The Synthesis and Pharmacology of Some Substituted 1,3-Benzodioxoles and 1,4-Benzodioxans

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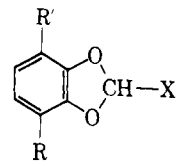
The synthesis of some nitrogenous substituted 1,3-benzodioxoles and 1,4-benzodioxans is described. The effects of these compounds, in particular the antihypertensive 2-guanidinomethyl-1,4-benzodioxan, on the peripheral sympathetic nervous system are discussed.

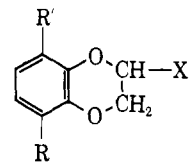
The biological activity of 2-phenoxyethylamines and cyclic compounds containing the same structural features has a long history which has been reviewed comprehensively.[2] In more recent years a wide variety of highly active compounds has been described; these include stimulants of autonomic ganglia[3] and of skeletal muscles,[4] inhibitors of amine oxidase,[5] long-lasting local anesthetics,[6] and the adrenergic-neurone blocking drugs.[7-9]

2-Aminomethyl-1,4-benzodioxans have been studied in some detail,[2] but at the outset of our work little was known of derivatives with guanidine[10] or quaternary ammonium side chains. We considered that the combination of these structural features would prove interesting, since 1,4-benzodioxans are known to have an affinity for adrenergic receptor sites (causing antagonism to epinephrine),[2] and the strongly basic or quaternary side chains seem to be a prerequisite for adrenergic-neurone blockade.[7-9,11]

We have prepared two series of compounds, 2-substituted 1,3-benzodioxoles (Ia) and 2-substituted 1,4-benzodioxans (IIa). In each case we have studied the effect of methyl substitution in the aromatic ring, that is compounds derived from Ib, Ic, and IIc.



I



II

a, R = R′ = H
b, R = H; R′ = CH_3
c, R = R′ = CH_3

One of the compounds studied, 2-guanidinomethyl-1,4-benzodioxan (IIa, X = $NHC(NH_2)=NH$),[12] has recently been described by Augstein and Green[10] as an active antihypertensive agent. The pharmacology of this compound[13] and the other compounds which have been studied will be discussed later.

1,3-Benzodioxoles.—Surprisingly little use of 1,3-benzodioxoles has been made as a nucleus for the synthesis of drugs. The ester Ia (X = $CO_2C_2H_5$) is best prepared by the method of Hartzfeld, *et al.*[14]; the pure ester and its derivatives which are described later are not particularly unstable.[15] The esters Ib (X = $CO_2C_2H_5$) and Ic (X = $CO_2C_2H_5$) were prepared in a similar way. The removal of the last traces of hydroxylic impurity from all these esters is costly in terms of material and for many purposes we did not effect complete purification at this stage.

The amides Ia–c (X = $CONH_2$)[16] are readily prepared by the action of ammonia on the ethyl esters. The substituted amides Ia–c [X = $CON(CH_3)_2$ and $CON(C_2H_5)_2$] have been prepared similarly, but the conditions were rather critical if the amides were to be sufficiently pure to crystallize. The reactivity of amines towards the esters was in the order NH_3 >> $NH(CH_3)_2$ >> $NH(C_2H_5)_2$, and the reactivity of the esters was in the order Ia > Ib > Ic (X = $CO_2C_2H_5$). The reaction between the last named of each reagent was so sluggish that decomposition and hydrolysis were the major reactions, and the pure amide could not be isolated.

Reduction of the amides was effected by lithium aluminum hydride in refluxing ether. High yields of tertiary amines were obtained. The primary amines were obtained in lower and variable yields owing to the relative insolubility of the amides necessitating a prolonged reaction (while the amide was being introduced from a Soxhlet thimble). Decomposition occurred in the higher boiling tetrahydrofuran.

In the first experiments on these reductions, ethyl acetate was used to decompose the excess reagent. From these reactions, the N-acetylamine was isolated, evidently due to reaction of the anion [Ia (or b), X =

(1) Correspondence should be addressed to this author.

(2) D. Bovet and F. Bovet-Nitti, "Structure et Activité Pharmacodynamique des Médicaments du Système Nerveux Végétatif," Verlag S. Karger, Basel, 1948, p. 170, *et seq.*

(3) P. Hey, *Brit. J. Pharmacol.*, **7**, 117 (1952).

(4) G. L. Willey, *ibid.*, **10**, 466 (1955).

(5) B. G. Brown and P. Hey, *ibid.*, **11**, 58 (1956).

(6) P. Hey and G. L. Willey, *Nature*, **198**, 390 (1963).

(7) R. A. McLean, R. J. Geus, R. J. Mohrbacher, P. A. Mattis, and G. E. Ullyot, *J. Pharmacol. Exptl. Therap.*, **129**, 11 (1960); R. A. McLean, R. J. Geus, J. Pasternack, P. A. Mattis, and G. E. Ullyot, *ibid.*, **129**, 17 (1960).

(8) R. Fielden, A. M. Roe, and G. L. Willey, *Brit. J. Pharmacol.*, in press.

(9) D. I. Barron, P. M. G. Bavin, G. J. Durant, I. L. Natoff, R. G. W. Spickett, and D. K. Vallance, *J. Med. Chem.*, **6**, 705 (1963); A. L. A. Boura, F. C. Copp, A. F. Green, H. F. Hodson, G. K. Ruffell, M. F. Sim, E. Walton, and E. M. Grivsky, *Nature*, **191**, 1312 (1961).

(10) J. Augstein and S. M. Green, *Nature*, **201**, 628 (1964); W. S. Peart and M. T. MacMahon, *Brit. Med. J.*, **1**, 398 (1964).

(11) K. A. Exley, *Brit. J. Pharmacol.*, **12**, 297 (1957); A. L. A. Boura and A. F. Green, *ibid.*, **14**, 536 (1959); **20**, 36 (1963); R. A. Maxwell, A. J. Plummer, F. Schneider, H. Povalski, and A. I. Daniel, *Schweiz. Med. Wochschr.*, **90**, 109 (1960); *J. Pharmacol. Exptl. Therap.*, **128**, 22 (1960); F. C. Copp in "Advances in Drug Research," Vol. I, N. J. Harper and A. B. Simmonds, Ed., Academic Press Inc., London, 1964, p. 161, *et seq.*

(12) This compound has been given the approved name guanoxan.

(13) The compounds described in this paper were first disclosed in Smith Kline and French Laboratories Provisional Patent Application No. 46075/61 (Dec. 22, 1961) and 3340/62 (Jan. 29, 1962).

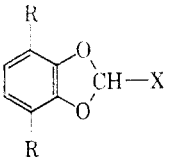
(14) H. A. Hartzfeld, R. G. Johnson, and H. Gilman, *J. Org. Chem.*, **22**, 1717 (1957).

(15) A. Burger, D. G. Markees, W. R. Nes, and W. L. Yost [*J. Am. Chem. Soc.*, **71**, 3307 (1949)] state that similar compounds are unstable, even to dilute alkali.

(16) Ia (X = $CONH_2$) has been described as having m.p. 110–112°[14] and 105–106°.[15] We find m.p. 110–112°.

