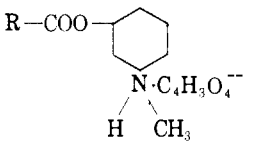
TABLE II

BIFUMARATE SALTS OF ESTERS OF N-METHYL-3-HYDROXYPIPERIDINE



No.	R	Yield, %	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1	$C_6H_5C(OH)C_2H_5$	16[a]	173–175[b]	$C_{20}H_{27}NO_7$	61.10	6.92	3.55	61.50	6.99	3.29
2	$C_6H_5C(OH)CH{=}CH_2$	14[a]	163–165[c]	$C_{20}H_{25}NO_7$	61.37	6.43	3.57	61.41	6.29	3.69
3		13[c]	154–156[b]	$C_{21}H_{25}NO_6$	65.10	6.50	3.51	65.12	6.22	3.63
4		41[d]	172–174[e]	$C_{19}H_{25}NO_5$[f]	65.68	7.25	4.02	65.66	7.33	4.09

[a] Na used in transesterification. [b] From anhydrous 1-butanol. [c] Triturated in anhydrous ether. [d] Sodium methoxide used in transesterification. [e] From anhydrous 2-propanol. [f] This compound was isolated as the fumarate salt, rather than as the bifumarate.

140–141.5°[6] and 142–143°.[14] An infrared spectrum of this compound (10% in $CHCl_3$) showed a peak at 5.96 μ (conjugated C=O).

Pharmacology.—Preliminary biological evaluation[15] of the four N-methyl-3-piperidyl esters (Table II) is summarized as follows. The compounds were administered intravenously. The ester of ethylphenylglycolic acid (**1**, Table II) produced in mice initial CNS stimulating effects followed by CNS depressant effects, at dose levels between 10 and 100 mg./kg. The stimulant activity was of short duration. The ester of vinylphenylglycolic acid (**2**, Table II) could not be clearly classified either as a CNS stimulant or as a depressant. It prolonged the hexobarbital sleeping time in mice at dose levels of 5 mg./kg., and at 3 mg./kg. it produced increased gross activity in mice. Dose levels between 10 and 100 mg./kg. produced transient initial hyperactivity and mydriasis, followed by prolonged (4–24 hr.) miosis and decreased gross activity. The ester of indene-3-acetic acid (**3**, Table II) showed CNS depressant and hypotensive properties in mice at doses of 10–30 mg./kg. However, it was not an anticonvulsant at a dose of 17 mg./kg., and at a similar dose level it did not prolong hexobarbital sleeping time. The ester of 1-hydroxytetralin-1-carboxylic acid (**4**, Table II), at dose levels of 31 mg./kg. in mice, showed slight CNS depressant activity, preceded by initial short-term signs of central stimulation. A dose of 5.6 mg./kg. had a slight hypotensive effect in rats, which seemed to be of longer duration than that seen following administration of the ester of indene-3-acetic acid (**3**). No anticonvulsant activity was observed.

Preliminary screening of the four esters in mice, using the intravenous route for hyperactivity cage and swimming maze evaluation tests,[16] revealed that **3** and **4** were inactive and that **1** and **2** (at a dose of 1 mg./kg.) were approximately as potent as atropine and $^1/_{10}$ as active as N-ethyl-3-piperidyl cyclopentylphenylglycolate[17] in producing hyperactivity and confused behavior in the swimming maze.

(15) The following biological data were provided by the Hazleton Laboratories, Inc., under the supervision of the scientific staff of the Psychopharmacology Service Center and the testing was supported under Contract No. PH43-63-555 from the National Institute of Mental Health, Bethesda, Md.

(16) We are indebted to Dr. Leo G. Abood, Illinois Neuropsychiatric Institute, Chicago, Ill., for these preliminary data.

(17) Ditran®.

Adrenergic Neurone Blocking Agents Derived from 1,4-Benzodioxan

J. ALGSTEIN, S. M. GREEN, A. M. MONRO, G. W. H. POTTER, C. R. WORTHING, AND T. I. WRIGLEY

Research Division, Pfizer Ltd., Sandwich, Kent, England

Received November 11, 1964

The structure–activity relationships existing between closely related groups of adrenergic neurone blocking agents are reviewed. 2-Guanidinomethyl-1,4-benzodioxan is an antihypertensive agent which acts primarily by preventing the release of the sympathetic transmitter from postganglionic adrenergic nerve endings. A summary of the pharmacology is given. A number of related compounds have been synthesized, and their structure–activity relationships are discussed.

In recent years great progress has been made in the drug treatment of hypertension with the advent of compounds which interfere with stimulus–release coupling at postganglionic adrenergic nerve endings, in contrast to earlier compounds which prevented transmission at the ganglionic synapse, and which caused many side effects through their indiscriminate blockade of both sympathetic and parasympathetic ganglia.

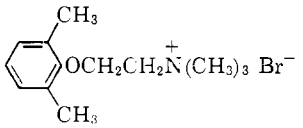
Xylocholine (I)[1] and bretylium (II)[2] have been shown to prevent the release of the adrenergic transmitter at sympathetic nerve endings. Later, guanethidine (III) emerged as an effective antihypertensive agent and was shown to exert its effects by preventing the release

(1) "TM-10": P. Hey and G. L. Wiley, *Brit. J. Pharmacol.*, **9**, 171 (1954).

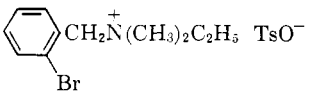
(2) (a) A. L. A. Boura, F. C. Copp, W. G. Duncombe, A. F. Green, and A. McCombrey, *ibid.*, **15**, 265 (1960); (b) A. L. A. Boura and A. F. Green, *ibid.*, **14**, 536 (1959).

of the sympathetic transmitter.[3] In addition, it produces a depletion of tissue stores of norepinephrine.[4] A recent modification of guanethidine, N-(2-guanidinoethyl)-**1**,2,3,4,5,6-hexahydro-3-benzazocine, has been reported[5] to have a similar adrenergic neurone blocking power; however, it lacks the initial transitory sympathomimetic properties of guanethidine and appears to cause only slight depletion of catechol amines.

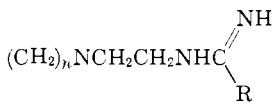
The guanidine group in III may be replaced by an amidine group to give a compound (IV)[6] of similar pharmacological action, although the optimum ring size is now seven atoms instead of eight. The compound V, containing an amidoxime group instead of the guanidine group, and previously shown to have antihypertensive properties,[7a] had no adrenergic neurone blocking properties when examined for relaxation of the cat nictitating membrane; on the other hand, tissue stores of norepinephrine were extensively depleted, and the pressor effects of indirectly acting sympathomimetic amines were antagonized.[7b]



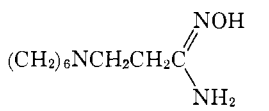
I



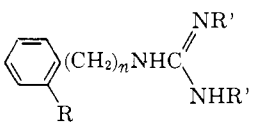
II

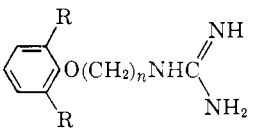


III, $n = 7$; R = NH_2
IV, $n = 6$; R = CH_3



V



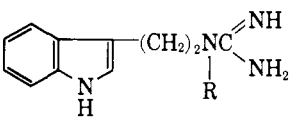


VIa, n = 1;	R = H;	R' = CH_3	VIIa, n = 2;	R = CH_3
b, n = 1;	R = Cl;	R' = CH_3	b, n = 3;	R = CH_3
c, n = 2;	R = H;	R' = CH_3	c, n = 2;	R = H
d, n = 2;	R = R' = H		d, n = 3;	R = H
e, n = 3;	R = R' = H		e, n = 3;	R = Cl

Recently, several of the structural features in the above compounds have been combined to give interesting results. Thus, bethanidine (VIa), which contains the benzyl group of II and the guanidine group of III, has an action intermediate in nature between guanethidine and bretylium, while its *o*-chloro derivative (VIb) is entirely bretylium-like in action.[8] Compound VIb, when assessed in terms of its ability to prevent guanethidine-induced release of catechol amines, was far more potent than bretylium. Further such comparisons revealed that N-alkylation of benzylguanidines led to an enhancement of activity; such compounds exerted only a slight depleting action on catechol amine stores.[9a] The introduction of an additional methylene group between the ring and the guanidine group (VIc) led to a decrease in bretylium-like activity, while simultaneous removal of the N-alkyl groups gave rise to a compound (VId) displaying primarily a guanethidine-like depletion of tissue catechol amines.[9]

Another hybrid molecule VIIa, comprising the 2,6-xylyloxyethyl group of I and the guanidine group of III, has been reported to have guanethidine-like activity.[8c,10] N-Alkylated derivatives of VIIa, and the homolog VIIb, exhibited reduced adrenergic neurone blocking properties as measured by relaxation of the cat nictitating membrane. Similar variants of 2-phenethylguanidine (VId), *viz.*, derivatives VIc and VIe, produced a reduced depletion of norepinephrine in rat hearts.[9] Compound VIIc, deficient in the 2,6-dimethyl substituents of VIIa, also gave rise to reduced adrenergic neurone blocking properties. However, 3-phenoxypropylguanidine (VIId)[11] elicited an initial pressor response followed by a prolonged hypotensive phase in dogs, paralleled by a powerful depletion of tissue stores of norepinephrine in rats. This compound did not display any adrenergic neurone blocking properties. Introduction of 2,6-dichloro substituents into VIId to give VIIe, resulted in a compound, the activity of which falls into the above pattern in that a powerful adrenergic neurone blockade was again observed on the cat nictitating membrane.[12]

The complexity of the structure–activity pattern arising from N-alkylation of guanidines is further illustrated by the claim[13] that in compounds of type VIII, good hypotensive activity was obtained from compounds in which R represents an alkyl group.



VIII

Thus, it seems that molecules consisting of a strongly basic group attached to a suitable ring by a short alkylene or oxyalkylene chain can give rise to a considerable spectrum of activity on the peripheral adrenergic nervous system. This can range from a predominant bretylium-like inhibition of the release of the sympathetic transmitter to a predominant depletion of the transmitter with no initial inhibition of its release in response to nerve stimulation. It can be seen that slight molecular variations within this class of compounds can swing the activity from one extreme to the other, and it is important when discussing structure–activity relationships within this area to indicate

(3) (a) R. P. Mull, M. E. Egbert, and M. R. Dapero, *J. Org. Chem.*, **25**, 265 (1960); (b) C. Hertting, J. Axelrod, and R. W. Patrick, *Brit. J. Pharmacol.*, **18**, 161 (1962); (c) R. Cass and T. L. B. Spriggs, *ibid.*, **17**, 442 (1961); (d) R. A. Maxwell, A. J. Plummer, H. Povalski, and F. Schneider, *J. Pharmacol. Exptl. Therap.*, **129**, 24 (1960).

