Researches in the Series of 1,4-Benzodioxane. XXIV. Synthesis and Pharmacological Properties of Some 2-(1-Aminoethyl)-1,4-benzodioxanes

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The preparation and some pharmacological properties of sixteen 2-(1-aminoethyl)-1,4-benzodioxanes are described. The pharmacological data obtained for these amines have been compared with those of the corresponding 2-aminoethyl-1,4-benzodioxanes. This comparison showed that, in this series, branching of the side chain results in a lowering of activity.

A number of 2-aminomethyl-1,4-benzodioxane derivatives have been studied and shown to possess a variety of pharmacodynamic activities: sympatholytic and hypotensive,[1a-g] centrally depressing,[2a-c] stimulating,[2c] deconditioning,[3] myorelaxant,[3] monoamine oxidase inhibiting[4] and analgesic.[5] However, as yet no work has been undertaken to study the influence of the α-substitution of the side chain upon the pharmacodynamics of these molecules. In this paper we report the synthesis and some pharmacological data on a series of N-substituted 2-(1-aminoethyl)-1,4-benzodioxanes, which include branched homologs of some of the most potent sympatholytic agents of this series, namely, 2-diethylaminomethyl-1,4-benzodioxane (prosympal), 2-piperidinomethyl-1,4-benzodioxane (piperoxan) and N,N′-bis-2-(1,4-benzodioxan-2-yl-methyl)-piperazine (dibozane). The new products have the general formula I and are listed in Table I.

Chemistry.—The possibility of using a general scheme of synthesis involving the reaction of the various amines with 2-(1-chloroethyl)-

(1) (a) E. Fourneau and D. Bovet, *Arch. int. Pharmacodyn.*, **46**, 178 (1933); (b) D. Bovet and A. Simon, *Arch. int. Pharmacodyn.*, **55**, 15 (1937); (c) G. L. Gatti and D. Bovet, *Atti Accad. naz. Lincei*, **14**, 645 (1953); (d) J. F. O'Leary, *Fed. Proc.*, **12**, 355 (1953). (e) W. H. Rosenblatt, T. A. Haymond, S. Bellet, and G. B. Koelle, *Am. J. Med. Sc.*, **227**, 179 (1954); (f) B. L. Kramer, R. Van Horne, S. Bellet, and G. B. Koelle, *Am. J. Med. Sc.*, **228**, 614 (1954). (g) G. L. Gatti, J. Pecori Giraldi, R. Landi-Vittory, and M. Beguin, *Boll. Soc. ital. Biol. Sper.*, **35**, 1851 (1959).

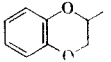
(2) (a) J. F. O'Leary, *Fed. Proc.*, **12**, 348 (1953); (b) A. P. Swain and S. K. Naegele, *J. Am. Chem. Soc.*, **76**, 5089 (1954); (c) J. Koo, *J. Org. Chem.*, **26**, 635 (1961).

(3) H. Klupp and I. Streller, *Arzneimittel-Forsch.*, **9**, 604 (1959).

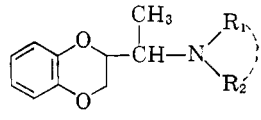
(4) A. Funke and A. Paulsen, *Gazz. chim. ital.*, **91**, 1268 (1961).

(5) F. Bovet-Nitti, O. Orsinger, R. Landi-Vittory, and D. Bovet, *Compt. rend.*, **252**, 614 (1961).