TABLE I

THE PROPERTIES AND ANALYSES OF THE 1,3-BENZODIOXOLES



R	R'	X	$n^{20}D$	M.p.[a] or b.p. (mm.), °C.	Yield, %	Crystn. solvent[b]
H	H	CH_2NH_2[c]	1.5477	87–89 (0.7)	49	
H	H	$CH_2NH_2 \cdot HCl$[d]		207–235* subl.		M + Pr
H	H	$CH_2NHCONH_2$[e]		100–101	83	W
H	H	$CONHCONH_2$[e]		188–189	24	Al
H	H	$CH_2NHC(NH_2)=NH \cdot HNO_3$		167–168.5*	45	Al
H	H	$CH_2NHCOCH_3$[e]		112–113*	[c]	B + P (60)
H	H	$CON(CH_3)_2$[e]		94–95	63	W + M
H	H	$CH_2N(CH_3)_2$	1.5158	62 (0.3)	90	
H	H	$CH_2N(CH_3)_2 \cdot HCl$[d]		245–248		Al
H	H	$CON(C_2H_5)_2$[e]		77–78*	39	Et + P (40)
H	H	$CH_2N(C_2H_5)_2$	1.5078	70–72 (0.05)	73	
H	H	$CH_2N(C_2H_5)_2 \cdot HCl$[d]		142–143		Ea + M
H	H	$CH_2N^+(CH_3)_3 \cdot I^-$[f]		245–247*	96	M
H	H	$CH_2N^+(C_2H_5)_3 \cdot I^-$[g]		144–145*	16	Ac + Et
H	CH_3	$CO_2C_2H_5$[c]	1.5050	92 (0.3)	41	
H	CH_3	CO_2H[c]		108–110*	40	B + P (60)
H	CH_3	$CONH_2$[c]		109–110	60	B
H	CH_3	CH_2NH_2		63 (0.05)	55	
H	CH_3	$CH_2NH_2 \cdot HCl$[d]		219–220		M + Et
H	CH_3	$CH_2NHCONH_2$		125.5–126	97	W
H	CH_3	$CONHCONH_2$[h]		181–183	[h]	B_3 or W + M
H	CH_3	$CH_2NHC(NH_2)=NH \cdot HNO_3$[c]		179–180	82	W
H	CH_3	$CH_2NHCOCH_3$[i]		120–122*	[i]	B + P (60)
H	CH_3	$CONH(C_6H_{11})$[j]		147–148	[j]	W + M
H	CH_3	$CON(CH_3)_2$[k]		87–89	51	M or P (60)
H	CH_3	$CH_2N(CH_3)_2$		80–82 (0.8)	72	
H	CH_3	$CH_2N(CH_3)_2 \cdot HCl$[d]		214–215		M + Ac
H	CH_3	$CON(C_2H_5)_2$[l]		60–61	60	P (60)
H	CH_3	$CH_2N(C_2H_5)_2$	1.5039	85–95 (0.05–0.1)	>95	
H	CH_3	$CH_2N(C_2H_5)_2 \cdot HCl$[d]		176–177		M + Ac
H	CH_3	$CH_2N^+(CH_3)_3 \cdot I^-$[f]		214–215	80	M + Ac
H	CH_3	$CH_2N^+(CH_3)(C_2H_5)_2 \cdot I^-$[g]		102–103	63	Pr + IPE
H	CH_3	$CH_2N^+(C_2H_5)_3 \cdot I^-$[g]		194–195	56	M + Ac
H	CH_3	$CONH(C_3H_6OCl)$[c]		181–182*	>95	W + Al
H	CH_3	$CH_2NH(C_3H_6OCl)$		104–106*		Et + H
H	CH_3	$CH_2NH(C_3H_6OCl) \cdot HCl$[d]		203–205		M + IPE
H	CH_3	$CONH(C_9H_9O_2)$[c]		133–135*	>95	W + Al
H	CH_3	$CH_2NH(C_9H_9O_2) \cdot HCl$[d]		218–222	77	M + IPE
CH_3	CH_3	$CO_2C_2H_5$[m]	1.4991[n]	77–80 (0.2), 22–24*	17	M at −70°
CH_3	CH_3	CO_2H[c]		179–180*	69	W + Al
CH_3	CH_3	$CONH_2$[o]		156–159*	73	W + M
CH_3	CH_3	CH_2NH_2		180 (2)	73	
CH_3	CH_3	$CH_2NH_2 \cdot HCl$[d]		274–275		Al + Et
CH_3	CH_3	$CH_2NHCONH_2$		195–196*	86	Al
CH_3	CH_3	$CH_2NHC(NH_2)=NH \cdot HNO_3$		183–183.5*	89	W
CH_3	CH_3	$CON(CH_3)_2$[p]		80–81*	76	H
CH_3	CH_3	$CH_2N(CH_3)_2 \cdot HCl$[d]		207–208		Al + Et
CH_3	CH_3	$CH_2N^+(CH_3)_3 \cdot I^-$[f]		233–233.5*	84	Al + Et

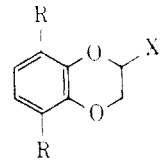
[a] Melting points marked with an asterisk were taken on a Kofler block and are corrected; others were determined in a capillary tube. [b] Ac = acetone, Al = ethanol, B = benzene, Ea = ethyl acetate, Et = ether, H = *n*-hexane, IPE = diisopropyl ether, M = methanol, P (40) = petroleum ether (b.p. 40–60°), P (60) = petroleum ether (b.p. 60–80°), Pr = 2-propanol, W = water. [c] See experimental details. [d] Prepared by treating an ethereal solution of the amine with 2-propanolic hydrogen chloride. [e] Prepared by reaction of the ethyl ester with excess of anhydrous diethylamine at room temperature for 17 hr. The product being distilled at 120° (0.25 mm.). [f] Methiodides were obtained from the tertiary bases by standing an ethereal or methanolic solution with methyl iodide at room temperature for 24 hr. [g] Ethiodides were obtained by reaction of tertiary bases with ethyl iodide under reflux. [h] Obtained by the method for unsubstituted compound, using dimethylformamide containing a few drops of pyridine as solvent, but preparation was unreproducible. [i] Isolated from the reduction of the amide with lithium aluminum hydride when ethyl acetate was used to destroy the excess of reagent; also prepared by acetylation of the amine (*cf.* experimental details for 2-acetamidomethyl-1,3-benzodioxole). [j] The cyclohexylamide

Formula	% calcd. C	H	N	Hal.	% found C	H	N	Hal.
$C_8H_9NO_2$	63.55	6.0	9.27		62.96	5.90	9.21	
$C_8H_{10}ClNO_2$	51.22	5.37	7.47	18.90	51.03	5.23	7.60	18.71
$C_9H_{10}N_2O_3$	55.66	5.19	14.43		55.62	5.52	14.35	
$C_9H_8N_2O_4$	51.92	3.88	13.46		52.04	3.92	13.62	
$C_9H_{12}N_4O_5$	42.19	4.73	21.87		42.32	4.69	21.77	
$C_{10}H_{11}NO_3$	62.17	5.74	7.25		62.48	5.54	7.39	
$C_{10}H_{11}NO_3$	62.17	5.74	7.25		62.09	5.65	7.44	
$C_{10}H_{13}NO_2$	67.02	7.31	7.82		67.33	7.15	8.06	
$C_{10}H_{14}ClNO_2$	55.68	6.54	6.50	16.44	55.70	6.54	6.61	16.03
$C_{12}H_{15}NO_3$	65.12	6.83	6.33		65.02	6.83	6.46	
$C_{12}H_{17}NO_2$	69.52	8.27	6.76		69.32	8.11	6.77	
$C_{12}H_{18}ClNO_2$	59.14	7.45	5.75	14.55	58.78	7.36	5.85	14.69
$C_{11}H_{16}INO_2$	41.13	5.02	4.36	39.52	41.19	5.10	4.11	39.54
$C_{14}H_{22}INO_2$	46.30	6.11	3.86	34.94	46.36	6.04	3.92	34.72
$C_{11}H_{12}O_4$	63.45	5.81			63.22	5.90		
$C_9H_8O_4$	59.98	4.48			60.15	4.37		
$C_9H_9NO_3$	60.34	5.06	7.82		60.28	5.03	7.82	
$C_9H_{11}NO_2$	65.44	6.71	8.48		65.56	6.64	8.48	
$C_9H_{12}ClNO_2$	53.60	6.00	6.95	17.58	53.91	5.78	7.09	17.41
$C_{10}H_{12}N_2O_3$	57.68	5.81	13.45		57.90	5.94	13.89	
$C_{10}H_{10}N_2O_4$	54.05	4.54	12.61		53.85	4.46	12.98	
$C_{10}H_{14}N_4O_5$	44.44	5.22	20.73		44.17	5.28	20.32	
$C_{11}H_{13}NO_3$	63.76	6.32	6.76		64.06	6.44	6.70	
$C_{15}H_{19}NO_3$	68.93	7.33	5.36		69.17	7.53	5.40	
$C_{11}H_{13}NO_3$	63.75	6.32	6.76		63.78	6.37	6.82	
$C_{11}H_{15}NO_2$	68.37	7.82	7.25		68.61	7.82	7.28	
$C_{11}H_{16}ClNO_2$	57.51	7.02	6.09	15.43	57.42	7.10	6.20	15.43
$C_{13}H_{17}NO_3$	66.36	7.28	5.95		66.44	7.05	5.97	
$C_{13}H_{19}NO_2$	70.56	8.68	6.33		70.30	8.28	6.69	
$C_{13}H_{20}ClNO_2$	60.57	7.82	5.43	13.75	60.61	7.85	5.42	13.49
$C_{12}H_{18}INO_2$	43.00	5.41	4.18	37.86	43.06	5.32	4.20	37.61
$C_{14}H_{22}INO_2$	46.29	6.11	3.86	34.94	46.49	5.75	3.98	35.22
$C_{15}H_{24}INO_2$	47.75	6.41	3.71	33.64	47.96	6.51	3.70	33.89
$C_{17}H_{14}ClNO_4$	61.54	4.25	4.22	10.69	61.51	4.03	4.37	10.50
$C_{17}H_{16}ClNO_3$	64.24	5.07			64.09	4.88		
$C_{17}H_{17}Cl_2NO_3$	57.65	4.84	3.96	20.02	58.06	5.00	4.00	19.79
$C_{18}H_{17}NO_5$	66.04	5.23	4.28		65.93	5.21	4.68	
$C_{18}H_{20}ClNO_4$	61.80	5.76	4.00	10.14	61.86	5.37	4.18	9.89
$C_{12}H_{14}O_4$	64.85	6.35			64.89	6.40		
$C_{10}H_{10}O_4$	61.85	5.19			61.78	5.40		
$C_{10}H_{11}NO_3$	62.17	5.74	7.25		62.22	5.62	7.31	
$C_{10}H_{13}NO_2$			7.81				8.02	
$C_{10}H_{14}ClNO_2$	55.68	6.54	6.49	16.44	55.71	6.51	6.51	16.64
$C_{11}H_{14}N_2O_3$	59.47	6.33	12.61		59.51	6.52	12.63	
$C_{11}H_{16}N_4O_5$	46.48	5.67	19.71		46.53	5.63	19.58	
$C_{12}H_{15}NO_3$	65.14	6.83	6.33		65.15	6.93	6.53	
$C_{12}H_{18}ClNO_2$	59.13	7.44	5.75	14.55	59.20	7.56	5.58	14.72
$C_{13}H_{20}INO_2$			4.01	36.34			3.93	35.87