(4) (a) R. Cass, R. Kuntzman, and B. B. Brodie, *Proc. Soc. Exptl. Biol. Med.*, **103**, 871 (1960); (b) H. Sheppard and J. Zimmerman, *Pharmacologist*, **1**, 69 (1959).

(5) K. Hermansen, *Acta Pharmacol. Toxicol.*, **20**, 201 (1963).

(6) F. C. Copp, A. L. A. Boura, and A. F. Green, *Nature*, **195**, 1213 (1962).

(7) "Su 4029"; (a) R. P. Mull, P. Schmidt, M. R. Dapero, J. Higgins, and M. J. Weisbach, *J. Am. Chem. Soc.*, **80**, 3769 (1958); (b) R. A. Maxwell and F. L. Schneider, *J. Pharmacol. Exptl. Therap.*, **134**, 347 (1961).

(8) (a) A. L. A. Boura and A. F. Green, *Brit. J. Pharmacol.*, **20**, 36 (1963); (b) A. F. Green and R. D. Robson, *ibid.*, **22**, 349 (1964); (c) 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).

(9) (a) E. Costa, R. Kuntzman, G. L. Gessa, and B. B. Brodie, *Life Sci.*, **1**, 75 (1962). (b) For a discussion of structure–activity relationships in phenyl- and phenoxyalkylguanidines see F. C. Copp in "Advances in Drug Research," Vol. 1, N. J. Harper and A. B. Simmonds, Ed., Academic Press Inc., New York, N. Y., 1964, p. 182.

(10) 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).

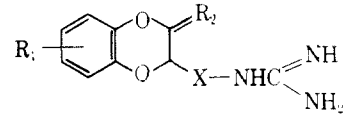
(11) (a) G. Chen, C. R. Ensor, D. A. McCarthy, J. R. McLean, and A. Campbell, *J. Pharmacol. Exptl. Therap.*, **143**, 374 (1964); (b) A. L. Bartlett, *Brit. J. Pharmacol.*, **18**, 475 (1962).

(12) Parke, Davis and Co., French Patent 1788M (March 26, 1962).

(13) N. V. Philips, Belgian Patent 642,025 (Jan. 3, 1963).

TABLE I

2-GUANIDINOALKYL-1,4-BENZODIOXANS

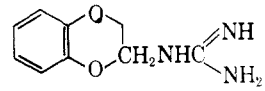


No.	Effect on N.M.[a] 5 mg./kg.	20 mg./kg.	R1	R2	X	Method of prepn.[b]	M.p., °C.	Solvent[c]	Formula	Calcd., % C	H	N	Found, % C	H	N
1	+	+ + +	H	H2	CH2	A	205–208	W	$C_{10}H_{13}N_3O_2 \cdot 0.5H_2SO_4$[d]	46.87	5.51	16.40	46.71	5.36	16.68
						C	170–175	W	$C_{10}H_{13}N_3O_2 \cdot C_7H_8O_3S$[e]	53.82	5.58	11.08	53.75	5.80	11.20
2	+	+ + +	H	H2	$(CH_2)_2$	A	246–248	W	$C_{11}H_{15}N_3O_2 \cdot 0.5H_2SO_4$	48.88	5.97	15.55	48.62	6.02	15.51
3	+	+ +	1C	H2	$(CH_2)_3$	A	202–205	W	$C_{12}H_{17}N_3O_2 \cdot 0.5H_2SO_4$	50.69	6.38	14.78	50.58	6.33	14.68
4	+	+ +	H	H2	CH(CH3)	B	250–251	W	$C_{11}H_{15}N_3O_2 \cdot 0.5H_2SO_4$	48.88	5.97	15.55	48.52	5.73	15.21
5	0	+	5-CH3	H2	CH2	C	206–207	1-W	$C_{11}H_{15}N_3O_2 \cdot C_7H_8O_3S$[e]	54.95	5.89	10.68	55.35	5.86	11.00
6	+	+ +	6-CH3	H2	CH2	A	215–218	W-E	$C_{11}H_{15}N_3O_2 \cdot 0.5H_2SO_4$	48.88	5.97	15.55	49.02	6.01	15.16
7	+ +	+ + +	7-CH3	H2	CH2	A	214–216	W	$C_{11}H_{15}N_3O_2 \cdot 0.5H_2SO_4$	48.88	5.97	15.55	48.84	5.79	15.39
8S	+	+ + +	8-CH3	H2	CH2	A	260–262	W	$C_{11}H_{15}N_3O_2 \cdot 0.5H_2SO_4$	48.88	5.97	15.55	48.85	5.82	15.84
8T						C	174–175	M	$C_{11}H_{15}N_3O_2 \cdot C_7H_8O_3S$[e]	54.95	5.89	10.68	54.90	5.81	10.99
9	0	0	5,7-$(CH_3)_2$	H2	CH2	C	162–164	W	$C_{12}H_{17}N_3O_2 \cdot C_7H_8O_3S$[e]	56.01	6.19	10.31	56.08	6.08	10.13
10	0	−	5,8-$(CH_3)_2$	H2	CH2	C	214–215	E	$C_{12}H_{17}N_3O_2 \cdot C_7H_8O_3S$[e]	56.01	6.19	10.31	56.30	6.27	10.30
11	0	0	6,7-$(CH_3)_2$	H2	CH2	C	187–188	E	$C_{12}H_{17}N_3O_2 \cdot C_7H_8O_3S$[e]	56.01	6.19	10.31	55.89	6.23	9.67
12	0	0	7-CH3O	H2	CH2	A	224–227	W	$C_{11}H_{15}N_3O_3 \cdot 0.5H_2SO_4$	46.15	5.63	14.68	45.88	5.40	14.53
13	0	0	6-CH3CO	H2	CH2	C	216–219	W	$C_{13}H_{17}N_3O_4 \cdot C_7H_8O_3S$[e]	54.15	5.50	9.97	54.06	5.68	9.76
14	0	0	5-Cl	H2	CH2	C	201–203	W	$C_{11}H_{12}ClN_3O_2 \cdot C_7H_8SO_4$[f]	49.36	4.88	10.15	49.81	4.75	9.93
15	0	+ + +	7-Cl	H2	CH2	A	222–224	W	$C_{11}H_{12}ClN_3O_2 \cdot 0.5H_2SO_4$	41.31	4.51	14.49	41.56	4.21	14.42
16	−	+ −	6,7-Cl2	H2	CH2	A	277–279	W	$C_{11}H_{11}Cl_2N_3O_2 \cdot 0.5H_2SO_4$	36.91	3.72	12.93	36.58	3.40	12.99
17	0	0	6-NO2	H2	CH2	C	224–227	W	$C_{11}H_{12}N_4O_4 \cdot C_7H_8O_3S$[e]	48.14	4.75	13.20	48.14	4.28	13.56
18	0	0	7-NO2	H2	CH2	A	256–265	W	$C_{11}H_{12}N_4O_4 \cdot 0.5H_2SO_4$	39.87	4.35	18.60	39.76	4.38	18.43
19	0	0	8-NO2	H2	CH2	C	162–164	E	$C_{11}H_{12}N_4O_4 \cdot C_7H_8O_3S$[e]	48.14	4.75	...	47.68	4.51	...
20	−	+ + +	H	H, CH3	CH2	A	265–268	W	$C_{11}H_{15}N_3O_2 \cdot 0.5H_2SO_4$	48.88	5.97	15.55	48.67	6.01	15.86
21	0	0	H	(CH3)2	CH2	C	168–170	W	$C_{12}H_{17}N_3O_2 \cdot C_7H_8O_3S$[e]	56.01	6.19	10.31	55.86	6.46	10.03
22	0	0	2-Guanidinomethylnaptho-[2,3-b]-1,4-dioxan			A	256–258	W-E	$C_{15}H_{17}N_3O_2 \cdot 0.5H_2SO_4$	54.90	5.27	13.72	54.95	5.55	13.42

[a] N.M. = nictitating membrane: percentage of eye covered: 0 (<15%), + (15–30%), ++ (30–50%), +++ (>50%). On this scale guanethidine was rated ++ to 5 mg./kg.) and +++ to 20 mg./kg.). [b] See Experimental section. Yields varied from approximately 20–70% and were not necessarily optimal. [c] Recrystallization solvents: E = ethanol, Et = ether, I = 2-propanol, M = methanol, W = water. [d] Other salts (all giving satisfactory analytical figures) prepared from the sulfate were: nitrate, m.p. 163–165°; hydrochloride, m.p. 147–148°; hydrogen maleate, m.p. 129–131°; bicarbonate, m.p. 175–176°. [e] *p*-Toluenesulfonate.

which pharmacological action is under consideration, and what parameters are being used to evaluate it.

One might deduce from the above review that the structural requirements for a compound to show activities of the types in question are (a) features which provide specific affinity for adrenergic nerve endings (bretylium has been shown to be selectively accumulated in adrenergic nerve fibers[2a]), and (b) a strongly basic grouping such as guanidine, amidine, amidoxime, or quaternary ammonium. As early as 1938, Kuroda reported[14] that 2-phenoxyethylguanidine (VIIc) lowered the blood pressure in the rabbit, presumably due, at least in part, to the recently demonstrated adrenergic neurone blockage.[10] We have previously shown that 2-(*o*-methoxyphenoxy)ethylamine derivatives apparently possess a greater affinity for adrenergic structures than do unsubstituted 2-phenoxyethylamines.[15] Applying these two findings to a search for adrenergic neurone blocking agents, we prepared 2-(*o*-methoxyphenoxy)ethylguanidine.[16] This compound was found to be slightly more potent, although its duration of action was shorter, than bretylium in the pharmacological tests described below. The structural relationship of 2-(*o*-methoxyphenoxy)ethylamine to 2-aminomethyl-1,4-benzodioxan is apparent, and the similarity in their biological properties was pointed out many years ago by Bovet.[17] This analogy led us to synthesize 2-guanidinomethyl-1,4-benzodioxan (IX). This compound was found to produce considerable adrenergic neurone blockade and to have useful antihypertensive properties. Consequently, a number of related compounds were synthesized and their structure–activity relationships investigated.



IX

Pharmacology[18]

Compounds were administered subcutaneously at two dose levels to conscious cats, and the degree of relaxation of the nictitating membrane was observed after 20 hr. (Tables I and II). This relaxation, in the absence of mydriasis, was considered to be an indication of this adrenergic neurone blocking potency. The more active compounds were examined for their ability to deplete tissue catechol amine levels in rats and for cardiovascular effects in dogs.

A study of the detailed pharmacology of **1** showed that it has a potency similar to, although slightly shorter

(14) A. Kuroda, *Folia Pharmacol. Japon.*, **19**, 1 (1934); *Chem. Abstr.*, **29**, 1504 (1935).

(15) J. Aogstein, W. C. Anstin, R. J. Boscott, S. M. Green, and C. R. Worthing, *J. Med. Chem.*, **8**, 356 (1965).

