Piperidino Groups in Antitussive Activity

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Additional evidence supporting a hypothesis previously presented by the authors[1] that a piperidino group strengthens and increases antitussive activity is presented. The role of pyrrolidino groups in antitussive activity has also been studied.

In a study of structure-activity relationship in antitussive agents, a working hypothesis has been presented[1] that the introduction of a piperidino group into a compound showing any actions on the central nervous system, can produce antitussive activity if the activity has been latent, or strengthen it if such activity is already manifest. This is more pronounced than in the case of monomethylamino, dimethylamino, diethylamino, morpholino, methylpiperazino and N-β-hydroxyethylpiperazino groups.

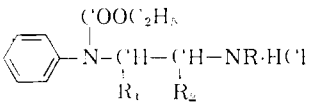
In this paper the results obtained with 73 compounds in five series, such as analgesics, antitussives in the phenothiazine series, adrenergic amines, antihistaminics and camphor derivatives, are described. The antitussive activities of piperidino compounds were found to be the highest of all the amino compounds tested, and the hypothesis was thus consolidated as a guide for further studies on antitussive agents.

Methods.—Antitussive effects were evaluated by Kasé's method[2] in unanesthetized dogs and/or in slightly pentobarbitalized cats (20 mg./kg. intraperitoneally). Changes in respiration by coughing, caused by mechanical stimulation with a bristle stimulator on the mucosa of the tracheal bifurcation through a chronic tracheal fistula, were recorded. The antitussive effect of each test drug was determined from the decreases in both amplitude and frequency of cough curves, and from the duration of such an effect. The effective dose was taken as that necessary to decrease amplitude and/or frequency of coughing by more than 20% as compared with the control, and the duration of such an effect for more than 20 min. The 50% antitussive dose (AtD_{50}) was calculated by the Litchfield-Wilcoxon method[3] ($p = 0.05$). As the same animals can be used by this method repeatedly for the experiment after 2 or 3 days rest, the antitussive effect of each drug belonging to the same group was determined with the same animals, minimizing errors arising from individual differences in animals.

Results.—The results obtained are shown in Tables I–X. A description such as "ineffective at 20 mg./kg." in the Tables means that no effect was observed with various doses up to 20 mg./kg., because of shortages of drug supply or of serious side-effects at increased doses. When it was impossible to calculate the AtD_{50} because

TABLE I

SERIES 1. ANALGESIC TYPES. GROUP A.[a] ETHYL N-(2-*tert*-AMINOALKYL)-CARBANILATE HYDROCHLORIDES[4]

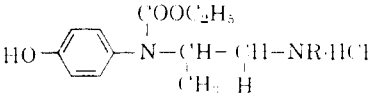


Compd.	R_1	R_2	NR	M.p., °C.	Antitussive activity: Animals used	Antitussive activity: AtD_{50} (mg./kg.) dog, i.v.
I	CH_3	H	$N(CH_3)_2$	163–165	2	Ineffective at 20.0
II	CH_3	H	$N(C_2H_5)_2$	118	2	Ineffective at 20.0
III	CH_3	H	Morpholino	176–178	20	21.8 (18.5–25.8)
IV	CH_3	H	Piperidino	183–185	25	18.6 (16.3–21.2)[b,c]
V	H	CH_3	$N(CH_3)_2$	156–158[c]	3	Ineffective at 10.2
VI	H	CH_3	$N(CH_3)(C_2H_4{-}C_6H_5)$	135–137[c]	2	Ineffective at 8.0
VII	H	CH_3	Morpholino	178–180[c]	20	16.9 (14.6–19.6)
VIII	H	CH_3	Piperidino	170–172[c]	24	7.3 (6.2–8.6)

[a] The A group was synthesized and supplied by N. Shigematsu.[4,5] [b] Convulsion with AtD_{50}. [c] Oxalate.