was the only product isolated when the carboxylic acid was heated in dimethylformamide (90–120° for 24 hr.) with urea and dicyclohexylcarbodiimide in an attempt to prepare the acylurea. [k] From ethyl ester and dimethylamine in ethanol (1.2 mole of 37% w./w.) at −10 to −15° for 1 hr., then poured into dilute HCl and extracted into ether. [l] Reaction of ester and excess of diethylamine at 0° for 6 days, then poured into dilute hydrochloric acid and extracted into ether. [m] The ester was very hard to free from hydroxylic impurities (as indicated by infrared). The ester darkened rapidly on keeping and appeared to be much less stable than its lower homologs. [n] Taken at 27°. [o] Prepared by hydrolysis of ester with KOH in aqueous ethanol (2:3). [p] Reaction of ester and excess of 35% w./w. aqueous ammonia in methanol at −70°, reaction allowed to warm to 0° during 45 min., dilution with water gave the amide. [q] Reaction of ester and excess dimethylamine in methanol at −70°; reaction was allowed to reach room temperature during 1 hr.; kept at room temperature for 45 min., diluted with water, and the product was collected in ether.

TABLE II

THE PROPERTIES AND ANALYSES OF THE 1,4-BENZODIOXANS



R	R'	X	n_D (temp.)	M.p.[a] or b.p. (mm.), °C.	Yield, %	Crystn. solvent[b]
CH_3	CH_3	CH_2OH[d]	1.5442 (25)	110–120 (0.5)	52	
CH_3	CH_3	$CH_2OSO_2C_6H_4CH_3$-*p*[c]		87	70	Al
CH_3	CH_3	CH_2Br[d]	1.5588 (25)	102–103 (0.2)	23	
CH_3	CH_3	$CO_2C_2H_5$[d]	1.5253 (25)	100 (0.25)	52	
CH_3	CH_3	$CONH_2$[d]		120–121	98	P (60)
CH_3	CH_3	$CH_2NH_2 \cdot HCl$		254.5–255.5	83	W + M
CH_3	CH_3	$CH_2NHCONH_2$		179–180	95	M
CH_3	CH_3	$CH_2NHC(NH_2)=NH \cdot HNO_3$		150–151	84	W
CH_3	CH_3	$CON(CH_3)_2$[f]		70–71	71	P (40)
CH_3	CH_3	$CH_2N(CH_3)_2$	1.5200 (27)	80 (0.08)	69	
CH_3	CH_3	$CH_2N(CH_3)_2 \cdot HCl$[g]		168–169		M + Et
CH_3	CH_3	$CH_2N(C_2H_5)_2 \cdot HCl$[d]		215–216	92	Al
CH_3	CH_3	$CH_2N^+(CH_3)_3 \cdot I^-$[h]		210–211	94	M + Et
CH_3	CH_3	$CH_2N^+(CH_3)_2(C_2H_5) \cdot I^-$[i]		181–182	95	M + Et
CH_3	CH_3	$CH_2N^+(C_2H_5)_3 \cdot I^-$[j]		223–224	96	M + Et
CH_3	CH_3	$CH_2N^+(C_2H_5)_2(CH_3) \cdot I^-$[h]		190–191	66	M + Et
CH_3	CH_3	$COCH_3$[d]		48–49*	25	W + M
CH_3	CH_3	$C(CH_3)=NOH$		115–117*	78	H + Et
CH_3	CH_3	$CH(CH_3)NH_2$	1.5332 (25)	118–120 (1.25)	84	
CH_3	CH_3	$CH(CH_3)NH_2 \cdot HCl$[g]		272–277		Pr + IPE
CH_3	CH_3	$CH(CH_3)NHC(NH_2)=NH$[d] $0.5\ H_2SO_4$		223–230*		W
CH_3	CH_3	$CH(CH_3)N(CH_3)_2$[k]	1.5177 (27)	96 (0.4)	50	
CH_3	CH_3	$CH(CH_3)N^+(CH_3)_3 \cdot ClO_4^-$[l]		193–195*		Al
H	H	$CH_2OSO_2C_6H_4CH_3$-*p*[c]		80–81	94	M
H	H	$CH_2NH_2 \cdot HCl$[g,m]		217–218		M + Ac
H	H	$CH_2N(CH_3)_2 \cdot HCl$[g,m]		175–176		M + Ac
H	H	$CH_2NHCONH_2$[n]		88–89	82	Et (Soxhlet)
H	H	$CONHCONH_2$[o]		175–176	70	M or Ac
H	H	$CH_2NHC(NH_2)=NH \cdot HNO_3$		164–165	71	W
H	H	$CH_2N^+(C_2H_5)_3 \cdot I^-$[j]		135–136		Ac + Et
H	H	$COCH_3$[p]	1.5370 (25)	88 (0.05), 34–35*	48	P (40)
H	H	$C(CH_3)=NOH$[p]	1.5627 (22.5)	123–124 (0.4)	97	
H	H	$CH(CH_3)NH_2$[q]	1.5457 (25)	140–150 (14)	83	
H	H	$CH(CH_3)NH_2 \cdot HCl$[g]		219–220		M + IPE
H	H	$CH(CH_3)NHCONH_2$		142–143	81	Et (Soxhlet)
H	H	$CH(CH_3)NHC(NH_2)=NH \cdot HNO_3$		164–166		W + Al
H	H	$CH(CH_3)NHC_2H_5$[r,s]	1.5222 (25)	75–79 (0.2)	65	
H	H	$CH(CH_3)N(CH_3)_2$[s]	1.5229 (25)	101 (1.5)	80	
H	H	$CH(CH_3)N(CH_3)_2 \cdot HCl$[g]		217–219		Pr + IPE
H	H	$CH(CH_3)N(C_2H_5)_2$[s,t]	1.5116 (26)	102–103 (0.3)	79	
H	H	$CH(CH_3)N(C_2H_5)_2 \cdot HI$		242–248		Al
H	H	$CH(CH_3)N^+(CH_3)_3 \cdot p\text{-}CH_3C_6H_4SO_3^-$[u]		163–168*	95	Pr + IPE
H	H	$CH(CH_3)N^+(C_2H_5)_2(CH_3) \cdot ClO_4^-$[v]		110–133		Al + Et

[a] See footnote *a* in Table I. [b] See footnote *b* in Table I. [c] Halogen or sulfur. [d] See experimental details. [e] Prepared by the method described in ref. 22. [f] From ethyl ester and excess of dimethylamine in methanol (30% w./w.) at 0° for 20 hr. [g] From an ethereal solution of the amine with 2-propanolic hydrogen chloride. [h] From the tertiary amine by reaction with methyl iodide in ether or methanol at room temperature for 24 hr. [i] From the tertiary amine with ethyl iodide under reflux. [j] Analysis was precluded by very rapid formation of a carbonate. [k] From the primary amine by the Clarke–Eschweiler procedure. [l] From the gummy iodide by treatment with silver perchlorate in ethanol. [m] The base has been described many times but there is apparently no record of the hydrochloride. [n] This compound is described in Belgian Patent 613,215 (1962) as having m.p. 84–85°. [o] Prepared by the method of R. W. Stoughton, H. L. Dickison, and O. G. Fitzhugh [*J. Am. Chem. Soc.*, **61**, 408 (1939)]. [p] The ketone and oxime are described in British

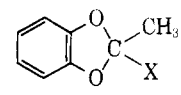
CH_2NH^-] with ethyl acetate. This anion may be stabilized by the inductive effect of the oxygen atoms.[17] In later reductions a mixture of ethanol and ether was used to decompose the excess lithium aluminum hydride. Derivatives of these amines which have been prepared are listed in Table I.