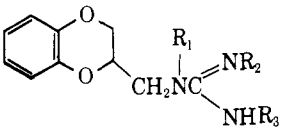
(16) This compound is mentioned in ref. 8c, as possessing adrenergic neurone blocking properties.

(17) D. Bovet and F. Bovet-Nitti, "Structure et Activité Pharmacodynamique des Médicaments du Système Nerveux Végétatif," Verlag S. Karger, S. A., Basel, 1948, p. 275.

(18) We wish to thank our colleagues in the Pharmacology Department who have supplied us with the biological results discussed in this paper. For the detailed pharmacology of guanoxan, see M. J. Davey and H. Rener, *Brit. J. Pharmacol.*, **24**, 29 (1965). For a preliminary announcement see J. Angstein and S. M. Green, *Nature*, **201**, 628 (1964).

TABLE II

N-SUBSTITUTED 2-GUANIDINOMETHYL- AND OTHER 2-SUBSTITUTED 1,4-BENZODIOXANS



No.	Effect on N.M.[a] 5 mg./kg.	20 mg./kg.	R_1	R_2	R_3	Method of prepn.[b]	M.p., °C.	Solvent[c]	Formula	Calcd., % C	H	N	Found, % C	H	N
23	0	0	H	H	CH_3	A[d]	156–159	M–Et	$C_{11}H_{15}N_3O_2 \cdot C_{20}H_{18}O_8$[e]	61.28	5.47	6.92	61.51	5.36	6.93
24	0	0	H	CH_3	CH_3	A[f]	144	M	$C_{12}H_{17}N_3O_2 \cdot C_{20}H_{18}O_8$[e]	61.83	5.68	6.76	62.16	5.96	6.60
25	0	0	CH_3	H	H	A	267–269	W	$C_{11}H_{15}N_3O_2 \cdot 0.5H_2SO_4$	48.88	5.97	15.55	49.30	5.86	15.22
26	0	0	H	$-CH_2CH_2-$		A[g]	173–174	M	$C_{12}H_{15}N_3O_2 \cdot C_{20}H_{18}O_8$[e]	62.03	5.37	6.78	61.78	5.29	6.86
27	0	0	H	H	NH_2	A[h]	110–111	E-Et	$C_{10}H_{14}N_4O_2 \cdot HI$	34.30	4.32	16.00	33.95	4.30	16.18
28	0	+	H	NH_2	NH_2	A[i]	220–221	W	$C_{10}H_{15}N_5O_2 \cdot HI$	32.88	4.42	19.18	33.00	4.40	19.44
29	0	+	H	H	$C(=NH)NH_2$	[j]	169	W	$C_{11}H_{15}N_5O_2 \cdot C_7H_8O_3S$[j]	51.30	5.50	16.62	51.37	5.40	16.62
30	+	++	2-(1,4-Benzodioxanyl)acetamidine			[b]	225–227	E-Et	$C_{11}H_{12}N_2O_2 \cdot HCl$	52.50	5.73	12.25	52.68	5.73	12.27
31	+	[k]	2-(1,4-Benzodioxyanyl)acetamidoxime			[h]	123–124	E	$C_{11}H_{12}N_2O_3$	57.68	5.81	13.46	57.30	6.05	13.21
32	0	+	2-(1,4-Benzodioxanyl)methylisothiourea			[b]	188–190	E	$C_{11}H_{12}N_2O_2S \cdot HBr$	39.35	4.29	9.18	39.22	4.28	9.31

[a] Footnote *a*, Table I. [b] Footnote *b*, Table I. [c] Footnote *c*, Table I. [d] By reaction with N,S-dimethylisothiourea hydriodide [M. Schenk, *Arch. Pharm.*, **249**, 478 (1911)] in dimethylformamide (DMF) containing a little water. [e] Di-*p*-toluoyltartrate. [f] By reaction with N,N',S-trimethylisothiourea hydriodide (ref. *d*) as in *d*. [g] By reaction with 2-methylthio-2-imidazoline hydriodide [S. R. Aspinall and E. J. Bianco, *J. Am. Chem. Soc.*, **73**, 602 (1951)] as in *d*. [h] By reaction with S-methylisothiosemicarbazide hydriodide (ref. *d*) in water. [i] By reaction with S-methylisothiocarbohydrazide hydriodide [E. S. Scott and L. F. Audrieth, *J. Org. Chem.*, **19**, 1231 (1954)] in DMF, the product being isolated by addition of methanol and ether to the cooled reaction mixture. [j] *p*-Toluenesulfonate. [k] Cat convulsed and died.

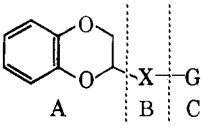
in duration, than guanethidine in causing relaxation of the nictitating membrane. Experiments with the isolated cross-perfused cat spleen indicated that the adrenergic neurone blockade was due to a prevention of the release of norepinephrine on nerve stimulation, this effect being reversed by (+)-amphetamine. The adrenergic neurone blockade induced by xylocholine, guanethidine, and bretylium was similarly reversed by (+)-amphetamine,[19] thus suggesting a common mechanism of action. In addition, **1** antagonized the effects of epinephrine and norepinephrine at α-receptor sites. Guanethidine, on the other hand, potentiates the effects of epinephrine and norepinephrine.[3d] Compound **1** depleted the norepinephrine content of the heart and spleen, and by contrast with guanethidine, also the hypothalamus in dogs and rabbits. Chronic oral administration of **1** (10 mg./kg.) to conscious beagle dogs with chronic nephrogenic or neurogenic hypertension produced a pronounced antihypertensive effect with gradual onset of action; no tolerance developed over 17 weeks' administration. During this period the pressor effects of tyramine were abolished. Injection of **1** into the lateral ventricle antagonized the defense reaction evoked by hypothalamic and epithalamic stimulation in cats. The compound has been the subject of several clinical trials[20] and was shown to have valuable antihypertensive properties in man.

When viewed in the context of the types of pharmacological actions discussed in the introduction, it is apparent that this compound lies close to guanethidine with respect to its ability both to cause adrenergic neurone blockade and to deplete peripheral stores of catechol amines. By contrast, it does deplete hypothalamic and adrenal catechol amine stores, which guanethidine does not,[4] and possesses a potent classical adrenolytic action in the dog.

(19) M. D. Day, *Brit. J. Pharmacol.*, **18**, 421 (1962).

(20) W. S. Peart and M. T. McMahon, *Brit. Med. J.*, **1**, 398 (1964). This compound has been given the generic name of guanoxan [*ibid.*, **1**, 216 (1964)]; Envacar®.

Structure-Activity Relationships.—Ability of the compounds to relax the nictitating membrane in the cat has been taken as a measure of adrenergic neurone blocking activity. The relative activity of the compounds can be discussed in terms of the structural features indicated as A, B, and C.



A.—In 2-guanidinomethyl-1,4-benzodioxans, introduction of single methyl groups into the benzene ring gives rise to an increasing activity as the substitution changes from position 5 through 8. Compound **5** is almost inactive, **7** is about equiactive with **1**, and 8, at the higher dose level, caused the most pronounced relaxation of the nictitating membrane yet observed in our laboratories. However, introduction of a second methyl group into **7** and 8, giving 5,7-, 6,7-, and 5,8-disubstitution (**9**–**11**) caused the loss of all activity.

Compound 8 was examined further for its cardiovascular effects in dogs. In anesthetized animals, it behaved like **1** in antagonizing the effects of norepinephrine and reversing those of epinephrine. In small doses (1–5 mg./kg.) the compound potentiated the pressor effects of tyramine, whereas in large doses (10 mg./kg.) such effects were antagonized. When administered orally (10 mg./kg.) for 12 days to conscious dogs, it produced a satisfactory fall in blood pressure, without development of tolerance. At 20 mg./kg. the pressor response to tyramine was inhibited by approximately 50%. A determination of catechol amine levels in rat tissues indicated that the compound, when compared with **1**, had relatively little effect on tissue stores of catechol amines.

Chlorine substitution follows a somewhat similar pattern. Substitution in the 7-position (**15**) maintained a fair activity, while this was lost by substitution in the

5-position (**14**). However, the 6,7-disubstituted compound (**16**) retained some activity (*cf.* **11**).

Compounds **7** and **15** exhibited similar effects on the cardiovascular system in anesthetized dogs. At 5 mg./kg., neither compound affected the pressor responses to epinephrine and norepinephrine, while the former markedly potentiated and the latter only slightly antagonized the pressor effects of tyramine.

Substitution by one methyl group in the 3-position (**20**, a mixture of *cis* and *trans* isomers) shortened the duration of action relative to **1**. The separation of the isomers is under investigation to determine whether the biological activity is derived from one or both isomers. Introduction of a second methyl group (**21**) abolished activity. All other ring substitutions described in this paper abolish the activity shown by **1**.

B.—The pattern here follows approximately that reported for 2-(2,6-xylyloxy)ethylguanidines.[10] Compound **2**, in which the chain has been extended by one carbon atom maintained the adrenergic neurone blocking capacity, whereas introduction of a branch methyl group (**4**) or a three-carbon chain (**3**) gave rise to analogs with considerably diminished activity.

Determination of catechol amine levels in rat tissues revealed that **2** had a depleting power intermediate between that of **1** and **8**. In anesthetized dogs (5 mg./kg.) it showed only a brief antagonism toward the pressor effects of tyramine (*cf.* **1** which caused prolonged blockade and **8** which, at the same dose level, potentiated the effect).

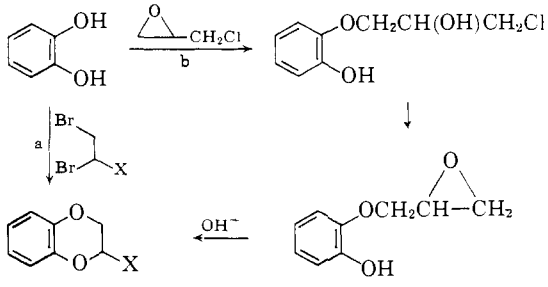
C.—In parallel with the findings in other series of antihypertensive guanidines,[3a,10,21] substitution by alkyl groups in any position on the guanidine group (**23–26**) led to a decrease in activity. This is in direct contrast to benzylguanidines[8c] in which activity increases upon N-alkylation. Only marginal activity was observed with the diaminoguanidine (**28**), the biguanide (**29**), and the amidine (**30**).

To summarize, maximum adrenergic neurone blocking activity is displayed by 2-guanidinomethyl- and 2-(2-guanidinoethyl)-1,4-benzodioxan, optionally substituted in the 7- or 8-position by a methyl group. Substitution in the 7-position abolishes the adrenolytic effects shown by the parent compound.