TABLE II

GROUP B.[a] N-(1-METHYL-2-*tert*-AMINOETHYL)-4-HYDROXYPROPIONANILIDE HYDROCHLORIDES[5]



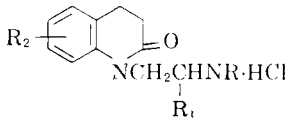
Compd.	NR	M.p., °C.	Antitussive activity: Animals used	Antitussive activity: AtD_{50} (mg./kg.) dog i.v.
IX	$N(CH_3)_2$	240–242	20	19.2 (16.4–21.7)
X	$N(C_2H_5)_2$	218–220	2	Ineffective at 20.0
XI	Morpholino	245–247	2	20.0[b]
XII		214–216	2	Ineffective at 20.0
XIII	Piperidino	245–246	30	14.8 (12.8–17.2)

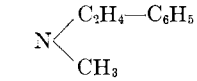
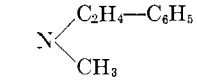
[a] Group B was synthesized and supplied by N. Shigematsu.[4,5] [b] Minimal effective dose (MED).

(1) Y. Kasé and T. Yuizono, *Chem. Pharm. Bull.* (Tokyo), **7**, 378 (1959).
(2) Y. Kasé, *ibid.*, **2**, 298 (1954); *Japan. J. Pharmacol.*, **4**, 130 (1955).
(3) J. T. Litchfield and F. W. Wilcoxon, *J. Pharmacol. Expl. Therap.*, **96**, 99 (1949).
(4) N. Shigematsu, *Yakugaku Zasshi*, **81**, 123 (1961).
(5) N. Shigematsu, *ibid.*, **81**, 815 (1961).

TABLE III

GROUP C.[g] 1-(2-*tert*-AMINOALKYL)-3,4-DIHYDRO-2-QUINOLONE HYDROCHLORIDES

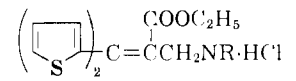


Compd.	R_1	R_2	NR	M.p., °C.	Antitussive activity: Animals used	Antitussive activity: AtD_{50} (mg./kg.) dog i.v.
XIV	H	None	$N(CH_3)_2$	193–195	24	14.2 (11.7–17.2)
XV	H	None	$N(C_2H_5)_2$	122–124[e]	2	20.0[a,b]
XVI	H	None	Morpholino	220–222	2	Ineffective at 20.0
XVII	H	None	Piperidino	142–144	25	6.8 (5.3–8.9)
XVIII	CH_3	None		179–181[f]	20	10.5 (8.3–13.3)
XIX	CH_3	None	Piperidino	168–170	24	5.2 (4.4–6.0)
XX	H	7-OH	Piperidino	187–189	25	6.2 (4.9–7.9)
XXI	CH_3	7-OH		153–155[f]	25	6.8 (5.6–8.8)
XXII	CH_3	7-OH	Piperidino	238–240	30	3.2 (2.7–3.8)[c]
XXIII	H	6-OH	Piperidino	229–231	20	8.2 (5.9–11.3)[d]
XXIV	CH_3	6-OH	Piperidino	200–202	30	3.4 (2.7–4.2)

[a] Minimal effective dose (MED). [b] Convulsion with MED. [c] Convulsion with AtD_{50}. [d] Respiratory excitation with AtD_{50}. [e] Picrate. [f] Oxalate. [g] Synthesized and supplied by N. Shigematsu.[7]

TABLE IV

GROUP D.[a] ETHYL 2-*tert*-AMINOMETHYL-3,3-DI-(2-THIENYL)ACRYLATE HYDROCHLORIDES



Compd.	NR	M.p., °C.	Antitussive activity: Animals used	Antitussive activity: AtD_{50} (mg./kg.) Dog i.v.	Antitussive activity: Animals used	Antitussive activity: AtD_{50} (mg./kg.) Cat i.v.
XXV	$N(CH_3)_2$	110–112[b]	4	Ineffective at 20.0	2	Ineffective at 20.0
XXVI	$N(C_2H_5)_2$	130–132	4		2	
XXVII	Morpholino	121–123	4	Ineffective at 20.0	20	9.5 (7.6–11.7)
XXVIII		189–191	4		20	10.3 (8.1–13.1)
XXIX	Piperidino	127–129[b]	25	7.8 (6.4–9.6)	20	5.8 (4.7–7.1)

[a] Synthesized and supplied by N. Shigematsu and G. Hayashi.[9] [b] Picrate.

of insufficient amounts of drug, the minimal effective dose (MED) was determined.