TABLE I

No.	R = 	Formula	B.p., °C.	B.p., Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Pharmacological data Mice LD_{50} mg./kg. i.p.	Blood pressure (chloralosed dog) Action hypotension −, hypertension +	Adrenolytic dose (mg./kg., i.v.)
1	$RCH(CH_3)NH_2$	$C_{10}H_{13}NO_2$	71	0.04	67.02	66.78	7.31	7.11	7.82	7.62	80	−	>10
2	$RCH(CH_3)NHCH_3$	$C_{11}H_{15}NO_2$	67	0.03	68.37	68.47	7.82	7.60	7.25	7.33	75	−	>10
3	$RCH(CH_3)NHC_2H_5$	$C_{12}H_{17}NO_2$	73	0.03	69.54	69.67	8.27	8.06	6.76	6.53	40	+, −	5
4	$RCH(CH_3)NHC_3H_7$	$C_{13}H_{19}NO_2$	82	0.08	70.55	70.62	8.65	8.87	6.33	6.34	75	−	10
5	$RCH(CH_3)NHCH(CH_3)_2$	$C_{13}H_{19}NO_2$	65	0.02	70.55	70.37	8.65	8.52	6.33	6.35	100	−	5
6	$RCH(CH_3)NHCH_2C(CH_3)_3$	$C_{15}H_{23}NO_2$	94	0.04	72.25	72.30	9.30	9.43	5.62	5.26	125	−, +	5
7	$RCH(CH_3)NH(CH_2)_2$-$NHCH(CH_3)R$	$C_{22}H_{28}N_2O_4$	186	0.01	68.72	68.76	7.34	7.31	7.29	7.51	150	−	>10
8	$RCH(CH_3)N(CH_3)_2$	$C_{12}H_{17}NO_2$	77	0.07	69.54	69.20	8.27	8.33	6.76	6.72	90	+[a]	>10
9	$RCH(CH_3)N(CH_3)C_2H_5$	$C_{13}H_{19}NO_2$	76	0.02	70.55	70.45	8.65	8.71	6.33	6.57	150	−	5
10	$RCH(CH_3)N(C_2H_5)_2$	$C_{14}H_{21}NO_2$	80	0.07	71.45	71.74	9.00	9.23	5.95	5.75	90	−	10
11	$RCH(CH_3)N$ 	$C_{14}H_{19}NO_2$	106	0.06	72.07	72.02	8.21	8.37	6.00	5.77	120	−	10
12	$RCH(CH_3)N$ 	$C_{15}H_{21}NO_2$	105	0.01	72.84	72.61	8.58	8.46	5.66	5.86	120	−	5
13	$RCH(CH_3)N$ 	$C_{14}H_{19}NO_3$	100	0.01	67.44	67.29	7.68	7.76	5.62	5.79	300	−	2
14	$RCH(CH_3)N$  NCH_3	$C_{15}H_{22}N_2O_2$	144	0.03	68.67	68.79	8.45	8.47	10.68	10.47	75	−	>10
15	$RCH(CH_3)N$  NC_2H_5	$C_{16}H_{24}N_2O_2$	123	0.03	69.53	69.59	8.75	8.47	10.14	10.11	35	−	>10
16	$RCH(CH_3)N$  $NCH(CH_3)R$	$C_{24}H_{30}N_2O_4$	180	0.02	70.22	70.25	7.37	7.44	6.82	6.85	150	−	5

[a] Nicotinic hypertension.



I

1,4-benzodioxane was first considered. However, the latter compound could not be obtained by treating 2-(1-hydroxyethyl)-1,4-benzodioxane[6] with the usual chlorinating agents. In this reaction actually elimination of water occurs instead of chlorine substitution, the reaction product being an unstable non-halogenated material. The simplest member of this series, the 2-(1-aminoethyl)-1,4-benzodioxane (1) (Table I), was therefore used as starting material. The different methods used in introducing the various nitrogen substituents on this primary amine are briefly outlined here.