Chemistry

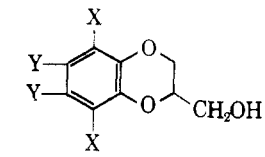
2-Substituted 1,4-benzodioxans have been synthesized in the past by two general methods. Treatment of catechol with a vicinal dibromide or an epihalohydrin (or suitable precursor such as 1,3-dihalopropan-2-ol) in the presence of a base yields 1,4-benzodioxans, as illustrated in Scheme I. Under the appropriate conditions, the intermediate chlorohydrin and glycide ether can be isolated.[22]

SCHEME I

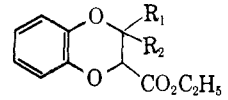


Route a, X = H, $COCH_3$, CO_2R
Route b, X = CH_2OH

These two general methods have been applied by us to obtain 1,4-benzodioxans with functional groups in the 2-position, in which the benzene ring is either unsubstituted or symmetrically disubstituted. Thus, by reaction of the appropriate disubstituted catechol with epichlorohydrin, 1,4-benzodioxans Xa–d were obtained, and condensation of catechol with ethyl α,β-dibromobutyrate or ethyl α,β-dibromoisovalerate yielded XIa and b, respectively, the former as a mixture of *cis* and *trans* isomers.



Xa, X = H; Y = CH_3
b, X = H; Y = Cl
c, X = CH_3; Y = H
d, X = H; Y_2 =

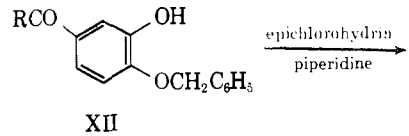


XIa, R_1 = H; R_2 = CH_3
b, R_1 = R_2 = CH_3

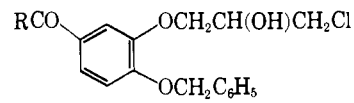
If unsymmetrically substituted catechols are subjected to either of the above two reactions, two isomers can arise, and special methods are often necessary for their synthesis.

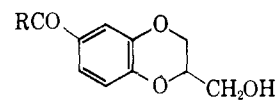
6-Acyl-2-hydroxymethyl-1,4-benzodioxans (XIII, R = H or CH_3) were prepared according to the method of Paulsen,[23] which is based on a selective monobenzylation of the appropriate acylcatechols to give XII. These others were subsequently treated as shown in Scheme II to yield the 6-acyl-1,4-benzodioxans.

SCHEME II



XII





XIII

By this procedure,[24] 6-formyl-2-hydroxymethyl-1,4-benzodioxan was obtained and reduced to the corresponding 6-methyl compound. This was shown to be identical with the major product of a reaction between 4-methylcatechol and epichlorohydrin. The identity was confirmed by contrasting the infrared spectra and vapor phase chromatographic (v.p.c.) characteristics of the alcohol and its derivatives with those of the

(21) J. H. Short, U. Biermacher, D. A. Dunnigan, and T. H. Lerk, *J. Med. Chem.*, **6**, 275 (1963).

(22) O. Stephenson, *J. Chem. Soc.*, 1571 (1954).

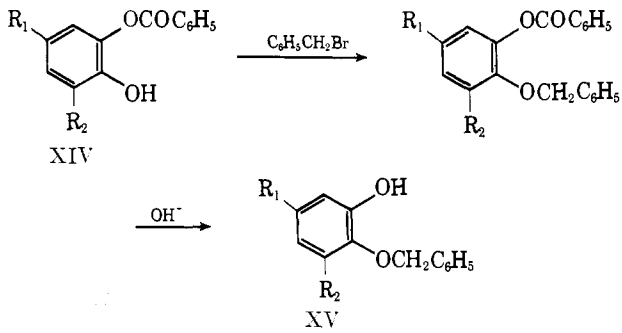
(23) A. Paulsen, *Acta Polytech. Scand., Chem. Met. Ser.*, **6**, 11 (1960); *Chem. Abstr.*, **55**, 22318 (1961).

(24) A. Funke and A. Paulsen, *Gazz. Chim. Ital.*, **91**, 1268 (1961).

corresponding 7-methyl isomer, which was prepared by a different unambiguous route (*vide infra*).

The reaction of 3-methylcatechol with epichlorohydrin has been claimed[25] to yield 2-hydroxymethyl-5-methyl-1,4-benzodioxan, although no proof of structure was given. We have concluded from infrared spectroscopy and v.p.c. that the product of this reaction was, in fact, largely (*ca.* 90%) the 8-methyl isomer. In a similar manner, reaction of 3-methylcatechol with ethyl 2,3-dibromopropionate yielded a mixture of the 5- and 8-methyl-2-ethoxycarbonyl-1,4-benzodioxans, with the latter predominating. In order to characterize the above two mixtures, pure 2-hydroxymethyl-8-methyl-1,4-benzodioxan was prepared by the reduction of the corresponding 8-formyl compound, itself prepared by the unambiguous synthesis of Paulsen.[23] This pure 2-hydroxymethyl-8-methyl-1,4-benzodioxan was converted *via* the tosylate ester to the corresponding 2-guanidinomethyl derivative (**8T**, Table I). As this synthesis proved unsuitable for the preparation of a sufficient quantity of 8, pharmacological studies were carried out on material **8S** derived from the readily available product of the reaction of 3-methylcatechol and epichlorohydrin. The biological acitivity of **8S**, when contrasted with the virtual inactivity of **5**, indicated that the former indeed consisted mainly of the 8-methyl isomer.

To prepare the 6- and 8-nitro-1,4-benzodioxan analogs, *o*-hydroxyphenyl benzoate was nitrated.[26] The two mononitro products XIVa and b were separated and



XV

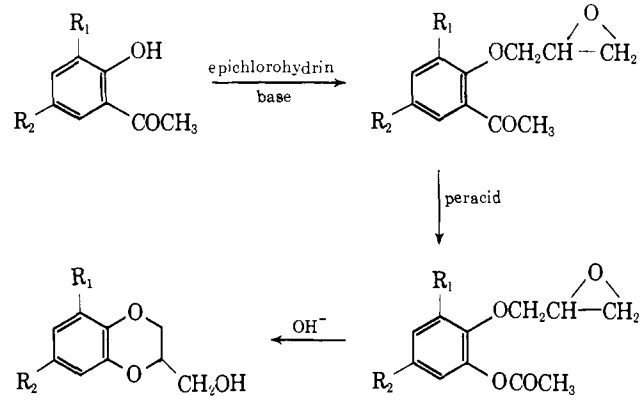
a, R_1 = H; R_2 = NO_2
b, R_1 = NO_2; R_2 = H

each was treated as shown in the reaction scheme. The nitrated monobenzyl ethers (XV) were subsequently treated with epichlorohydrin, debenzylated, and cyclized as depicted in Scheme II to give the corresponding 2-hydroxymethyl-1,4-benzodioxans.

7-Chloro- and 7-methoxy-2-chloromethyl-1,4-benzodioxans were prepared according to the literature[27] *via* direct nitration of 2-chloromethyl-1,4-benzodioxan, followed by classical synthetic steps. The product from the reaction of 4-chlorocatechol and epichlorohydrin was treated with thionyl chloride, and the 2-chloromethyl derivative so obtained was compared with authentic 7-chloro-2-chloromethyl-1,4-benzodioxan prepared by the direct nitration procedure. The close similarity of the infrared spectra and the failure to separate (v.p.c.) the authentic material from the major component (*ca.* 95%) of the product obtained from 4-chlorocatechol led us to assume that the major component was the 7-chloro isomer. The desired 2-guanidinomethyl derivative (**15**) was therefore prepared *via* the 2-chloromethyl intermediate derived from 4-chlorocatechol.

A new method, illustrated in Scheme III, was developed for the preparation of other unsymmetrically substituted 1,4-benzodioxans. The appropriate *o*-

SCHEME III



XVIa, R_1 = CH_3; R_2 = H
b, R_1 = H; R_2 = CH_3
c, R_1 = Cl; R_2 = H
d, R_1 = R_2 = CH_3

hydroxyacetophenones were prepared by Fries rearrangement and then treated with epichlorohydrin and alkali to give the glycide ethers. These were subjected to Baeyer–Villiger oxidation to yield the acetoxy intermediates, which were saponified and cyclized in one step. When the acidic conditions of the Baeyer–Villiger oxidation led to opening of the epoxide ring, the epoxides were converted to chlorohydrins prior to the oxidation. The 1,4-benzodioxans XVIa–d were obtained by this new procedure.

The required 2-guanidinoalkyl derivatives were elaborated by two general methods; the appropriate amines were treated with S-methylisothiourea sulfate[28] or with a salt of 1-amidino-3,5-dimethylpyrazole[21,29]; alternatively, the tosylate of a 2-hydroxymethyl-1,4-benzodioxan was treated with guanidine.[30]

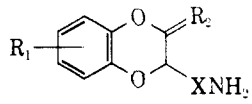
The appropriate amines were prepared by a variety of methods. Esters XI were subjected to ammonolysis and subsequent lithium aluminum hydride reduction. 2-Halomethyl derivatives were converted to amines by one of three methods: (a) preparation of the corresponding 2-benzylamino derivative and subsequent catalytic hydrogenolysis; (b) preparation of the 2-azidomethyl derivative, followed by lithium aluminum hydride reduction; and (c) preparation of the 2-N-phthalimidomethyl derivative and subsequent cleavage with hydrazine.

The precursor amines for **3** and **4** were prepared by methods representing improvements over those described in the literature. 2-Acetyl-1,4-benzodioxan, prepared by a simple condensation of catechol with 3,4-dibromobutan-2-one rather than by the circuitous literature method,[31] was converted to the oxime and re-

(25) J. R. Geigy, British Patent 565,573 (Nov. 16, 1944).
(26) D. H. R. Barton, W. H. Linnell, and N. Senior, *Quart. J. Pharm. Pharmacol.*, **18**, 41 (1945).
(27) G. B. Marini-Bettolo and R. Landi-Vittory, *Gazz. chim. ital.*, **87**, 1038 (1957).
(28) B. Rathke, *Ber.*, **14**, 1774 (1881).
(29) F. L. Scott, D. G. O'Donovan, and J. Reilly, *J. Am. Chem. Soc.*, **75**, 4053 (1953).
(30) A. M. Monro, *Chem. Ind.* (London), 1806 (1964).
(31) V. Rosnati and F. De Marchi, *Tetrahedron*, **18**, 289 (1962).