(17) The inductive effect of the oxygen atoms is shown by the high frequency of the amide I band of the 1,3-benzodioxole primary amides, all of which have $\nu_{max}^{CHCl_3}$ at 1716 cm.$^{-1}$. 1,4-Benzodioxan-2-carboxamide (prepared by method described in ref. 23) has $\nu_{max}^{CHCl_3}$ at 1699 cm.$^{-1}$. It may be of interest to point out some features of the infrared spectra of the 1,3-benzodioxoles which are described in this paper. The following ν_{max} refer to Nujol mulls or liquid films; all show two strong ether bands: Ia at 1248–1230 and 1098–969 cm.$^{-1}$, Ib at 1255–1237 and 1124–1084 cm.$^{-1}$, Ic at 1260–1250 and 1120–1098 cm.$^{-1}$. All derivatives of Ia and Ib have a strong aromatic band at 1490–1480 cm.$^{-1}$.

Formula	% calcd. C	H	N	c	% found C	H	N	c
$C_{11}H_{14}O_3$	68.02	7.26			68.19	7.12		
$C_{18}H_{20}O_5S$	62.05	5.79		9.20	61.85	5.72		8.77
$C_{11}H_{13}BrO_2$	51.38	5.10		31.08	51.52	5.03		30.84
$C_{13}H_{16}O_4$					*d*			
$C_{11}H_{13}NO_3$	63.75	6.32	6.76		63.58	6.36	6.48	
$C_{11}H_{16}ClNO_2$	57.51	7.02	6.10	15.43	57.68	6.82	6.01	15.19
$C_{12}H_{16}N_2O_3$	61.00	6.83	11.86		60.84	6.64	12.00	
$C_{12}H_{18}N_4O_5$	48.32	6.08	18.78		48.49	6.24	18.60	
$C_{13}H_{17}NO_3$	66.36	7.28	5.95		66.54	7.41	6.21	
$C_{13}H_{19}NO_2$	70.55	8.65	6.33		70.50	8.42	6.48	
$C_{13}H_{20}ClNO_2$	60.58	7.82	5.43	13.78	60.51	7.83	5.32	13.50
$C_{15}H_{24}ClNO_2$	63.03	8.46	4.90	12.40	62.94	8.49	4.66	12.30
$C_{14}H_{22}INO_2$	46.29	6.11	3.86	34.94	46.50	6.11	3.71	34.72
$C_{15}H_{24}INO_2$	47.75	6.41	3.71	33.64	47.96	6.45	3.51	33.41
$C_{17}H_{28}INO_2$	50.37	6.96	3.46	31.31	50.18	6.95	3.46	31.13
$C_{16}H_{26}INO_2$	49.11	6.69	3.58	32.43	49.12	6.65	3.67	32.61
$C_{12}H_{14}O_3$	69.88	6.84			69.82	6.87		
$C_{12}H_{15}NO_3$	65.14	6.83	6.33		65.02	6.86	6.31	
$C_{12}H_{17}NO_2$					*j*			
$C_{12}H_{18}ClNO_2$	59.13	7.45	5.74	14.54	59.13	7.49	5.56	14.37
$C_{26}H_{40}N_6O_8S\cdot H_2O$	50.80	6.89	13.67		50.81	6.70	13.89	
$C_{14}H_{21}NO_2$	71.45	9.00	5.95		71.46	9.01	6.04	
$C_{15}H_{24}ClNO_6$	51.50	6.91	4.00		51.07	7.01	4.29	
$C_{16}H_{16}O_5S$	59.98	5.03		10.01	59.88	5.11		10.20
$C_9H_{12}ClNO_2$	53.60	6.00	6.95	17.58	53.34	5.81	6.93	17.62
$C_{11}H_{16}ClNO_2$	57.52	7.02	6.10	15.44	57.54	7.00	6.03	15.34
$C_{10}H_{12}N_2O_3$	57.68	5.81	13.46		57.91	5.57	13.70	
$C_{10}H_{10}N_2O_4$	54.05	4.54	12.61		54.18	4.52	12.76	
$C_{10}H_{14}N_4O_5$	44.44	5.22	20.73		44.60	5.43	20.42	
$C_{15}H_{24}INO_2$	47.75	6.41	3.71		47.99	6.39	3.57	
$C_{10}H_{10}O_3$	67.39	5.65			67.33	5.69		
$C_{10}H_{11}NO_3$	62.17	5.74	7.25		62.36	5.98	7.22	
$C_{10}H_{13}NO_2$	67.02	7.31	7.82		66.91	7.20	7.89	
$C_{10}H_{14}ClNO_2$	55.69	6.54	6.49	16.44	55.52	6.34	6.24	16.31
$C_{11}H_{14}N_2O_3$	59.45	6.35	12.61		59.43	6.17	12.41	
$C_{11}H_{16}N_4O_5$	46.47	5.67	19.71		46.64	5.81	19.65	
$C_{12}H_{17}NO_2$	69.54	8.27	6.76		69.42	8.40	6.73	
$C_{12}H_{17}NO_2$	69.52	8.27	6.76		69.69	8.22	6.74	
$C_{12}H_{18}ClNO_2$	59.14	7.45	5.75	14.55	59.28	7.31	5.49	14.60
$C_{14}H_{21}NO_2$	71.45	9.00	5.95		71.38	8.85	5.82	
$C_{14}H_{22}INO_2$	46.28	6.11	3.86	34.93	46.15	5.99	3.81	34.69
$C_{20}H_{27}NO_5S$	61.04	6.92	3.56		60.82	6.86	3.50	
$C_{15}H_{24}ClNO_6$	51.50	6.92	4.00	10.14	51.34	7.13	4.04	10.00

Patent 948,478 (1964). The ketone has also been prepared by a very indirect route by V. Rosnati and F. De Marchi [*Tetrahedron*, **18**, 289 (1962)]. [q] This amine is recorded in ref. 20, but the method of preparation and intermediates are not disclosed. [r] Prepared by lithium aluminum hydride reduction of the acetamide [b.p. 160° (bath) (2 mm.)]; picrate, needles from aqueous methanol, had m.p. 134–138°* (*Anal.* Calcd. for $C_{18}H_{20}N_4O_9$: C, 49.54; H, 4.62; N, 12.84. Found: C, 49.81; H, 4.75; N, 12.71). [s] Described in ref. 20. [t] Prepared by lithium aluminum hydride reduction of the acetamide [b.p. 140° (0.15 mm.) $n^{26}D$ 1.5323)]. [u] The iodide is described in ref. 20. [v] From equimolar amounts of tertiary base and methyl *p*-toluenesulfonate at 85° for 12 hr. The product, in ethanol, was treated with perchloric acid.

Compounds of the type III are known[18] and were all obtained by the condensation of a catechol with a ketone in the presence of phosphorus pentoxide.[19] Attempts to apply this method to aldehyde derivatives



III

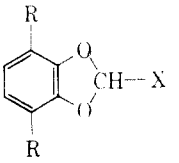
such as 2-amino- or 2-halogenoacetaldehyde diethylacetal failed, as did attempted cyclization by azeotropic distillation of a benzene solution of catechol

(18) J. Druey, *Bull. soc. chim. France*, **2**, 2261 (1935); G. Benoit and B. Millet, *ibid.*, 638 (1960); R. T. Arnold, N. Bortnick, and E. McMullen, *J. Am. Chem. Soc.*, **64**, 1410 (1942).

(19) J. Boeseken and G. Slooff, *Proc. Acad. Sci. Amsterdam*, **35**, 170, 1250 (1932); G. Slooff, *Rec. trav. chim.*, **54**, 995 (1935).