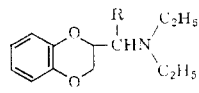
The synthesis of the N-monomethyl derivative (2) was first tried by the well known method involving tosylation of the primary amine, methylation of the corresponding sulfonamide and finally removal of the tosyl group. However, surprisingly, the easily obtained 2-(1-tosylaminoethyl)-1,4-benzodioxane could not be methylated with either dimethyl sulfate, or diazomethane or methyl iodide in the presence of sodium ethoxide. Compound (2) was obtained in very good yield by simply treating the amine (1) with methyl bromide at higher temperature. The fact that in this reaction no dimethylamino derivative was formed can hardly be explained in terms of steric hindrance since, under the same experimental conditions, ethyl bromide did not react at all, while isopropyl bromide gave the N-monoisopropylamine (5) in 85% yield.

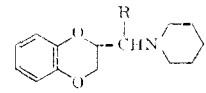
The N-monoethylamine (3) was synthesized by lithium aluminum hydride reduction of 2-(1-acetamidoethyl)-1,4-benzodioxane, which had been prepared easily by treating amine (1) with acetic anhydride. The N-mono-*n*-propylamine (4) and the N-mononeopentylamine (6) were also prepared by lithium aluminum hydride reduction from 2-(1-propionamidoethyl)-1,4-benzodioxane and from 2-(1-trimethylacetamidoethyl)-1,4-benzodioxane, respectively; these amides were prepared by the usual procedure. The ethylenediamine (7) could be obtained, under proper experimental conditions, as the only product of the reaction between dibromoethane and amine (1). By further reaction of diamine (7) with dibromoethane, the piperazine (16) was obtained easily.

The N-dimethylamine (8) and the N-methylethylamine (9) were prepared by reductive alkylation with formaldehyde and formic

(6) V. Rosnati and F. De Marchi, *Tetrahedron* **18**, 289 (1962).

TABLE II





	R		R	
	H	CH_3	H	CH_3
LD_{50} (mice, (mg./kg. i.p.)	200	100	175	120
Adrenolytic activity[a] (blood pressure, mg./kg. i.v.)	1	10	0.5	5
Acetylcholinolytic activity[b] (mg./l.)	10	10	—	2
Adrenolytic activity[c] (mg./l.)	1	—	1	1
Oxytocic activity[d] (mg./l.)	2–4	2–4	10	4–10
Adrenolytic activity[e] (mg./l.)	1	—	0.2	1–2

[a] Inversion of epinephrine (0.001–0.005 mg./kg. i.v.) hypertension in the chloralosed dog.[8] [b] Antagonism of acetylcholine (0.05–0.1 mg./l.) on rabbit isolated intestine.[9] [c] Antagonism of epinephrine (0.1–0.2 mg./kg.) relaxation on rabbit isolated intestine.[9] [d] Motor stimulation and tonic contraction on rabbit isolated uterus.[10] [e] Antagonism of epinephrine (0.05–0.1 mg./l.) contraction on rabbit isolated uterus.[11]

acid, respectively, from the amine (1) and from the monoethylamine (3). The N-diethylamine (10) was prepared by the lithium aluminum hydride reduction of the 2-(N-ethylacetamidoethyl)-1,4-benzodioxane obtained by acetylation of the N-monoethylamine (3). The pyrrolidine (11) was obtained by treating amine (1) with succinic anhydride to give the N-[1-(1,4-benzodioxan-2-yl)ethyl]-succinimide, which was then reduced with lithium aluminum hydride. In this reduction, in addition to pyrrolidine (11), 2-[1-(4-hydroxybutylamino)-ethyl]-1,4-benzodioxane was isolated as a secondary reaction product.[7] It may be noted that an attempt to synthesize the pyrrolidine (11) by the direct condensation of amine (1) with 1,4-dibromobutane led to the destruction of the dihalo compound and

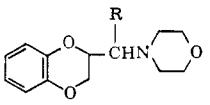
(7) The formation of N-substituted 1,4-aminobutanols, in addition to N-pyrrolidine derivatives, in the course of lithium aluminum hydride reduction of N-substituted succinimides has been reported recently by K. C. Schreiber and V. P. Fernandez, *J. Org. Chem.*, **26**, 1744 (1961).

