 mole) of 2-phenoxyethyl bromide, 2.1 g. (0.02 mole) of anhydrous sodium carbonate and 250 ml. of methanol was refluxed for 58 hours. The inorganic salts were removed by filtration. Addition of hydrogen chloride to the filtrate caused 2.4 g. (56%) of a white solid to separate. Crystallization from a mixture of methanol and ether gave 0.5 g., m.p. 235–239° dec.

Anal. Calcd. for $C_{21}H_{26}N_2O_3 \cdot 2HCl$: N, 6.6. Found: N, 6.5.

(14) C. B. Pollard and N. MacDowell, THIS JOURNAL, **56**, 2199 (1934).

(15) Mewburn, Ellis and Co., British Patent 420,078 (1934); (*Chem. Zentr.*, **106**, 2216 (1935)).

(16) T. S. Moore, M. Boyle and V. M. Thorn, *J. Chem. Soc.*, 39 (1929).

PHILADELPHIA, PENNA.

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGY AND VITAL ECONOMICS, THE UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE AND DENTISTRY]

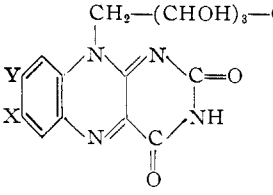
The Synthesis of 6-Chloro-7-methyl-9-(1′-D-ribityl)-isoalloxazine and 6-Methyl-7-chloro-9-(1′-D-ribityl)-isoalloxazine[1]

BY EDWARD E. HALEY AND JOHN P. LAMBOOY

RECEIVED APRIL 22, 1954

Two new isoalloxazines, 6-chloro-7-methyl-9-(1′-D-ribityl)-isoalloxazine and 6-methyl-7-chloro-9-(1′-D-ribityl)-isoalloxazine have been synthesized. Both are inhibitors of riboflavin in *Lactobacillus casei*.

With Kuhn's demonstration that the substitution of both methyl groups on the benzene nucleus of the riboflavin molecule by chlorine atoms results in a compound which antagonizes riboflavin in certain microörganisms,[2] it was of interest to us to study the effects of replacing each methyl group individually by a chlorine atom. 6-Chloro-7-methyl-9-(1′-D-ribityl)-isoalloxazine (I) and 6-methyl-7-chloro-9-(1′-D-ribityl)-isoalloxazine (II) were synthesized and found to be effective as inhibitors of riboflavin in *Lactobacillus casei*.



I, X = Cl, Y = CH_3
II, X = CH_3, Y = Cl
III, X = Cl, Y = Cl

Weygand, *et al.*,[3] in a study of the specificity of

(1) This work was supported in part by Research Grant Number G 3326 C from the National Institute of Health, Public Health Service.

(2) R. Kuhn, F. Weygand and E. F. Möller, *Ber.*, **76**, 1044 (1943).

(3) F. Weygand, R. Löwenfeld and E. Möller, *Chem. Ber.*, **84**, 106 (1951).