In groups A and B of series I, ethyl N-(2-*tert*-aminoalkyl) carbanilate[4] and N-(1-methyl-2-*tert*-aminoalkyl)-4′-hydroxypropionanilide,[5] which may be regarded as containing a tertiary nitrogen atom in place of the quaternary C-atom in methadone,[6] show meperidine-like analgesic activity. The piperidino compounds IV, VIII and XIII are more potent than others which have groups such as dimethylamino, diethylamino, morpholino, N-methylphenethylamino and N-methylpiperazino. Group C lists 1-(2-*tert*-aminoalkyl)-3,4-dihydro-2-quinolone derivatives,[7] which have the same order of antipyretic and analgesic activity as aminopyrine and may be regarded as cyclization products of the compounds of group B; here the piperidino compounds are the most potent in antitussive activity. Among the piperidino compounds, the three with methyl side chain (XIX, XXII, XXIV) are 1.3 to 2.4 times more potent than the unbranched derivatives (XVII, XX, XXIII). Analgesic, antitussive and other pharmacological activities of isopropylamino-type drugs are, in general, stronger than those of ethylenamino-type compounds in the methadone series.[8] The piperidino group neither abolishes or reduces such a tendency. The antitussive activities of two compounds (XXII and XXIV) are superior to that of codeine phosphate.

In groups D,[9] E, and F,[10] some of which show thiambutene-like structure and weak analgesic activity, piperidino compounds are definitely superior to the others in antitussive activity. The piperidino compound XXXVI, an amide of benactyzine,[11] which possesses weak analgesic as well as antispasmodic actions,[12] is also more potent than the dimethylamino analog, and

(6) W. B. Wright, H. J. Brabander, and R. A. Hardy, *J. Am. Chem. Soc.*, **81**, 1518 (1959).

(7) N. Shigematsu, *Chem. Pharm. Bull.* (Tokyo), **9**, 970 (1961).

(8) O. J. Braenden, N. B. Eddy, and H. Halbach, *Bull. World Health Org.*, **13**, 969 (1955).

(9) N. Shigematsu and G. Hayashi, *Yakugaku Zasshi*, **81**, 421 (1961).

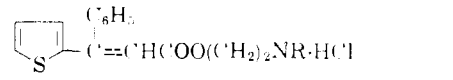
(10) R. Kimura, unpublished.

(11) A. H. Ford-Moore and H. R. Ing, *J. Chem. Soc.*, 55 (1947).

(12) H. Fujimura, T. Ueshima, H. Tomodo, T. Koyazu, and Y. Yamakawa, *Nippon Yakurigaku Zasshi*, **51**, 70 (1955).

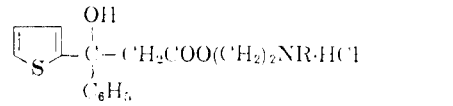
TABLE V

GROUP E.[a] *β-tert*-AMINOETHYL 3-PHENYL-3-(2-THIENYL)-ACRYLATE HYDROCHLORIDES



Compd.	NR	M.p., °C.	Antitussive activity: Animals used	Antitussive activity: AtD_{50} (mg./kg.) Dog i.v.
XXX	$N(CH_3)_2$	179–180	20	7.20 (6.31–8.21)
XXXI	Morpholino	172	20	7.35 (6.74–8.01)
XXXII	Piperidino	160–161	30	4.12 (3.12–5.40)