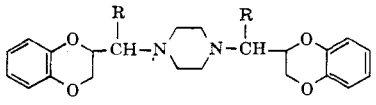
(8) D. Bovet and A. Simon, *Arch. int. Pharmacodyn.*, **52**, 413 (1936); G. L. Gatti and D. Bovet, *Arch. int. Pharmacodyn.*, **105**, 317 (1956).

(9) J. H. Burn, "Practical Pharmacology," Oxford Press, New York, N. Y., 1952, p. 7.

(10) F. Bovet-Nitti and D. Bovet, *Arch. int. Pharmacodyn.*, **96**, 327 (1954); G. L. Brown and H. H. Dale, *Proc. Roy. Soc. London* **B118**, 446 (1935).

(11) W. A. Broom and A. J. Clark, *J. Pharmacol. Exptl. Therap.*, **22**, 59 (1923).





R		R	
H	CH_3	H	CH_3
350	300	600	150
0.5	2	0.1–.02	5
—	—	1	4
1	—	0.1	2
—	10	1	—
1	—	0.1	2–4

the recovery of the starting amine as its hydrobromide. However, the reaction between amine (1) and the suitable α,ω-dihalogenated compounds has been employed successfully for the synthesis of the piperidine (12), morpholine (13), N-methylpiperazine (14) and N-ethylpiperazine (15) derivatives.

Pharmacological Results.—The amines listed in Table I were tested for activity in the cardiovascular system, in the central nervous system and in involuntary muscles, with particular reference to sympatholytic activity. Some pharmacological data have been summarized in a section of Table I. All compounds, administered intravenously in the chloralosed dog (1–10 mg./kg.), with the exception of the N,N-dimethyl derivative, provoked a transient decrease in blood pressure. This latter compound produced at a dose of 2 mg./kg. a marked increase in the blood pressure which was most likely due to a nicotine-like ganglionic stimulation. As expected this effect was even more pronounced with the corresponding quaternary derivative, which was active at 0.2 mg./kg.

In their action in smooth muscles, compounds (10), (12), (13), (16) showed a weak acetylcholinolytic activity in the isolated rabbit uterus. When tested for adrenolytic activity, with the exception of the morpholine derivative (13), the remaining compounds showed only a weak antagonism to the hypertensive activity of epinephrine in chloralosed dog. In rabbit isolated intestine and uterus they were found inactive. The amines described in this article were found to

be practically devoid of any important sedative or central analeptic activity.

Table II summarizes a comparison between some pharmacological data obtained for prosympal, piperoxan and dibozane with those obtained with the corresponding branched homologs. It is evident that in this series of benzodioxane derivatives branching of the side chain results in a lowering of activity.

Experimental[12]

N-[1-(1,4-Benzodioxan-2-yl)-ethyl]-*p*-toluenesulfonamide.—A mixture of 2-(1-aminoethyl)-1,4-benzodioxane (3.75 g.), *p*-toluenesulfonyl chloride (4.2 g.) and anhydrous pyridine (4 g.) was heated for 2 hr. at 120°. After cooling, water was added and the solution extracted three times with ether. The combined ether layers were washed with dilute hydrochloric acid, water and sodium bicarbonate and finally dried over calcium chloride. After removal of the solvent, the residue on treatment with benzene gave crystals of crude product with m.p. 122–123°. After recrystallization from ethyl alcohol–water (1:1), the pure sulfonamide melted at 130–132°; yield 5.8 g. (85%).

Anal. Calcd. for $C_{17}H_{19}NO_4S$: C, 61.25; H, 5.75; N, 4.20. Found: C, 61.05; H, 5.83; N, 4.33.