TABLE III

ADRENOLYTIC AND ADRENERGIC-NEURONE BLOCKING ACTION OF DERIVATIVES OF 1,3-BENZODIOXOLE



R	R′	X	Dose, mg./kg., s.c., to relax cat nictitating membranes to cover 30% of eye	Action on nictitating membranes of cats anesthetized with chloralose: Dose, mg./kg., I.V.	% reduction (−) or increase (+) in response to: Electrical stimulation[a]	10 γ of epinephrine
H	H	$CH_2NH_2 \cdot HCl$		25	0	−65
H	H	$CH_2N(CH_3)_2 \cdot HCl$	[b]	10	0	−85
H	H	$CH_2N(C_2H_5)_2 \cdot HCl$	[b]	25	−25	−65
H	H	$CH_2N^+(CH_3)_3 \cdot I^-$	[c]	25	−75	+100
H	H	$CH_2N^+(C_2H_5)_3 \cdot I^-$	>50	10	0[d]	+150
H	H	$CH_2NHC(NH_2)=NH \cdot HNO_3$	25–50	10	−100	+400
H	CH_3	$CH_2NH_2 \cdot HCl$		10	0	+350
H	CH_3	$CH_2N(CH_3)_2 \cdot HCl$	[b]	10	0	−65
H	CH_3	$CH_2N(C_2H_5)_2 \cdot HCl$	[b]	25	0	−90[e]
H	CH_3	$CH_2N^+(CH_3)_3 \cdot I^-$	[c]	25	−25	+85
H	CH_3	$CH_2N^+(CH_3)(C_2H_5)_2 \cdot I^-$	10–25	10	−100	+300
H	CH_3	$CH_2N^+(C_2H_5)_3 \cdot I^-$	50[b]	25	−15[d]	0
H	CH_3	$CH_2NHC(NH_2)=NH \cdot HNO_3$	25–50	10	35	+100
CH_3	CH_3	$CH_2NH_2 \cdot HCl$		10	0	0
CH_3	CH_3	$CH_2N(CH_3)_2 \cdot HCl$		10	0	−5
CH_3	CH_3	$CH_2N^+(CH_3)_3 \cdot I$	[c]	25	0[d]	+600
CH_3	CH_3	$CH_2NHC(NH_2)=NH \cdot HNO_3$	[b]	25	−20	−60

[a] Periodic stimulation (15 sec. every 2 min.) of postganglionic cervical sympathetic nerve (50 pulses/sec., 0.5 msec.). [b] No relaxation of nictitating membranes at a dose of 25 mg./kg. [c] Powerful nicotine-like drug; toxic to conscious cats. [d] Blocks effects of preganglionic nerve stimulation. [e] 10 mg./kg. increases responses to epinephrine.

and various aldehydes in the presence of *p*-toluenesulfonic acid.

1,4-Benzodioxans.—Many substituted 1,4-benzodioxans have varied and interesting biological activities. The best known compounds are the epinephrine antagonists 2-(1-piperidylmethyl)-1,4-benzodioxan (Piperoxan)[2] and 2-diethylaminomethyl-1,4-benzodioxan (Prosympal).[2] Recent variations of these structures and references are listed by Misiti, *et al.*,[20] who describe a number of related compounds prepared since the present investigation.

3,6-Dimethylcatechol (*vide infra*) reacted with epichlorhydrin, in the same way as the unsubstituted catechol,[21] to give the alcohol IIc (X = CH_2OH). The bromide IIc (X = CH_2Br) could only be obtained in poor yield, unlike the unsubstituted analog IIa (X = CH_2Br). However, the tosylates of both alcohols have been prepared in good yield using the method of Sekera and Marvel.[22] The ethyl ester IIc (X = $CO_2C_2H_5$) and both of the ketones IIa and c (X = $COCH_3$) have been obtained from the catechol and the appropriate 1,2-dibromide; the preparation of these compounds was based on the method[23] used for the ester IIa (X = $CO_2C_2H_5$). Although the ester IIc (X = $CO_2C_2H_5$) was not obtained in an analytically pure condition, its properties and quantitative conversion into the primary amide are evidence of its identity.

Reduction of the amides IIa and c (X = $CONH_2$) gave good yields of the primary amines from which the ureas and guanidines were obtained. The ester IIa (X = $CO_2C_2H_5$) gave the dimethylamide in good yield and this was reduced to the tertiary amine IIa [X = $CH_2N(CH_3)_2$]. The diethylamine IIc [X = $CH_2N(C_2H_5)_2$] was obtained in high yield, as the hydrochloride, directly from the tosylate IIc (X = $CH_2OSO_2C_6H_4CH_3$-*p*).

The 1-substituted ethylamines were synthesized from the ketones IIa and c (X = $COCH_3$) *via* the oximes which were reduced either catalytically or, better, by lithium aluminum hydride. Misiti, *et al.*,[20] record a number of compounds derived from the amine IIa [X = $CH(CH_3)NH_2$] but do not describe the preparation of this compound itself. Further derivatives are described in Table II and in the Experimental section.

3,6-Dimethylcatechol.—This catechol was required for the preparation of compounds derived from Ic and IIc; it is a constituent of coal tar, and has been synthesized[24] in small quantities. In order to obtain larger amounts, we prepared 3,6-dimethylsalicylic acid in 36% yield by the method of Baine, *et al.*,[25] but we were unable to convert this acid, or its acetate, into a suitable amide for the synthesis of the catechol (*via* the aldehyde). This failure is paralleled by our inability to esterify 3,6-dimethylsalicylic acid under conditions which are successful for salicylic acid itself. The

(20) D. Misiti, F. De Marchi, V. Rosnati, and D. Bovet, *J. Med. Pharm. Chem.*, **5**, 1285 (1962).

(21) E. Fourneau, P. Maderni, and Y. de Lestrange, *J. pharm. chim.*, **18**, 185 (1933).

(22) V. C. Sekera and C. S. Marvel, *J. Am. Chem. Soc.*, **55**, 345 (1933).

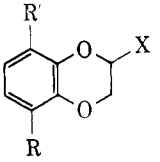
(23) J. Koo, S. Avakian, and G. J. Martin, *ibid.*, **77**, 5373 (1955).

(24) (a) W. Baker, H. F. Bondy, J. Gumb, and D. Miles, *J. Chem. Soc.*, 1615 (1953); (b) J. D. Loudon and J. A. Scott, *ibid.*, 265 (1953).

(25) O. Baine, G. F. Adamson, J. W. Barton, J. L. Fitch, D. R. Swayampati, and H. Jeskey, *J. Org. Chem.*, **19**, 510 (1954); D. Cameron, H. Jeskey, and O. Baine, *ibid.*, **15**, 233 (1950).

Table IV

Adrenolytic and Adrenergic-Neurone Blocking Action of Derivatives of 1,4-Benzodioxan



R	R′	X	Dose, mg./kg., s. c., to relax cat nictitating membranes to cover 30% of eye	Action on nictitating membranes of cats anesthetized with chloralose: Dose, mg./kg., i.v.	% reduction (−) or increase (+) in response to: Electrical stimulation[a]	10 γ of epinephrine
H	H	$CH_2NH_2 \cdot HCl$		25	0	−60
H	H	$CH_2N(CH_3)_2 \cdot HCl$	[b]	5	−40	−80
H	H	$CH_2N^+(CH_3)_3 \cdot I^-$[c]	25	25	−75	+45
H	H	$CH_2N^+(C_2H_5)_3 \cdot I^-$	[b]	25	0[d]	+50
H	H	$CH_2NHC(NH_2)=NH \cdot HNO_3$	10	10	−95	−30
CH_3	CH_3	$CH_2NH_2 \cdot HCl$		25	0	0
CH_3	CH_3	$CH_2N(CH_3)_2 \cdot HCl$	[b]	10	0	−95
CH_3	CH_3	$CH_2N(C_2H_5)_2 \cdot HCl$	[b]	10	−40	0
CH_3	CH_3	$CH_2N^+(CH_3)_3 \cdot I^-$	[f]	25	−60	+50
CH_3	CH_3	$CH_2N^+(CH_3)_2(C_2H_5) \cdot I^-$	10–20	10	−50	+200
CH_3	CH_3	$CH_2N^+(C_2H_5)_2(CH_3) \cdot I^-$	50	25	−30	+200
CH_3	CH_3	$CH_2N^+(C_2H_5)_3 \cdot I^-$	>25	25	−45[d]	[e]
CH_3	CH_3	$CH_2NHC(NH_2)=NH \cdot HNO_3$	>50	25	−40	−80
H	H	$CH(CH_3)NH_2 \cdot HCl$		25	0	−70[e]
H	H	$CH(CH_3)N(CH_3)_2 \cdot HCl$		10	−15	−80
H	H	$CH(CH_3)N(C_2H_5)_2 \cdot HI$		10	−10	−50
H	H	$CH(CH_3)N^+(CH_3)_3 \cdot C_7H_7SO_3^-$	[f]	25	−25[d]	−75
H	H	$CH(CH_3)NHC(NH_2)=NH \cdot HNO_3$	5–10	5	−100	
CH_3	CH_3	$CH(CH_3)N^+(CH_3)_3 \cdot ClO_4^-$	[f]	25	−35	+50
CH_3	CH_3	$CH(CH_3)NHC(NH_2)=NH \cdot 0.5H_2SO_4$		25	−50	−65

[a] Periodic stimulation (15 sec. every 2 min.) of postganglionic cervical sympathetic nerve (50 pulses/sec., 0.5 msec.). [b] No relaxation of nictitating membranes at a dose of 25 mg./kg. [c] M.p. 214–215°; G. B. Marini-Bettolo, R. Landi-Vittory, and L. Paoloni [*Gazz. chim. ital.*, **86**, 1336 (1956)] record m.p. 218–220°. [d] Blocks effects of preganglionic stimulation. [e] 10 mg./kg. increases responses to epinephrine. [f] Powerful nicotine-like drug; toxic to conscious cats.

methyl ester was obtained (13%) by reaction with dimethyl sulfate and potassium bicarbonate in acetone.