TABLE III

2-AMINOALKYL-1,4-BENZODIOXANS



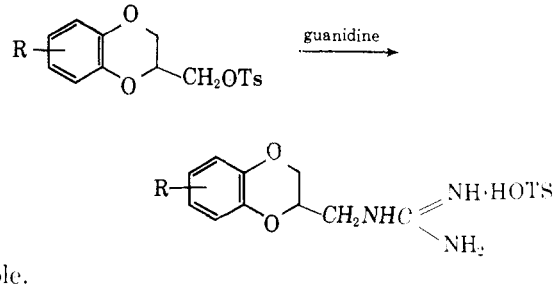
R_1	R_2	X	Method	M.p. or b.p. (mm.), °C.	$n^{25}D$	Formula	Calcd., % C	H	N	Found, % C	H	N
H	H_2	CH_2	1, J[a,b]	92–94 (0.4)	1.5583	$C_9H_{11}NO_2 \cdot HCl$[c]	53.60	5.95	6.95	53.61	5.76	6.89
H	H_2	$(CH_2)_2$	[d]	157–158[e]	...	$C_{10}H_{13}NO_2 \cdot HCl$	55.68	6.53	6.49	55.48	6.37	6.32
H	H_2	$(CH_2)_3$	[f]	100–102 (0.08)	1.5430	...	...	...	...	...	...	...
H	H_2	$CH(CH_3)$	[g]	...	...	...	...	...	...	...	...	...
6-CH_3	H_2	CH_2	1	124 (0.02)	1.5502	$C_{10}H_{13}NO_2$	67.02	7.31	...	67.13	7.18	...
7-CH_3	H_2	CH_2	1	96 (0.02)	1.5500	$C_{10}H_{13}NO_2$	...	...	7.82	...	...	7.87
8-CH_3	H_2	CH_2	1	110–120 (0.1)	1.5479	$C_{10}H_{13}NO_2$	67.02	7.31	...	67.22	7.21	...
7-CH_3O	H_2	CH_2	1	106–110 (0.01)	1.5562	$C_{10}H_{13}NO_3$	61.52	6.71	...	61.52	6.56	...
7-Cl	H_2	CH_2	J	112–116 (0.02)	1.5656	...	...	...	...	...	...	...
6,7-Cl_2	H_2	CH_2	J	58–60	...	...	...	...	...	...	...	...
7-NO_2	H_2	CH_2	h	142 (0.02)	...	...	...	...	...	...	...	...
2-Aminomethylnaphtho[2,3-*b*]-1,4-dioxan			J	171–173[i]	...	$C_{13}H_{13}NO_2 \cdot C_4H_4O_4$[j]	61.63	5.17	4.23	61.70	5.35	4.15
H	$CH(CH_3)$	CH_2	a, j	72–76 (0.03)	...	$C_{10}H_{13}NO_2$	67.02	7.31	7.82	66.72	7.46	7.78

[a] Ref. 47. [b] Also prepared *via* 2-phthalimidomethyl derivative (see text). [c] M.p. 220–222°. [d] Prepared in 89% yield by reduction in ether of the 2-cyanomethyl derivative[30] with an equimolar quantity of $LiAlH_4$–$AlCl_3$ (1:1). [e] Hydrochloride (from ethanol–ether). [f] Prepared by reduction with $LiAlH_4$ in ether of 2-(2-cyanoethyl)-1,4-benzodioxan (see text and ref. 33). [g] Prepared by reduction with $LiAlH_4$ in ether of 2-(1-oximinoethyl)-1,4-benzodioxan and used in the crude state. This amine has been prepared by catalytic hydrogenation of the same oxime (see ref. 32). An improved preparation of 2-acetyl-1,4-benzodioxan is described in the text. [h] Prepared according to G. B. Marini-Bettolo, R. Landi-Vittory, and D. Bovet, *Croat. Chem. Acta*, **29**, 363 (1957); *Chem. Abstr.*, **53**, 16,137 (1959). [i] Hydrogen maleate (from ethanol). [j] 2-Ethoxycarbonyl-3-methyl-1,4-benzodioxan, an intermediate in this synthesis was shown by v.p.c. to contain *cis* and *trans* isomers in approximately equal proportions. It is probable that the amine and guanidine (**20**) were also mixtures.

duced to give 2-(1-aminoethyl)-1,4-benzodioxan.[32] The 3-aminopropyl derivative[33] was prepared by reduction of the corresponding nitrile. This was obtained by alkylation of ethyl cyanoacetate with 2-bromomethyl-1,4-benzodioxan, followed by saponification and decarboxylation.

When it was desirable to avoid reductive procedures employed in the preparation of amines (*e.g.*, in the presence of Cl or NO_2 groups), conversion of the appropriate 2-hydroxymethyl derivatives to the corresponding tosylates and subsequent nucleophilic displacement with guanidine proved to be a useful alternative (Scheme IV), although yields in the latter step were variable.

SCHEME IV



Compounds substituted in the guanidine group (**23**–**28**) were prepared from 2-aminomethyl-1,4-benzodioxans and the appropriately substituted derivative of S-methylisothiourea. The remaining compounds (**29**–**32**) were prepared by well-established methods.[34]

Experimental[35]

The final products and the biological results are listed in Tables I and II; details of the synthesis of the corresponding precursor compounds and the methods of guanidine synthesis referred to in Tables I and II are described below.

Guanidines were synthesized by three methods.

A.—Equimolar quantities of the appropriate amine (Table III) and S-methylisothiourea sulfate in water, ethanol, or dimethylformamide were heated under reflux for 4–6 hr. The solvent was removed, and the residue was either recrystallized directly or converted to a suitable salt for characterization.

B.—Alternatively, the amine was treated with 1-amidino-3,5-dimethylpyrazole sulfate[36] under the same conditions as in A. The greater solubility of this reagent in the solvents used over that of S-methylisothiourea sulfate enabled products to be freed from unchanged reagent more easily, and in addition, it avoided the evolution of obnoxious mercaptans.

C.—Tosylates (Table IV) were treated with guanidine in the following manner. Sodium hydride (50% dispersion in oil, 2 equiv.), followed by guanidine hydrochloride (2 equiv.), was added to dry *t*-butyl alcohol, and after refluxing the mixture for 30 min., the NaCl was filtered. The filtrate was added to the appropriate tosylate (1 equiv.) in *t*-butyl alcohol, and the mixture refluxed for 8–16 hr. The solvent was evaporated under reduced pressure, and the residue was extracted with hot water. Unchanged ester could sometimes be recovered from the water-insoluble residue. When the aqueous extract was cooled, the product generally crystallized as the tosylate salt. However, difficulty was often encountered by contamination with guanidine tosylate which was difficult to remove by crystallization. Addition of *p*-toluenesulfonic acid (1 equiv.) after stripping the *t*-butyl alcohol often helped the purification.

Other General Procedures. D. 2-Hydroxymethyl-1,4-benzodioxans.—Symmetrically substituted catechols were stirred vigorously at 100° for 4 hr. with epichlorohydrin (3 equiv.) and 10% aqueous caustic alkali (1 equiv.) The mixture was cooled and extracted with ether. The ethereal extract was washed with dilute alkali and water, dried, and evaporated. Alcohols

(32) D. Misiti and F. De Marchi, *Gazz. chim. ital.*, **93**, 46 (1963).

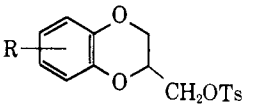
(33) R. Landi-Vittory, C. Milani, and G. B. Marini-Bettolo, *Rend. Ist. Super. Sanita*, **22**, 217 (1959); *Chem. Abstr.*, **54**, 1523 (1960).

(34) Since the preparation of this manuscript, the biological activity of **1**, **4**, and **10** has been reported by M. W. Baines, D. B. Cobb, R. J. Eden, R. Fielden, J. N. Gardner, A. M. Roe, W. Tertbrk, and G. L. Willey, *J. Med. Chem.*, **8**, 81 (1965).

(35) Melting points were taken on an Electrothermal melting point apparatus, Series IA, and are corrected. Infrared spectra were obtained on a Perkin-Elmer Infracord 137 instrument, solids as Nujol mulls and liquids as thin films. Vapor phase chromatography (v.p.c.) was carried out on a Pye Argon Chromatograph.

(36) Other workers have used the nitrate[29] and hydrochloride[29] of the reagent. The sulfate was not obtained when acetylacetone was treated with aminoguanidine sulfate, but could be obtained from the nitrate by ion exchange on Amberlite IRA 400. It had m.p. 170–171°, and was recrystallized from 2-propanol–water. *Anal.* Calcd. for $C_{14}H_{22}N_8O_4S \cdot H_2O$: C, 36.72; H, 6.17; N, 28.56. Found: C, 37.01; H, 6.48; N, 28.70.

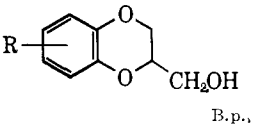
TABLE IV



R	M.p., °C.
H	79[a]
5-CH_3	80–81[b]
8-CH_3	84[a,c]
5,7-$(CH_3)_2$	...[d]
5,8-$(CH_3)_2$	84–85
6,7-$(CH_3)_2$	93.5–95
6-$COCH_3$[e]	72–75
5-Cl	83–84
6-NO_2	119–122
8-NO_2	96–98
3,3-$(CH_3)_2$	...[d]

[a] From ethanol. [b] From ethanol–hexane. [c] See text. [d] Obtained as an oil with satisfactory infrared spectrum. [e] Prepared from 6-acetyl-2-hydroxymethyl-1,4-benzodioxan.[23]

TABLE V



R	B.p., °C. (mm.)
5,8-$(CH_3)_2$[a]	104–108 (0.05)
6,7-$(CH_3)_2$[b]	139–150 (1.0)
6,7-Cl_2	100–102[c]
2-Hydroxymethylnaphtho[2,3-*b*]-1,4-dioxan[d]	

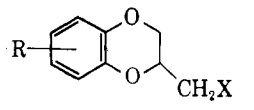
[a] Prepared from 3,6-dimethylcatechol [J. D. Loudon and J. A. Scott, *J. Chem. Soc.*, 265 (1953)]. [b] Prepared from 4,5-dimethylcatechol [P. Karrer and E. Schick, *Helv. Chim. Acta*, **26**, 800 (1943)], itself prepared from 4,5-dimethylveratrole [J. M. Bruce and F. K. Sutcliffe, *J. Chem. Soc.*, 3824 (1956)]. [c] Melting point; crystallized from benzene. [d] Converted directly to the bromide (Table VI) without purification.[25]

prepared in this way (50–80% yields) are listed in Table V. Other alcohols are described in the text.

E. 2-Tosyloxymethyl-1,4-benzodioxans.—These were prepared in 80–95% yields from the corresponding 2-hydroxymethyl-1,4-benzodioxans by treating the latter with *p*-toluenesulfonyl chloride (1.05 equiv.) in dry pyridine at room temperature for 16 hr., and working up with ice-cold HCl and ether. The esters were identified by their characteristic infrared absorption at 1190 and 1175 $cm.^{-1}$, and lack of O–H absorption. Compounds prepared are listed in Table IV.

F. 2-Halomethyl-1,4-benzodioxans.—The corresponding 2-hydroxymethyl-1,4-benzodioxans were heated with thionyl chloride (1 equiv.) in dry pyridine for 3 hr. at 100°. The mixture was allowed to cool and worked up with ice-cold HCl and ether.