2-(1-Methylaminoethyl)-1,4-benzodioxane (2).—A mixture of 2-(1-aminoethyl)-1,4-benzodioxane (5.8 g.), methyl bromide (3 g.) and triethylamine (3.3 g.) was heated in a sealed tube for 4 hr. at 130°. Sodium carbonate (5 *N*, 10 ml.) was added and the mixture was extracted three times with ether. The ether extracts were combined and dried over anhydrous sodium carbonate. After removal of the solvent, distillation of the residue gave (2) as a colorless liquid, b.p. 66–67° (0.03 mm.); yield 5.5 g. (82%).

2-(1-Acetamidoethyl)-1,4-benzodioxane.—A solution of 2-(1-aminoethyl)-1,4-benzodioxane (10 g.) in acetic anhydride (25 ml.) was heated under reflux for 4 hr. The excess acetic anhydride was removed under reduced pressure, the residue was dissolved in ether, the solution washed with dil. hydrochloric acid and water, and dried over calcium chloride. After removal of the solvent, the residue was distilled giving a colorless oil, b.p. 140–145° (0.05 mm.), which on standing solidified completely. Recrystallization from benzene-hexane (1:1) gave crystals, m.p. 83–84°; yield 12 g. (98%).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33; O, 21.99. Found: C, 65.14; H, 6.66; N, 6.23; O, 21.70.

2-(1-Ethylaminoethyl)-1,4-benzodioxane (3).—A solution of 2-(1-acetamidoethyl)-1,4-benzodioxane (12 g., 0.054 mole) in absolute ether (100 ml.) was added slowly to a solution of lithium aluminum hydride (6.2 g., 0.16 mole) in absolute ether (100 ml.). The mixture was heated under reflux with stirring for 10 hr. Ethyl acetate (10 ml.) in ether (100 ml.) was added slowly under stirring. Then water (6 ml.), 20% aqueous sodium hydroxide (6 ml.) and more water (18 ml.) were added. The mixture was filtered and the precipitate was extracted with ether. The combined ether layers were extracted with dil. hydrochloric acid. The aqueous solution was made basic with K_2CO_3, the free base was extracted

(12) Melting and boiling points are uncorrected.

with ether, washed with water and dried over potassium carbonate. After removal of the solvent, the product was distilled giving (3) as a colorless liquid of b.p. 82–84° (0.05 mm.); yield 10 g. (90%).

2-(1-Propionamidoethyl)-1,4-benzodioxane.—Propionyl chloride (5.3 g.) in benzene (20 ml.) was added slowly with stirring to a solution of 2-(1-aminoethyl)-1,4-benzodioxane (6 g.) and triethylamine (6 g.) in benzene (30 ml.). The mixture was heated under reflux for 3 hr., cooled and filtered with suction. The precipitate was extracted with benzene and the benzene solutions after washing with 2 *N* NaOH, 2 *N* HCl and H_2O were dried over potassium carbonate. After filtration and removal of the solvent, the product was distilled giving a colorless liquid (7.5 g., 96%), b.p. 145–150° (0.05 mm.).

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.20; H, 7.21; N, 5.80.

2-(1-Propylaminoethyl)-1,4-benzodioxane (**4**) was prepared by $LiAlH_4$ reduction of 2-(1-propionamidoethyl)-1,4-benzodioxane (7.5 g.) using the above procedure. The free base was obtained as a colorless liquid in 86% yield.

2-(1-Isopropylaminoethyl)-1,4-benzodioxane (**5**) was prepared from 2-(1-aminoethyl)-1,4-benzodioxane (4.1 g.), isopropyl bromide (3 g.) and triethylamine (2.5 g.) in a way similar to that for compound (2). The base was obtained as colorless liquid in 83% yield.

2-(1-Trimethylacetamidoethyl)-1,4-benzodioxane was prepared from trimethylacetyl chloride (5 g.) in xylene (30 ml.), 2-(1-aminoethyl)-1,4-benzodioxane (5.4 g.) and triethylamine (5 g.) in xylene (30 ml.) by the procedure used for 2-(1-propionamidoethyl)-1,4-benzodioxane. The crude reaction product was distilled giving a colorless liquid (6 g., 76%), b.p. 120–125° (0.04 mm), which on standing solidified completely. Recrystallization from petroleum ether gave crystals, m.p. 87–88°.

Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.26; H, 7.96; N, 5.44.

2-(1-Neopentylaminoethyl)-1,4-benzodioxane (**6**) was prepared by $LiAlH_4$ reduction of 2-(1-trimethylacetamidoethyl)-1,4-benzodioxane (4 g.) by the usual procedure. The base was distilled giving (6) as a colorless liquid; yield 3.5 g. (94%).

N,N′-Bis-[1-(1,4-benzodioxan-2-yl)-ethyl]-ethylenediamine (**7**) was prepared from 2-(1-aminoethyl)-1,4-benzodioxane (8.2 g.), dibromoethane (4.8 g.) and triethylamine (5.1 g.) by the procedure described for compound (2). The base was a yellow oil, yield 5.3 g. (62%).

2-(1-Dimethylaminoethyl)-1,4-benzodioxane (**8**).—A solution of 2-(1-aminoethyl)-1,4-benzodioxane (7.16 g.), formic acid (10.8 g., 90%) and aqueous formaldehyde (11 g., 35%) was heated under reflux for 20 hr. After cooling, hydrochloric acid (5 ml., sp. gr. 1.19) was added and most of the solvent was distilled under reduced pressure. The residue was diluted with water and the acid solution was made basic with sodium carbonate and extracted three times with ether. The ether layers were combined and dried over anhydrous sodium carbonate. After removal of the ether the product was distilled giving (8) as a colorless liquid, b.p. 76–78° (0.07 mm.); yield 7 g. (80%). The corresponding trimethylammonium iodide, m.p. 142–144°, was obtained by adding methyl iodide to a solution of (8) in anhydrous acetone.

Anal. Calcd. for $C_{13}H_{20}INO_2$: C, 44.71; H, 5.77; N, 4.01; I, 36.33. Found: C, 44.67; H, 5.74; N, 4.17; I, 36.05.

2-(1-Methylethylaminoethyl)-1,4-benzodioxane (**9**) was prepared by treating 2-(1-ethylaminoethyl)-1,4-benzodioxane (4.4 g.), 99% formic acid (2.7 g.) and 35% aqueous formaldehyde (3 g.). The procedure was the same as that described for compound (8). The free base was a colorless liquid; yield 4.4 g. (92%).

2-(N-Ethylacetamidoethyl)-1,4-benzodioxane.—A solution of 2-(1-ethylaminoethyl)-1,4-benzodioxane (8 g.) in acetic anhydride (10 ml.) was heated under reflux for 2 hr. After working up the reaction mixture as described for 2-(1-acetamidoethyl)-1,4-benzodioxane, the residue was distilled giving a colorless liquid, b.p. 130–132° (0.02 mm.); yield 8 g. (85%).

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.10; H, 7.43; N, 5.61.

2-(1-Diethylaminoethyl)-1,4-benzodioxane (**10**) was prepared by $LiAlH_4$ reduction of 2-(N-ethylacetamidoethyl)-1,4-benzodioxane (8 g.). The procedure was identical with that described for compound (3). The free base was a colorless liquid; yield 7 g. (83%).

N-[1-(1,4-Benzodioxan-2-yl)-ethyl]-succinimide.—A solution of 2-(1-aminoethyl)-1,4-benzodioxane (10.5 g.) and succinic anhydride (6.5 g.) in anhydrous dioxane (100 ml.) was heated under reflux for 7 hr. After removal of the solvent, the residue was distilled giving a colorless liquid (12.5 g., 81%), b.p. 165–167° (0.05 mm.), which on standing solidified completely. Recrystallization from benzene-hexane (1:2) gave crystals m.p. 125–127°.

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.63; H, 5.99; N, 5.24.