The desired catechol was finally prepared by carbonation of 3-methylcatechol under controlled conditions.[26] The 2,3-dihydroxy-4-methylbenzoic acid was esterified and reduced to the benzyl alcohol, which was surprisingly unstable in many solvents above about 40°, making its purification difficult. Hydrogenolysis of the alcohol in ethanol, or acetic acid containing a trace of concentrated hydrochloric acid, afforded 3,6-dimethylcatechol.

No product was obtained from methyl 2,3-dihydroxy-4-methylbenzoate and either lithium aluminum hydride–aluminum chloride[27] or potassium borohydride–lithium chloride in tetrahydrofuran.[28]

Pharmacological Results.—Compounds were investigated for adrenolytic and adrenergic-neurone blocking activity in cats.[29] The results are summarized in Tables III and IV.

Little can be said regarding the relation between structure and adrenolytic action of these compounds. The primary and tertiary amines were, in general, antagonists of epinephrine. Activity was lost by quaternization, and the guanidines gave no consistent picture. The 2-dimethylaminomethyl- and 2-diethylaminomethyl-1,4-benzodioxans were more active than the corresponding dioxoles. Introducing a methyl group into the 4-position of 2-dimethylaminomethyl- or 2-diethylaminomethyl-1,3-benzodioxole had little effect, but 2-dimethylaminomethyl-4,7-dimethyl-1,3-benzodioxole had greatly decreased adrenolytic properties. Similarly, the substitution of methyl in the 5- and 8-positions of 2-dimethylaminomethyl-1,4-benzodioxan reduced activity. An interesting compound was 2-diethylaminomethyl-4,8-dimethyl-1,4-benzodioxan, which reduced the responses to sympathetic nerve stimulation, but did not antagonize responses to epinephrine. Branching of the side chain also slightly reduced adrenolytic actions. At lower doses, several of these amines markedly increased the contraction of the nictitating membrane evoked by epinephrine, although reducing the rise in blood pressure.

True adrenergic-neurone blocking action was found only among the guanidine and quaternary ammonium compounds. 2-Guanidinomethyl-1,4-benzodioxan was a potent adrenergic-neurone blocking drug; its 1,3-benzodioxole analog was less active. Substitution of

(26) Baine, *et al.*,[25] showed that catechol reacts with carbon dioxide to give either 2,3-dihydroxybenzoic acid or 2,3-dihydroxybenzene-1,4-dicarboxylic acid, according to the reaction time and temperature. At 225° (110 atm.) for 3–4 hr., 3-methylcatechol gave an intractable mixture; but at 120–140° (70 atm.) for 4–6 hr., 2,3-dihydroxy-4-methylbenzoic acid was obtained in an average yield of 67%. This yield is the average of seven runs on 250-g. scale, it may vary from 27–79% when operating within the temperature and time range indicated.

(27) R. F. Nystrom and C. R. A. Berger, *J. Am. Chem. Soc.*, **80**, 2896 (1958).

(28) R. Paul and N. Joseph, *Bull. soc. chim. France*, 550 (1952).

(29) Experimental methods have been described in ref. 8.

methyl groups into the aromatic ring consistently reduced activity; but substitution in the side chain gave the most active compound examined, 1-(1,4-benzodioxan-2-yl)ethylguanidine.

In the trimethylammonium series, the unsubstituted benzodioxoles and benzodioxans were approximately equipotent and less active than 2-guanidinomethyl-1,4-benzodioxan. Methyl substitution in the aromatic ring of [(1,4-benzodioxan-2-yl)methyl]trimethylammonium iodide reduced activity only a little, but substitution in the side chain caused a marked fall in adrenergic-neurone blocking activity, which is in contrast to the guanidines. However, in the benzodioxole series, activity decreased following the introduction of methyl groups in the aromatic ring in either the 4- or the 4,7-positions.

Trimethylammonium was not the most effective cationic head. In the derivatives of 5,8-dimethyl-1,4-benzodioxan, the most active quaternary cationic head was ethyldimethylammonium. This compound was more active than the corresponding guanidine. Diethylmethyl[(4-methyl-1,3-benzodioxol-2-yl)-methyl]ammonium iodide was considerably more active than the trimethylammonium or the guanidine analog. Triethylammonium compounds showed little adrenergic-neurone blocking action but blocked ganglionic transmission.

Norepinephrine Depletion.—Norepinephrine was estimated[30] in the hearts of mice 6 hr. or 24 hr. after subcutaneous injection of the compounds shown in Table V. Of the six new compounds tested, only one, 2-guanidinomethyl-1,4-benzodioxan, caused a marked and long-lasting depletion, as does guanethidine.

TABLE V

EFFECT OF GUANIDINES[a] ON NOREPINEPHRINE LEVELS OF MOUSE HEART TISSUE[b]

Compd.	R	R′	X	% reduction in norepinephrine content after 6 hr.	24 hr.
I	H	H	$CH_2NHC(NH_2)=NH$	40	15
	CH_3	H	$CH_2NHC(NH_2)=NH$	0	5
	CH_3	CH_3	$CH_2NHC(NH_2)=NH$	0	5
II	H	H	$CH_2NHC(NH_2)=NH$	70	75
	CH_3	CH_3	$CH_2NHC(NH_2)=NH$	0	10
	H	H	$CH(CH_3)NHC(NH_2)=NH$	35	10
Guanethidine			$(CH_2)_7NCH_2CH_2NHC(NH_2)=NH$	85	10

[a] 20 mg./kg., s.c. [b] Each estimation was made on the pooled hearts from six animals.

2-Guaindinomethyl-1,4-benzodioxan (Guanoxan). The pharmacology of this compound was investigated in detail in experiments on anesthetized cats.[29] A dose of 5 or 10 mg./kg. quickly and permanently abolished the contractions of the nictitating membranes evoked by stimulating the postganglionic cervical sympathetic nerves, but responses to epinephrine were only transiently reduced.

Inhibitory responses were also blocked. One hour after an injection of 10 mg./kg. of guanoxan, the relaxation of the nonpregnant cat uterus, induced by hypogastric nerve stimulation, was reduced. A second dose of 10 mg./kg. abolished the response. The effect of epinephrine was unchanged. Similarly in innervated, isolated preparations of rabbit ileum, guanoxan (1.0 γ/ml.) abolished the responses to sympathetic nerve stimulation but not to epinephrine.

Parasympathetic nerve stimulation was little affected. Although the tachycardia resulting from stimulation of the inferior cardiac nerves was immediately blocked by injecting 5 mg./kg. of guanoxan, responses to vagal stimulation were unchanged. Epinephrine-induced tachycardia was antagonized for a short period. The flow of saliva from the submaxillary gland evoked by stimulating the cervical sympathetic nerve was abolished by guanoxan, but the secretion during chorda tympani stimulation was unaffected.

Experiments on the spleen showed that guanoxan acts like other adrenergic-neurone blocking drugs, namely by preventing the release, during nerve stimulation, of norepinephrine from the nerve endings.

In supine anesthetized cats the drug caused a fall in blood pressure that returned to its original level, or sometimes to a slightly lower level, within 30 min. The pressor response to bilateral carotid occlusion was reduced by 5 mg./kg. of guanoxan, but the response recovered slowly. Large doses produced a more lasting reduction. Pressor responses to tyramine were abolished, those to norepinephrine reduced for some time, and those to epinephrine transiently reversed following the injection of 5 mg./kg. of drug. Blood pressure responses to isoprenaline and to hypertensin were unchanged.

In summary, it may be stated that guanoxan is another typical adrenergic-neurone blocking agent with properties similar to those of drugs which have been described previously.[11]

Experimental[31]

Most of the new compounds prepared are listed in Tables I and II. The methods used for their preparation will be exemplified. The footnotes to the tables record any significant variation from these methods.

2-Aminomethyl-1,3-benzodioxole.—1,3-Benzodioxole-2-carboxamide[14] (18.75 g., 0.114 mole) was extracted from a Soxhlet thimble into a boiling suspension of lithium aluminum hydride (9.12 g., 0.24 mole) in ether (300 ml.). Almost all the amide had been dissolved after 24 hr., when the cooled solution was treated with ethyl acetate followed by saturated aqueous sodium sulfate until the solids adhered to the walls of the flask. The ether was decanted, and the solid washed with more ether. The combined ethereal solutions were extracted with 2 *N* HCl and dried ($MgSO_4$). Evaporation gave a pale, neutral solid (2.04 g.), whose constitution is described below.