TABLE VI



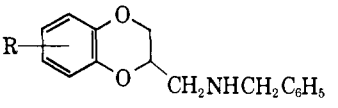
R	X	B.p., °C. (mm.)	$n^{25}D$
H	Cl[a]	80 (0.7)	1.5506
H	Br[a]	102–103 (1.0)	1.5734
6-CH_3	Cl	86–100 (0.15)	1.5446
7-CH_3	Cl	96–102 (0.35)	1.5478
8-CH_3	Cl[b]	91–92 (0.7)	1.5464
7-Cl	Cl[c]	95–96 (0.3)	1.5642
6,7-Cl_2	Br	124–127 (0.25)	55–58[d]
2-Bromomethylnaphtho-[2,3-*b*]-1,4-dioxan[b]		164 (0.3)	82–84[d]

[a] J. R. Geigy A. G., U. S. Patent 2,366,102 (Dec. 26, 1944). [b] Ref. 25. [c] See text and ref. 27. [d] Melting point, °C.

Alternatively, the alcohol in tetrachloroethane was treated slowly with PBr_3 (1.1 equiv.), and the reaction was maintained at 80–90° for 2 hr. The mixture was cooled, poured into water, and extracted with $CHCl_3$. The extract was washed with dilute alkali and water, dried, and distilled. Compounds prepared in these ways are listed in Table VI.

G. 2-Benzylaminomethyl-1,4-benzodioxans were prepared in 60–75% yields by heating the corresponding 2-chloromethyl-1,4-benzodioxans with benzylamine (5 equiv.) at 150° for 5 hr. The mixture was cooled, taken up in chloroform, and washed successively with 2 *N* HCl (which removed only benzylamine), dilute alkali, and water. After drying, the products were isolated by distillation (Table VII).

TABLE VII

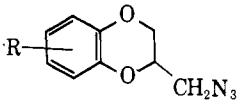


R	B.p., °C. (mm.)	$n^{25}D$
H[a]	180 (1.5)	1.5784
6-CH_3	156–178 (1.0)	1.5716
7-CH_3	160–164 (0.01)	1.5718
8-CH_3	165–180 (0.08)	1.5752
7-CH_3O	168 (0.07)	1.5762
7-Cl[b]	160–170 (0.1)	1.5832

[a] Ref. 48. [b] Treatment of this compound by general method I caused extensive loss of Cl.

H. 2-Azidomethyl-1,4-benzodioxans were prepared by heating the corresponding 2-bromomethyl-1,4-benzodioxans (0.04 mole) with sodium azide (0.05 mole) in dimethylformamide (40 ml.) and sufficient water to complete the solution, at 100° for 24 hr. The solvents were evaporated, and the residue was treated with water and ether. The ethereal layer was dried and distilled to yield the product (yields 75–95%). The products (Table VIII) were all characterized by a strong infrared absorption at 2120 $cm.^{-1}$.

TABLE VIII



R	B.p., °C. (mm.)	$n^{25}D$
H	106 (0.7)	1.5526
7-Cl	80–83 (0.04)	1.5636
6,7-Cl_2	146 (0.8)	43–45[a]
2-Azidomethylnaphtho[2,3-*b*]-1,4-dioxan		60–62[a]

[a] Melting point, °C.

2-Aminomethyl-1,4-benzodioxans were prepared by two general methods.

I.—The benzyl derivatives (Table VII) were hydrogenated at atmospheric pressure in acetic acid with palladium–charcoal catalyst at 70°. After removal of catalyst, the solvent was evaporated, the residue was basified, and the primary amine was isolated by extraction with an organic solvent.

J.—The azido derivatives (Table VIII) were reduced as in the following typical experiment. 2-Azidomethyl-1,4-benzodioxan (18 g., 0.094 mole) in dry ether (250 ml.) was added dropwise over 1 hr. to a stirred solution of $LiAlH_4$ (3.8 g., 0.1 mole) in ether (300 ml.) under nitrogen. During the addition, cooling of the reaction was necessary, but subsequently it was stirred at room temperature for 30 min., and then under reflux for 1 hr. The reaction was cooled and treated cautiously in succession with water (4 ml.), aqueous NaOH (15%, 4 ml.), and water (12 ml.). The product was isolated by evaporation of the filtered solution.

The amines prepared by these two methods, along with others required for preparation of the guanidines by methods A and B are listed in Table III.

2-Phthalimidomethyl-1,4-benzodioxan was prepared by reaction of 2-tosyloxymethyl-1,4-benzodioxan with potassium phthalimide (10% excess) in dimethylformamide at 100° for 4 hr. The reaction mixture was cooled, diluted with $CHCl_3$,

and poured into water, whereupon the product crystallized. More product (m.p. 208–209°, total yield 65%) was obtained by evaporation of the chloroform extract.

The phthalimide intermediate (5.9 g.) was heated under reflux with hydrazine hydrate (1 ml.) in ethanol for 3 hr. The reaction was cooled, made acid with concentrated HCl, and filtered. The filtrate was evaporated to dryness to give 2-aminomethyl-1,4-benzodioxan hydrochloride (4.0 g., 99%), m.p. 190–100°. This was recrystallized from 2-propanol to give the pure hydrochloride, m.p. 220–222°.

2-(2-Cyanoethyl)-1,4-benzodioxan.—Dioxane (300 ml.) was added to a solution of sodium (9 g.) in dry ethanol (150 ml.), and the mixture was distilled until the distillation temperature reached 100°. The residue was stirred while ethyl cyanoacetate (90 g.) was added slowly, and the ethanol formed was removed by distillation until the reflux temperature again reached 100°. More dioxane (200 ml.) was added, and after addition of 2-bromomethyl-1,4-benzodioxan (90 g.) over 30 min., the mixture was heated under reflux for 12 hr. It was allowed to cool and treated with ice and dilute HCl. The product (33.5 g., 33%), isolated by extraction with ether and distillation, had b.p. 160–170° (0.1 mm.), $n^{25}D$ 1.5200.

The cyano ester was saponified by heating under reflux for 3 hr. with NaOH (5.6 g.) in ethanol (100 ml.) and water (50 ml.). The cooled solution was acidified and extracted with ether. The crude cyano acid, which was obtained by evaporation of the dried ethereal extract, was decarboxylated by heating at 160° for 1 hr. When evolution of CO_2 had ceased, the residue was distilled to give 15 g. (62%) of product, b.p. 128° (0.02 mm.), m.p. 56–57° (from petroleum ether, b.p. 60–80°).

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.96; H, 5.86; N, 7.20.

2-Acetyl-1,4-benzodioxan.—Catechol (5 g.), 3,4-dibromobutan-2-one (15 g.) (freshly prepared by bromination in chloroform at room temperature of methyl vinyl ketone), anhydrous K_2CO_3 (15 g.), and KI (1.5 g.) in acetone (35 ml.) were stirred and heated under reflux in a nitrogen atmosphere for 9 hr. The mixture was allowed to cool, the solids were filtered, and the filtrate was evaporated. The residue was dissolved in ether, washed with aqueous NaOH, and dried, and the product (2.75 g., 34%) was isolated by distillation, b.p. 84° (0.4 mm.), m.p. 30–34° (lit.[32] m.p. 33°).

2-Hydroxy-3-methylacetophenone was prepared by the literature method[37] and purified by fractional distillation, b.p. 108–109° (14 mm.), $n^{25}D$ 1.5527.

2-(2,3-Epoxypropoxy)-3-methylacetophenone.—A mixture of epichlorohydrin (103 g.) and 2-hydroxy-3-methylacetophenone (56.8 g.) in ethanol (30 ml.) was stirred vigorously and heated under reflux, while KOH (25.8 g.) in ethanol (70 ml.) and water (10 ml.) was added slowly. After heating for 1 hr., the solvent was removed by distillation, and the residue was poured into water. Extraction with ether yielded the product, 45.1 g. (59%), b.p. 108–110° (0.05 mm.), $n^{25}D$ 1.5313.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.22; H, 7.08.

2-(2,3-Epoxypropoxy)-3-methylphenyl Acetate.—The above epoxy ketone (10 g.) was treated with *m*-chloroperbenzoic acid (11.5 g.) (FMC Corp.), in $CHCl_3$ (125 ml.) at 50° for 18 hr. The solution was washed with dilute sodium metabisulfite and bicarbonate, then with water, and after drying, the solvent was evaporated. The above operations were repeated until the infrared spectrum showed that the ketone band (1700 cm.$^{-1}$) had been completely replaced by the acetate band (1775 cm.$^{-1}$).

2-Hydroxymethyl-5-methyl-1,4-benzodioxan.—The above crude acetate was treated with alkali as in general procedure D to give the product in 60% yield, b.p. 106–110° (0.15 mm.), $n^{25}D$ 1.5488.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 67.08; H, 6.89.

2-Hydroxymethyl-6-methyl-1,4-benzodioxan.—4-Methylcatechol (37.25 g.) and epichlorohydrin (36 g.) were stirred together at 70°, and treated dropwise over 1 hr. with NaOH (13.2 g.) in water (110 ml.). After heating under reflux for another hour, the reaction was cooled and extracted with ether. The extract was washed with dilute NaOH and water and, after drying, was evaporated to give the product, b.p. 125–127° (0.25 mm.), $n^{25}D$ 1.5482.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.83; H, 6.50.

V.p.c. indicated approximately 95% purity; the main component was inseparable from material obtained from 6-formyl-2-hydroxymethyl-1,4-benzodioxan[24] by hydrogenation over palladium–charcoal in acetic acid containing 1% perchloric acid,[38] and subsequent saponification of the 2-acetoxymethyl group. The infrared spectra of the two materials were almost identical.

2-(3-Chloro-2-hydroxypropoxy)-5-methylacetophenone.—2-Hydroxy-5-methylacetophenone[39] (49.5 g.), epichlorohydrin (86 g.), and piperidine (0.5 ml.) were heated together on the steam bath for 6 hr. The excess epichlorohydrin was removed under reduced pressure, the residue was dissolved in chloroform, and the solution was washed with dilute HCl and water. The solution was dried and distilled to give 19.5 g. (29%), b.p. 166–172° (0.009 mm.), $n^{25}D$ 1.5508.

Anal. Calcd. for $C_{12}H_{15}ClO_3$: Cl, 14.61. Found, Cl, 14.27.

2-Hydroxymethyl-7-methyl-1,4-benzodioxan.—The above chlorohydrin (10 g.) in acetic acid (100 ml.) was stirred at 42° while acetic acid (100 ml.) containing peracetic acid (10 ml., 37%) and sodium acetate[36] (0.1 g.) was added dropwise over 1 hr. The reaction was maintained at this temperature for 24 hr., and then the excess peracid was neutralized with sodium metabisulfite. Acetic acid was removed under reduced pressure, and the residue was cyclized by stirring with NaOH (15 g.) in water (50 ml.) on a steam bath for 4 hr. The mixture was cooled and extracted with $CHCl_3$ and the extract was washed with aqueous NaOH and water. The dried extract was evaporated, and the residue was distilled, b.p. 100–102° (0.09 mm.), $n^{25}D$ 1.5478, yield 45%.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.44; H, 6.62.