2-(1-Pyrrolidinoethyl)-1,4-benzodioxane (**11**).—A solution of N-[1-(1,4-benzodioxan-2-yl)-ethyl]-succinimide (12.5 g., 0.05 mole) in dry tetrahydrofuran (200 ml.) was refluxed with $LiAlH_4$ (5.5 g., 0.15 mole) for 40 hr. After working up the reaction mixture as described for compound (3), the residue was distilled giving two fractions: (a) 2-(1-pyrrolidinoethyl)-1,4-benzodioxane, colorless liquid (9 g., 80%), b.p. 105–110° (0.06 mm.), and (b) 2-[1-(4-hydroxybutylamino)-ethyl]-1,4-benzodioxane, colorless liquid (2.5 g., 20%), b.p. 160–165° (0.06 mm.).

Anal. Calcd. for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 67.03; H, 8.43; N, 5.54.

2-(1-Piperidinoethyl)-1,4-benzodioxane (**12**) was prepared from 2-(1-aminoethyl)-1,4-benzodioxane (5 g.), 1,5-dibromopentane (6.3 g.) and triethylamine (6 g.) using the procedure described for compound (2). The base was obtained as a colorless liquid in 72% yield.

2-(1-Morpholinoethyl)-1,4-benzodioxane (**13**) was prepared from 2-(1-aminoethyl)-1,4-benzodioxane (2.2 g.), 2,2′-dichloroethyl ether (3.4 g.) and triethylamine (3 g.). The base was a colorless liquid, yield 2.5 g. (83%).

1-Methyl-4-[1-(1,4-benzodioxan-2-yl)-ethyl]-piperazine (**14**) was prepared from 2-(1-aminoethyl)-1,4-benzodioxane (5.4 g.), 2,2′-dichloro-N-methyldiethylamine (4.7 g.) and triethylamine (6.5 g.). The free base was a colorless liquid; yield 3 g. (60%).

1-Ethyl-4-[1-(1,4-benzodioxan-2-yl)-ethyl]-piperazine (**15**) was prepared from 2-(1-aminoethyl)-1,4-benzodioxane (4.2 g.), 2,2′-dichloro-N-ethyldiethylamine (4.4 g.) and triethylamine (4.8 g.). The base was a colorless liquid; yield 4.3 g. (82%).

1,4-Bis[1-(1,4-benzodioxan-2-yl)-ethyl]-piperazine (**16**) was prepared from N,N′-bis[1-(1,4-benzodioxan-2-yl)-ethyl]-ethylenediamine (4.3 g.), dibromoethane

(2.4 g.) and triethylamine (3.6 g.). The free base was a yellow oil, yield 4.3 g. (93%).

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The Effect of Methoxyphenyl Substitutions on the Strychnine-Like Activity of Aryldiazaadamantanones and Aryldiazaadamantanols[1]

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The synthesis and pharmacological testing of eight new phenyl substituted diazaadamantanols and six new phenyl substituted diazaadamantanones are reported. In most cases, the effect of methoxyl substitution in the aromatic rings of phenyldiazaadamantanones was to change the activity from a strychnine-like to a non-convulsive one. The diazaadamantanol's strychnine-like activity was lowered by these phenyl substitutions. In two cases, the 3,4-dimethoxy and the 3,4,5-trimethoxy derivatives, the convulsive activity disappeared completely.

Chiavarelli, Settimj, and Magalhaves Alves[4] synthesized a compound following the method of Kyi and Wilson,[5] which was believed to be 1,5-diphenyl-3,7-bispidin-9-one. Reduction of this bispidinone with lithium aluminum hydride gave what was also believed to be the corresponding 1,5-diphenyl-3,7-bispidin-9-ol. Preliminary screening of this compound showed that it had strychnine-like activity. Further chemical studies[6] proved the first compound to be 1,5-diphenyl-3,7-diazaadamantan-9-one and the second to be 1,5-diphenyl-3,7-diazaadamantan-9-ol.

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