The acid extract was basified by the addition of solid sodium carbonate and extracted with ether. The dried ($MgSO_4$) solution was distilled to give the amine (8.35 g.).

2-Acetamidomethyl-1,3-benzodioxole.—The neutral solid (1.0 g.) isolated in the previous experiment was filtered through neutral alumina (50 g., activity II) in methylene chloride solution to give a colorless solid (0.648 g.), m.p. 110–113.5°. After crystallization (see Table I) its melting point was undepressed on admixture with the product from reaction of the amine and acetic anhydride at 100° for 1 hr.

N,N-Dimethyl-1,3-benzodioxole-2-carboxamide.—Ethyl 1,3-benzodioxole-2-carboxylate[14] (35 g., 0.18 mole) was treated at 0° with dimethylamine (40 ml., 0.6 mole); after 20 min., the excess of amine was removed at reduced pressure, and the remaining orange solid was washed with ether. Crystallization

(30) Experimental methods have been described by R. Fielden and A. L. Green, *Brit. J. Pharmacol.*, in press.

(31) Melting points marked with an asterisk were determined on a Kofler block and are corrected; others were determined in a capillary tube.

from benzene–petroleum ether (b.p. 60–80°) followed by aqueous methanol gave the pure amide.

2-Ureidomethyl-1,3-benzodioxole.—Reaction between 2-aminomethyl-1,3-benzodioxole hydrochloride (0.5 g.) and sodium cyanate (0.21 g.) in water (2 ml.) at 60° gave the urea (0.43 g.).

1,3-Benzodioxole-2-carbonylurea.—A consistently successful preparation of this compound was not devised. It was obtained twice, but by different methods. One method was as follows. 1,3-Benzodioxole-2-carboxylic acid[15,32] (3.0 g., 0.018 mole) was converted into its acid chloride by boiling for 1 hr. in thionyl chloride (10 ml.) and then removing the excess of thionyl chloride at reduced pressure. This acid chloride in dry benzene (10 ml.) was added during 20 min. to finely powdered urea (1.17 g., 0.019 mole) in benzene (10 ml.) which was stirred and heated for 4 hr. Aqueous sodium bicarbonate was added, and the solid was filtered off and washed with a small amount of ethanol. Crystallization from ethanol gave needles (0.89 g.), m.p. 188–189°.

Ethyl 4-Methyl-1,3-benzodioxole-2-carboxylate.—Sodium (420 g., 18.2 g.-atoms) followed by 3-methylcatechol (1.13 kg., 9.1 moles) was dissolved in stirred ethanol (13.5 l.) under nitrogen. Ethyl dichloroacetate (1.13 l., 9.2 moles) was added during 4 hr., and the mixture was heated under reflux for 6 hr., after which most of the solvent was removed by distillation. The residue, dissolved in ether (6.5 l.), was washed exhaustively with 5% aqueous sodium bicarbonate (nine 4-l. portions), followed by water (two 2-l. portions). After drying ($MgSO_4$), the solution was distilled to give crude product (740 g.), b.p. 104–110° (0.4 mm.). A small amount of 3-methylcatechol was removed by percolation of this product in benzene through alumina, followed by redistillation.

4-Methyl-1,3-benzodioxole-2-carboxylic Acid.—The ethyl ester (70 g., 0.336 mole) was saponified by reaction under nitrogen with 9% aqueous potassium hydroxide (250 ml.) at 100° for 1 hr. After crystallization, the acid was sublimed for analysis at 105° (1 mm.).

4-Methyl-1,3-benzodioxole-2-carboxamide.—The ethyl ester (100 g., 0.48 mole) was shaken with 10% aqueous ammonia (300 ml.) for 15 min. The precipitate was dried and crystallized from benzene in needles (51.5 g.), m.p. 109–110°.

2-Guanidinomethyl-4-methyl-1,3-benzodioxole Nitrate.—2-Aminomethyl-4-methyl-1,3-benzodioxole hydrochloride (10 g., 0.05 mole) and cyanamide (10 g., 0.24 mole) were heated in boiling water (60 ml.) for 24 hr. After cooling at 0°, the mixture was filtered and solid potassium bicarbonate (5 g.) was added to the warmed filtrate. The guanidine bicarbonate was collected, suspended in hot water (40 ml.), and acidified with 8 *N* nitric acid. After refrigeration, the guanidine nitrate (11 g.) was collected.

N-(2,3-Dihydro-5-chlorobenzofuran-3-yl)-4-methyl-1,3-benzodioxole-2-carboxamide.—Ethyl 4-methyl-1,3-benzodioxole-2-carboxylate (5.17 g., 0.025 mole) and 3-amino-2,3-dihydro-5-chlorobenzofuran[8] (6.77 g., 0.04 mole) were warmed on a steam bath for 2 hr., by which time the mixture had solidified. The amide was ground up with dilute HCl and washed with water.

N-[(4-Methyl-1,3-benzodioxol-2-yl)methyl]-4-methyl-1,3-benzodioxole-2-carboxamide.—Ethyl 4-methyl-1,3-benzodioxole-2-carboxylate (2.13 g., 0.01 mole) and 2-aminomethyl-4-methyl-1,3-benzodioxole (1.86 g., 0.011 mole) were warmed on a steam bath for 2 hr. Trituration with 2 *N* HCl caused the amide to crystallize.

2-Hydroxymethyl-5,8-dimethyl-1,4-benzodioxan.—A mixture of 3,6-dimethylcatechol (16.5 g., 0.12 mole), epichlorhydrin (10 ml., 0.11 mole), and 12% aqueous KOH (50 ml.) was sealed under nitrogen and kept at 60° for 20 hr. After dilution with water, the product was extracted into ether, washed with dilute NaOH, dried ($MgSO_4$), and distilled. In addition, about 1.6 g. of 3,6-dimethylcatechol was recovered.

The **3,5-dinitrobenzoate** of the alcohol separated from ethanol in prisms, m.p. 134–135°.

Anal. Calcd. for $C_{18}H_{16}N_2O_8$: C, 55.67; H, 4.15; N, 7.21. Found: C, 55.71; H, 4.31; N, 7.32.

2-Bromomethyl-5,8-dimethyl-1,4-benzodioxan.—Phosphorus tribromide (2.2 ml., 0.023 mole) was added dropwise to the alcohol (6.0 g., 0.031 mole) in dichloromethane (5 ml.) at −70°. After 30 min. at this temperature the reaction vessel was placed in an ice bath and allowed to reach room temperature over night. Water was added and the bromide was collected in dichloromethane. The residue, after distillation of the bromide, was heated under reflux for 24 hr. with ethanol–10% aqueous KOH (1:1); ether extraction of this reaction gave the starting alcohol (4.4 g.). The yield of bromide is thus 88% based on alcohol consumed.

Ethyl 5,8-Dimethyl-1,4-benzodioxan-2-carboxylate.—3,6-Dimethylcatechol (36 g., 0.26 mole) and anhydrous potassium carbonate (26 g., 0.19 mole) were stirred under reflux in dry acetone (250 ml.) while ethyl 2,3-dibromopropionate (19.5 g., 0.075 mole) was added dropwise. Another portion of anhydrous potassium carbonate (26 g., 0.19 mole) was added in one portion, followed by more ethyl 2,3-dibromopropionate (19.5 g., 0.075 mole) dropwise. Three further portions of potassium carbonate and two of ester were added in the same way, and the mixture was stirred under reflux for 24 hr. more. After cooling, the solid was filtered off and washed with acetone. The solvent and washings were evaporated to an oil which was taken up in ether. The ethereal solution was washed with dilute NaOH and water, and the dried solution was evaporated and distilled twice, the product being collected at 100° (0.25 mm.).

This product did not give a satisfactory analysis although it was chromatographically homogeneous on alumina. The amide (see Table II) was prepared quantitatively when the ester was shaken with 35% w./w. ammonia solution.

2-Diethylaminomethyl-5,8-dimethyl-1,4-benzodioxan Hydrochloride.—2-*p*-Toluenesulfonyloxymethyl-5,8-dimethyl-1,4-benzodioxan (3.73 g., 0.0107 mole) was heated at 100° for 20 hr. with diethylamine (10 ml., 0.097 mole) in a sealed vessel. The oily residue, after evaporation, was dissolved in dilute HCl and ether; basification of the acidic layer liberated the amine, which was collected in ether and converted directly into the hydrochloride.