2-Hydroxymethyl-8-methyl-1,4-benzodioxan.—3-Methylcatechol and epichlorohydrin were treated with hot aqueous alkali by the general procedure D, to give the methyl-substituted 2-hydroxymethyl-1,4-benzodioxan in 77% yield, b.p. 114° (0.3 mm.), $n^{25}D$ 1.5510 [lit.[25] b.p. 129–130° (1 mm.)]. Although this material showed a slight impurity on v.p.c., a clearer analysis was obtained by v.p.c. of the 2-acetoxymethyl derivative (prepared by warming the 2-hydroxymethyl derivative with acetic anhydride at 90° for 30 min.), b.p. 124° (0.05 mm.), $n^{25}D$ 1.5201. Comparison with the 2-acetoxymethyl derivatives of the authentic 5-methyl (above) and 8-methyl (below) isomers indicated that the mixture contained *ca.* 92% of the latter isomer. This was confirmed by infrared spectroscopy. A tosylate prepared from the product of this reaction had m.p. 69–70°, but this melting point could not be raised by recrystallization. This alcohol was used to prepare the 2-chloromethyl, 2-benzylaminomethyl, and 2-aminomethyl derivatives in Tables VI, VII, and III, respectively, the latter being used to prepare compound **8S**.

Reaction between 3-methylcatechol and ethyl 2,3-dibromopropionate was carried out by the method described for 2-acetyl-1,4-benzodioxan in the presence of acetone and K_2CO_3. The product (39%) had b.p. 88–92° (0.1 mm.), $n^{25}D$ 1.5576. A portion of the product was reduced with $LiAlH_4$ and then acetylated. V.p.c. analysis on this material indicated that the mixture was similar in composition to that of the product derived from 3-methylcatechol and epichlorohydroin, *i.e.*, it contained *ca.* 90% 8-methyl and 10% 5-methyl isomer.

2-Hydroxymethyl-8-methyl-1,4-benzodioxan.—2-Hydroxymethyl-8-formyl-1,4-benzodioxan[41] (4.2 g.) was hydrogenated at 60° over palladium–charcoal in acetic acid (200 ml.) containing 1% of perchloric acid.[38] The product was shown by infrared spectroscopy to be a mixture of the 2-acetoxymethyl and 2-hydroxymethyl derivatives and was saponified with NaOH in aqueous ethanol to give the product (1.6 g., 41%), $n^{25}D$ 1.5510. This material was converted to the tosylate (Table IV), and thence to compound **8T**.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.92; H, 6.63.

(37) G. S. Chhaya, P. L. Trivedi, and G. V. Jadhav, *J. Univ. Bombay*, **A26** (Pt. 5), 22 (1958); *Chem. Abstr.*, **53**, 14038 (1959).

(38) A. S. Bailey and C. B. Worthing, *J. Chem. Soc.*, 1535 (1956), and references quoted therein.

(39) K. Kindler, H. Oelschläger, and P. Henrich, *Arch. Pharm.*, **287**, 210 (1954).

(40) R. L. Melzer and J. Dazzo, *J. Am. Chem. Soc.*, **72**, 4986 (1950).

(41) This was prepared by the method in ref. 23; in our hands the material was obtained crystalline, m.p. 62–63° (from benzene–petroleum ether, 40–60°). *Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 61.85; H, 5.19. Found: C, 61.63; H, 5.02.

3,5-Dimethyl-2-hydroxyacetophenone was obtained from 2,4-dimethylphenol in 82% yield by the facile procedure of Kindler, *et al.*,[39] using BF_3–CH_3CO_2H. The material had m.p. 54–55° (lit.[42] m.p. 53–54°).

3,5-Dimethyl-2-(2,3-epoxypropoxy)acetophenone.—3,5-methyl-2-hydroxyacetophenone could not be induced to react with epichlorohydrin in the presence of pyridine, piperidine, or aqueous NaOH. Instead, the following procedure was used. A mixture of the phenol (30.8 g.) and NaOH (12.6 g.) in ethanol (200 ml.) was stirred and heated under reflux while epichlorohydrin (55.5 g.) was added dropwise. After heating for a further 3 hr., the mixture was cooled and filtered, and the filtrate was evaporated. The product was extracted with ether, washed with strong aqueous NaOH and water, and isolated by distillation. Material (21.8 g., 53%) with b.p. 130–136° (0.5 mm.), $n^{25}D$ 1.5295, showed in its infrared spectrum no O–H absorption, and a nonhydrogen-bonded aromatic ketone band at 1695 cm.$^{-1}$.

5,7-Dimethyl-2-hydroxymethyl-1,4-benzodioxan.—As attempted Baeyer–Villiger oxidations on the above epoxy ketone failed, it was converted to the chlorohydrin by allowing a dry ethereal solution of the epoxide saturated with HCl to stand overnight. The volatile matter was removed under reduced pressure, and the residual oil was used directly in the next step. To a solution of the crude chlorohydrin (20.5 g.) in dry ether (50 ml.) was added a solution of freshly distilled boron trifluoride etherate (22.8 g.) containing 90% H_2O_2 (2.8 g.).[43] The mixture was stirred at room temperature for 1 hr., and then washed with aqueous sodium metabisulfite, bicarbonate, and water. The dried solution was evaporated to leave an oil (20.3 g., 93%), the infrared spectrum of which showed an ester absorption at 1750 cm.$^{-1}$ and no aromatic ketone band.

This acetoxy compound (25.5 g.) and KOH (13.2 g.) in water (125 ml.) were stirred and heated under reflux for 4 hr. The reaction was allowed to cool and extracted with $CHCl_3$. The organic extract was washed thoroughly with aqueous NaOH and water and dried, and the solvent was evaporated. The residue was distilled to give 5,7-dimethyl-2-hydroxymethyl-1,4-benzodioxan (7.5 g., 41%), b.p. 100° (0.2 mm.), $n^{25}D$ 1.5450.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.09; H, 7.32.

Attempted Preparation of 6,8-Dimethyl-2-hydroxymethyl-1,4-benzodioxan.—With the intention of applying the same method which was used for the synthesis of 5,7-dimethyl-2-hydroxymethyl-1,4-benzodioxan, 4,6-dimethyl-2-hydroxyacetophenone[39] was treated with epichlorohydrin in the presence of piperidine to give impure 4,6-dimethyl-2-(3-chloro-2-hydroxypropoxy)-acetophenone. (*Anal.* Calcd. for $C_{13}H_{17}ClO_3$: C, 60.82; H, 6.67; Cl, 13.81. Found: C, 61.78; H, 6.66; Cl, 11.38.) All attempts at Baeyer–Villiger oxidation of this material failed.

3-Chloro-2-(2,3-epoxypropoxy)acetophenone was prepared in 56% yield from 3-chloro-2-hydroxyacetophenone[44] (m.p. 44–45°, shown by v.p.c. to be free from 3-chloro-4-hydroxyacetophenone) and epichlorohydrin by the method used for 2-(2,3-epoxypropoxy)-3-methylacetophenone. The epoxide had b.p. 117–118° (0.01 mm.), $n^{25}D$ 1.5450.

Anal. Calcd. for $C_{11}H_{11}ClO_3$: C, 58.27; H, 4.89. Found: C, 58.95; H, 4.91.

5-Chloro-2-hydroxymethyl-1,4-benzodioxan.—The above epoxide was converted to the chlorohydrin by treating with ethereal HCl for 16 hr. The infrared spectrum of the chlorohydrin indicated the absence of epoxide bands (915 and 837 cm.$^{-1}$) and the introduction of a hydroxyl group. The crude chlorohydrin was treated with peracetic acid in the manner described for the 7-methyl analog to give material with strong infrared absorption at 1750 cm.$^{-1}$ (ester) instead of the original 1695 cm.$^{-1}$ (aromatic ketone). This oil was cyclized by general procedure D to give the product, b.p. 110° (0.03 mm.), m.p. 68–70°; over-all yield from the epoxide was 34%.

7-Chloro-2-hydroxymethyl-1,4-benzodioxan was prepared in the standard manner by heating 4-chlorocatechol and epichlorohydrin in the presence of alkali. It had b.p. 126–130° (0.1 mm.), $n^{25}D$ 1.5680, m.p. 60–61° (from petroleum ether, 60–80°).

Anal. Calcd. for $C_9H_9ClO_3$: C, 53.89; H, 4.52; Cl, 17.68. Found: C, 53.94; H, 4.60; Cl, 17.99.

The identity of this alcohol was established by conversion to the 2-chloromethyl derivative by general procedure F. V.p.c. on four different columns failed to separate this product from authentic 7-chloro-2-chloromethyl-1,4-benzodioxan prepared by the literature method.[27] The infrared spectra of the two materials exhibited one minor difference in the region 950–920 cm.$^{-1}$.

6- and 8-Nitro-2-hydroxymethyl-1,4-benzodioxan were made by the following parallel procedures.

Nitration of Catechol Monobenzoate.—Catechol monobenzoate (m.p. 128–129°) was nitrated according to the procedure of Barton, *et al.*[26] It was found that dinitration occurred if the reaction temperature was allowed to rise above 20°. The 4-nitro- and 6-nitrocatechol monobenzoates were separated and each treated as follows.

A. Benzylation.—Each monobenzoate (1 mole) and benzyl bromide (1.15 moles) and anhydrous $MgSO_4$[45] were refluxed in acetone (2 l.). Anhydrous K_2CO_3 (0.5 mole) was added in four portions over 12 hr., and after the addition was complete the mixture was refluxed for 1 hr. On cooling, the reaction mixture was filtered and evaporated to dryness *in vacuo*. The residue crystallized on standing and was recrystallized from benzene–petroleum ether to constant melting point to give (i) **2-benzyloxy-3-nitrophenyl benzoate** (61%), m.p. 100–102°, and (ii) **2-benzyloxy-5-nitrophenyl benzoate** (53%), m.p. 106–108°.

B. Saponification.—The above esters were each refluxed with KOH (2 moles) in ethanol for 4 hr. and cooled, and any solids were filtered and retained. The mother liquor was diluted with water and washed with ether. The aqueous layer was adjusted to pH 8 and extracted with ether. The material obtained on evaporation of the dried ethereal extract was combined with the solid which was filtered initially and recrystallized from benzene–petroleum ether (b.p. 40–60°) to give (i) **2-benzyloxy-3-nitrophenol** (77%), m.p. 44–52°, and (ii) **2-benzyloxy-5-nitrophenol** (68%), m.p. 82–85°.

C. Cyclization.—The monobenzyl ethers (50 g.) were each treated with epichlorohydrin (50 ml.) and piperidine (0.5 ml.) on the steam bath for 6 hr. Volatile material was evaporated *in vacuo*, and the residue was dissolved in $CHCl_3$. After standing overnight with a few milliliters of concentrated HCl, the solution was washed with water, dried, and evaporated. The residue was dissolved in glacial acetic acid (550 ml.) containing concentrated HCl (390 ml.) and heated on the steam bath for 5 hr. The solvent was removed by evaporation *in vacuo*, and the residue was cyclized by general procedure D to yield (i) **2-hydroxymethyl-8-nitro-1,4-benzodioxan** (78%) as an uncharacterized oil, and (ii) **2-hydroxymethyl-6-nitro-1,4-benzodioxan** (58%), m.p. 124–125° (from methanol).

Anal. of ii. Calcd. for $C_9H_9NO_5$: C, 51.19; H, 4.30. Found: C, 50.66; H, 4.17.

7-Nitro-2-hydroxymethyl-1,4-benzodioxan was prepared by the literature method.[27] In our hands this compound was induced to crystallize and had m.p. 131–134° (from methanol). On admixture with the 2-hydroxymethyl-6-nitro-1,4-benzodioxan [C (ii) above], the m.p. was 99–112°, and the infrared spectra showed significant differences. This confirms the assignment of structure made by the Italian workers.

3,3-Dimethyl-2-ethoxycarbonyl-1,4-benzodioxan was prepared in 15% yield from catechol and ethyl 2,3-dibromoisovalerate[46] in the presence of acetone and K_2CO_3 by the method used for 2-acetyl-1,4-benzodioxan. It had b.p. 165–168° (11 mm.), $n^{25}D$ 1.5256.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.93; H, 6.72.

The ester did not react with NH_3, either in ethanolic solution for 7 days or at 100° under pressure.

3,3-Dimethyl-2-hydroxymethyl-1,4-benzodioxan was prepared in 86% yield from the above 2-ethoxycarbonyl compound by reduction with $LiAlH_4$ in the usual manner. It had b.p. 125–127° (1.5 mm.), $n^{25}D$ 1.5448, and was converted directly to the tosylate (Table IV).

2-Methylaminomethyl-1,4-benzodioxan was obtained by treatment of 2-bromomethyl-1,4-benzodioxan with excess methyl-

(42) W. Baker, H. F. Bondy, J. Gumb, and D. Miles, *J. Chem. Soc.*, 1615 (1953).

(43) J. D. McClure and P. H. Williams, *J. Org. Chem.*, **27**, 24 (1962).

(44) N. M. Shah and S. R. Parikh, *J. Indian Chem. Soc.*, **36**, 784 (1959).

(45) Omission of $MgSO_4$ during benzylation of 4-nitrocatechol monobenzoate resulted in a product of m.p. 85–87°, from which, on attempted saponification, there was isolated material, m.p. 95–97°, considered from its infrared spectrum to be 4-nitrocatechol dibenzyl ether; H. Burton and D. F. G. Prail [*J. Chem. Soc.*, 522 (1951)] report m.p. 97.5° for this substance.

(46) H. Moureu, P. Chovin, and M. Ducros, *Bull. soc. chim. France*, 586 (1953).

amine in refluxing ethanol, or in higher yield (77%) by catalytic hydrogenation over palladium–charcoal of N-methyl-2-benzylaminomethyl-1,4-benzodioxan in acetic acid. The secondary amine had b.p. 82–84° (0.4 mm.), $n^{25}D$ 1.5396 [lit.[47a] b.p. 124° (4 mm.), $n^{23}D$ 1.5390].

N-Methyl-2-benzylaminomethyl-1,4-benzodioxan.—2-Benzylaminomethyl-1,4-benzodioxan[48] (14.5 g.) was added to formic acid (6.45 g.) at 0°, followed by slow addition of formaldehyde (5.4 g., 35% solution). When the effervescence had ceased, the mixture was heated under reflux for 4 hr., and allowed to cool. Concentrated HCl (5.7 ml.) was added, and the volatile material was removed *in vacuo*. The residue was treated with 5 *N* NaOH and extracted into benzene. The benzene solution was extracted with dilute HCl, and this acid extract, along with an oil which had separated, was basified and extracted with ether. Distillation of the dried ethereal extract gave the product in 90% yield, b.p. 144–147° (0.4 mm.), $n^{25}D$ 1.5658.

Anal. Calcd. for $C_{17}H_{19}NO_2$: N, 5.20. Found: N, 5.11.

2-(1,4-Benzodioxanyl)methylbiguanide tosylate was synthesized according to the method of Oxley and Short.[49] An intimate mixture of equimolar quantities of the tosylate salt (m.p. 176–178°) of 2-aminomethyl-1,4-benzodioxan and dicyandiamide was maintained at 150–160° (internal temperature) for 30 min. After cooling, the glassy solid crystallized on trituration with 2-propanol. It was recrystallized from water to give the product as the tosylate salt (68%), m.p. 169°.

S-2-(1,4-benzodioxanyl)methylisothiourea Hydrobromide.—Equimolar quantities of 2-bromomethyl-1,4-benzodioxan and thiourea in ethanol were heated under reflux for 8 hr. After removal of some of the solvent, the reaction was cooled, and the product was collected and recrystallized from ethanol. It had m.p. 191–193°, yield 52%.

2-(1,4-Benzodioxanyl)acetamidine Hydrochloride.—2-Cyanomethyl-1,4-benzodioxan[50] (20 g., 0.114 mole) and dry ethanol (7 ml., 0.12 mole) in dry ether (200 ml.) were protected from atmospheric moisture, cooled to −10°, and a slow stream of dry HCl was passed through the mixture for 14 hr. After 2 days at 0°, the imino ether hydrochloride, m.p. 134°, was filtered off and washed with dry ether. The salt was then stirred with NH_3 (10% solution in ethanol, 200 ml.) at room temperature for 18 hr. Concentration of the mixture to *ca.* 50 ml. caused the product to crystallize. It was filtered off and recrystallized from ethanol–ether. It had m.p. 225–227° dec.

2-(1,4-Benzodioxanyl)acetamidoxime.—2-Cyanomethyl-1,4-benzodioxan[50] (3.0 g.) in ethanol (20 ml.) was added to hydroxylamine hydrochloride (1.2 g.) and anhydrous Na_2CO_3 (0.9 g.) in water (10 ml.), and the mixture was heated under reflux for 24 hr. The ethanol was evaporated and the residue was extracted with ether. The extract was washed with dilute HCl, and the washings were combined with the original ether-insoluble residue. Treatment with solid $NaHCO_3$ yielded a brown tar, which after being washed with water, was dissolved in warm ethanol. After treatment with charcoal, concentration of the solution gave the amidoxime, 0.5 g. (14%), m.p. 123–124°.

Acknowledgment.—We wish to thank Mr. P. R. Wood for the microanalyses and Messrs. P. W. Clement, J. A. Davidson, J. B. Hare, A. R. Lane, B. W. Sneddon, V. F. Voss, and J. A. Zoro for their competent technical assistance.

(47) (a) G. B. Marini-Bettolo, R. Landi-Vittory, and D. Bovet, *Gazz. chim. ital.*, **83**, 144 (1953); (b) J. Koo, *J. Org. Chem.*, **26**, 339 (1961).

(48) R. E. Dunbar and G. A. Sweeney, *ibid.*, **22**, 1686 (1957).

(49) P. Oxley and W. F. Short, *J. Chem. Soc.*, 1252 (1951).

(50) C. Milani, R. Landi-Vittory, and G. B. Marini-Bettolo, *Bend. Ist. Super. Sanità*, **22**, 207 (1959); *Chem. Abstr.*, **54**, 1522 (1960).

Hydroxylamine Chemistry. V. Aralkoxyguanidines[1]

D. G. MARTIN, E. L. SCHUMANN, W. VELDKAMP, AND H. KEASLING

Research Laboratories of The Upjohn Company, Kalamazoo, Michigan

Received December 19, 1964

A series of aralkoxyguanidines was prepared including several possessing interesting anorexigenic activity.

Conversion of some previously prepared O-aralkylhydroxylamines[1] into the corresponding aralkoxyguanidines was desired as a means of increasing their basicity and thereby varying their pharmacological actions. Accordingly, seven representative aralkoxyamines were allowed to react with 2-methyl-2-thiopseudourea sulfate[2] to form the corresponding aralkoxyguanidine sulfates which were converted into crystalline nitrate salts for isolation and purification.

$$2(RONH_2) + [CH_3SC(=NH)NH_2]_2H_2SO_4 \rightarrow [RONHC(=NH)NH_2]_2H_2SO_4 + 2CH_3SH$$

In the course of this work an improved procedure for the preparation of alkoxyguanidines was developed based on the reaction of cyanamide[3] with an alkoxyamine hydrochloride suspended in an inert solvent.

$$RONH_2 \cdot HCl + H_2N \cdot CN \rightarrow RONHC(=NH)NH_2 \cdot HCl$$

This cyanamide procedure was mild enough to permit the conversion of 2-phenethyloxyamine hydrochloride, which is unstable on standing at room temperature, into 2-phenethyloxyguanidine in 69% yield.

One N-alkylated alkoxyamine derivative, N-methylbenzyloxyamine hydrochloride,[4] was included in the series of alkoxyamines converted into guanidines with cyanamide. Another alkylated guanidine, 1-benzyloxy-2,3-diisopropylguanidine, was prepared by the reaction of benzyloxyamine with diisopropylcarbodiimide.[5] Fusion of benzyloxyamine hydrochloride with dimethylcyanamide afforded 1-benzyloxy-3,3-dimethylguanidine.

(1) Part IV: E. L. Schumann, R. V. Heinzelman, M. E. Greig, and W. Veldkamp, *J. Med. Chem.*, **7**, 329 (1964).

(2) (a) *Cf.* D. D. Nyberg and B. E. Christensen, *J. Am. Chem. Soc.*, **78**, 781 (1956), and references cited. (b) Since the completion of this work, the preparation of aralkoxyguanidine sulfates by this procedure has been described: *cf.* J. G. Robert and G. M. Tartary, Rhone-Poulenc, Irish Patent 1140/63 (Nov. 24, 1963) (Derwent Basic No. 102961. Included in this patent were the sulfates corresponding to aralkoxyguanidines **1–3** and **6–8** of Table I.

(3) (a) *Cf.* A. T. Fuller and H. King, *J. Chem. Soc.*, 963 (1947). (b) Dr. J. J. Ursprung of these laboratories has prepared alkylguanidines by fusion of amine salts with cyanamide (private communication). In the present work with alkoxyamine hydrochlorides, attempted fusions often led to vigorous decomposition.

(4) B. J. R. Nicolaus, G. Pagani, and E. Testa, *Helv. Chim. Acta*, **45**, 1381 (1962).

(5) J. G. Moffatt and H. G. Khorana, *J. Am. Chem. Soc.*, **83**, 649 (1961), isolated the adduct of morpholine and dicyclohexylcarbodiimide in high yields.