2-Acetyl-5,8-dimethyl-1,4-benzodioxan.—3,6-Dimethylcatechol (26 g., 0.188 mole) was stirred in refluxing dry acetone (300 ml.) and treated alternatively with four lots of anhydrous potassium carbonate (19 g., 0.137 mole) and four lots of 3,4-dibromobutan-2-one (13 g., 0.057 mole), added dropwise. The additions took 5 hr., and the mixture was stirred under reflux for a further 22 hr. The reaction was worked up in the manner described for the ester. The redistilled product had b.p. 84–89° (0.4 mm.), $n^{25}D$ 1.5304.

The **2,4-dinitrophenylhydrazone** separated from ethanol, containing a small quantity of ethyl acetate, as yellow laths with a double m.p. at 89–93° (transition of crystal form) and 154.5–156.5°.

Anal. Calcd. for $C_{18}H_{18}N_4O_6$: C, 55.96; H, 4.70; N, 14.51. Found: 55.76; H, 4.78; N, 14.44.

1-(5,8-Dimethyl-1,4-benzodioxan-2-yl)ethylguanidine Sulfate.—The amine hydrochloride (0.9 g.), cyanamide (1.1 g.), and water (10 ml.) were heated at reflux for 24 hr. After extraction with ether and addition of an excess of potassium bicarbonate, the solution deposited a solid which was collected and dissolved in dilute sulfuric acid. This solution was filtered and on standing for several days gave the crystalline sulfate. Many crystallizations from water were required to give a product with invariable melting point.

3,6-Dimethylsalicylic Acid.—2,5-Xylenol (250 g., 2.005 moles) and potassium carbonate (500 g., 3.62 moles, dried over night at 150° *in vacuo*) were mixed in a 2-l. autoclave which was charged to 50 atm. with carbon dioxide. The temperature was raised to 200° (150 atm.) over 2.5 hr. The autoclave was kept under these conditions for 3 hr. and then allowed to cool. The reaction mixture was worked up as described[25] to yield the crude acid (337 g.). Crystallization from aqueous ethanol gave two crops of fairly pure material (83 g., m.p. 192–193°, and 40 g., m.p. 182–186°; 36%) and further crystallization gave needles, m.p. 203–203.5°, ν_{maxm}^{Nujol} 1641 and 1612 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.03; H, 6.06. Found: C, 64.77; H, 6.39.

The acetate was obtained with acetic anhydride and sulfuric acid in 90% yield. It separated as needles from benzene–petroleum ether (b.p. 40–60°), m.p. 90–91°* dec. (partial resolidification) and 101°*, ν_{max}^{Nujol} 1760 and 1700 cm.$^{-1}$, lit.[33] m.p. 85°.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.68; H, 5.81.

(32) W. G. Christiansen and M. A. Dolliver, *J. Am. Chem. Soc.*, **66**, 312 (1944).

(33) L. Palfray and M. Metayer, *Bull. soc. chim. France*, 956 (1948).

Methyl 3,6-Dimethylsalicylate.—The acid (20 g., 0.133 mole), dimethyl sulfate (16.8 g., 0.133 mole), and potassium bicarbonate (100 g., 1.0 mole) were stirred in refluxing acetone (230 ml.) for 17 hr. After addition of acetic acid (10 ml.), the reaction mixture was filtered, and the filtrate was concentrated to 50 ml., poured into water (800 ml.), and extracted with ether. The desired ester (13%) was isolated by extraction into 2 *N* NaOH. It was purified as needles from petroleum ether (b.p. 40–60°), m.p. 34–35°, ν_{max}^{Nujol} 1666 and 1615 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.67; H, 6.71. Found: C, 66.62; H, 6.65.

2,3-Dihydroxy-4-methylbenzoic Acid.—3-Methylcatechol (250 g., 2.01 moles) was carbonated in the same way as 2,5-xylenol. The temperature was raised to 140° (74 atm.) over 3 hr., and then the autoclave was allowed to cool over about 18 hr. The acid was crystallized from aqueous alcohol in two crops (220 g., m.p. 206–208°, and 9.5 g., m.p. 201–204°; 68%). The pure acid has m.p. 211–211.5°; ν_{max}^{Nujol} 3528, 3520, and 1660 cm.$^{-1}$.

Anal. Calcd. for $C_8H_8O_4$: C, 57.15; H, 4.80. Found: C, 57.12; H, 5.09.

The **methyl ester** was obtained (83%) by reaction of the acid with methanol and sulfuric acid. It crystallized from aqueous ethanol: m.p. 44–44.5°; ν_{max}^{Nujol} 3560, 3507, 3477, 1680, and 1665 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found: C, 59.17; H, 5.48.

Reduction of the ester with lithium aluminum hydride in the usual way afforded **2,3-dihydroxy-4-methylbenzyl alcohol** (55–94%). It crystallized from ether–petroleum ether (b.p. 60–80°), m.p. 108–112°*, ν_{max} 3600–3100 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{10}O_3$: C, 62.31; H, 6.54. Found: C, 62.53; H, 6.58.

3,6-Dimethylcatechol.—2,3-Dihydroxy-4-methylbenzyl alcohol (50 g., 0.325 mole, m.p. 102–105°) in ethanol (1 l.) containing 10% palladium on charcoal (4 g.) was shaken under hydrogen and absorbed 7.37 l. in 5 hr. (calcd., 7.9 l.). After filtration and evaporation under reduced pressure, the brown tarry residue was extracted into boiling petroleum ether (b.p. 40–60°; four 150-ml. portions). The extracts were concentrated to give two crops of the catechol (16.5 g., m.p. 100–100.5°, and 26.9 g., m.p. 99–100°; 95%). The pure catechol was identical with a sample, m.p. 101°, kindly supplied by Professor W. Baker.[25b]

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Diuretics. 6-Substituted 3-Ketoalkyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-Dioxides and Related Anils, Oximes, and Hydrazones[1]

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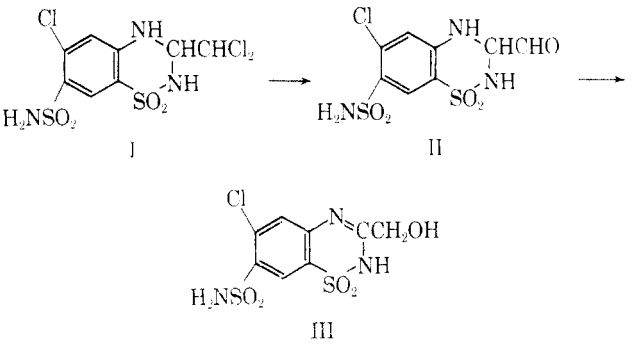
Condensation of appropriate ketoaldehydes with 5-substituted 2,4-disulfamylanilines under acid catalysis provided a group of 6-substituted 3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxides containing 3-ketoalkyl substituents. When β-ketoaldehydes were used and the 2-sulfamyl group was at least monosubstituted, either the usual ring-closure products or isomeric enol–anils were isolated depending on reaction conditions. Evidence for the enol–anil structures included interconversions between isomeric pairs and spectral and degradative studies. Unusual hydrazones and oximes were prepared and studied. Pharmacologic evaluation revealed several potent diuretic agents and other, less anticipated, biological properties for the compounds reported.

The pioneering work of Novello and Sprague, deStevens and Werner and their co-workers, as well as many other investigators, has led to an important class of diuretic and antihypertensive agents which contain a 1,2,4-benzothiadiazine ring system.[3] One especially potent member of this group reported by Topliss, *et al.*,[4] and others[3] is 6-chloro-3-dichloromethyl-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (I, trichlormethiazide). The present authors speculated that the *gem*-dichloro moiety present in this drug might be rapidly hydrolyzed *in vivo* to afford the corresponding aldehyde II. However, Sherlock[5] has shown that the acid-catalyzed reactions of glyoxaldehyde and phenylglyoxal with *o*-sulfamylanilines gave tautomeric alcohols analogous to III. This suggested that hydrolysis of I might form the alcohol rather than the isomeric aldehyde (Chart I).

CHART I



The rate of chloride ion formation from I in very dilute alkali was compared to, and found much greater than, the rate of ring opening as determined by appearance of arylamine. It was, therefore, postulated that the aldehyde II or tautomeric alcohol III might be the active metabolite of trichlormethiazide. To study this, a series of 3,4-dihydro-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxides substituted in the 6-position with chloro, trifluoromethyl, or nitro groups and in the 3-position with carbonyl-containing moieties was prepared. The well-known acid-catalyzed ring-closure reactions (Chart II) of *o*-sulfamylanilines (IV) with al-

(1) Presented before the Division of Medicinal Chemistry, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1962.

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(3) For a recent review see E. Schlittler, G. deStevens, and L. Werner, *Angew. Chem. Intern. Ed. Engl.*, **1**, 235 (1962).

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