GROUP F.[a] *β-tert*-AMINOMETHYL 3-HYDROXY-3-PHENYL-3-(2-THIENYL)-PROPIONATE HYDROCHLORIDES



Compd.	NR	M.p., °C.	Antitussive activity: Animals used	Antitussive activity: AtD_{50} (mg./kg.) Dog i.v.
XXXIII	$N(CH_3)_2$	128–129	3	Ineffective at 15.0
XXXIV	Piperidino	168–169	24	9.80 (8.75–11.0)

GROUP G. N-(2'-*tert*-AMINOETHYL)-BENZILIC ACID AMIDE HYDROCHLORIDES[11,12] $(C_6H_5)_2$—CONH$(CH_2)_2$NR·HCl

Compd.	NR	M.p., °C.	Antitussive activity: Animals used	Antitussive activity: AtD_{50} (mg./kg.) dog i.v.	Antitussive activity: Animals used	Antitussive activity: AtD_{50} (mg./kg.) cat i.v.
XXXV	$N(CH_3)_2$	213.8	3	5.0[b]	30	4.80 (3.90–5.90)
XXXVI	Piperidino	204.8	20	2.84 (2.45–3.30)	20	3.40 (2.81–4.12)

[a] Groups E and F were synthesized and supplied by Dr. R. Kimura.[10] [b] Minimal effective dose (MED).

TABLE VI

GROUP H.[a] 1,2-DIPHENYL-2-*tert*-AMINOETHANE HYDROCHLORIDES $C_6H_5CH_2CHC_6H_5 \cdot HCl$ (NR)

Compd.	NR		M.p., °C.	Antitussive activity: Animals used	Antitussive activity: AtD_{50} (mg./kg.) dog i.v.
XXXVII	$N(CH_3)_2$	(±)	187, 210	20	3.50 (2.92–4.20)
XXXVIII	$N(CH_3)_2$	(−)	218–219	20	1.28 (1.06–1.55)
XXXIX	$N(CH_3)_2$	(+)	218–219	25	10.2 (8.5–12.3)
XL	Morpholino	(±)	211	3	Ineffective at 6.2
XLI	Piperidino	(±)	207	30	1.98 (1.68–2.34)
XLII	Pyrrolidino	(±)	212	24	1.92 (1.55–2.38)
XLIII	Pyrrolidino	(−)	242	30	1.18 (1.05–1.32)
XLIV	Pyrrolidino	(+)	242	24	3.00 (2.56–3.51)

[a] Synthesized and supplied by Dr. K. Yamakawa.[14]

its antitussive activity is even superior to that of codeine phosphate in the dog.

Among the compounds of group H, *i.e.*, 1,2-diphenyl-1-*tert*-aminoethane derivatives, regarded as fragments of the morphine nucleus,[13] the *levo*-isomer of 1-dimethylamino-1,2-diphenylethane (XXXVIII) was reported recently[14] to be effective clinically for lumbago and muscular pain, and also as an antitussive in animals. It has now been found that the antitussive activity of the racemic piperidino compound (XLI) is 1.8 times greater than that of the racemic dimethylamino compound (XXXVII). The racemic pyrrolidino compound (XLII) shows almost the same degree of activity as the piperidino compound (XLI), and even the weakest one of the series, the *d*-isomer (XLIV) is more potent than codeine phosphate. In the series of phenothiazine antitussives,[15] adrenergic amines[16] and antihistaminics,[17] the piperidino compounds are always more potent as antitussives in dogs and cats. However, in the series of fluorinated diphenhydramine antihistaminics (LXII) as well as that of 1,2-diphenyl-1-*tert*-aminoethane (XLII) described above, the pyrrolidino group deepens activity more than the piperidino group although the latter is the most effective in increasing activity.

Among camphor derivatives,[18] similar results also were seen in two types of derivatives. However, quaternization of the piperidino group completely abolishes activity (LXIX, LXXIII).

Discussion

The results which are shown in both the previous[1] and present paper emphasize an important role of the piperidino group in manifesting and strengthening antitussive activity in various structures. Lindner[19] also recognized the same tendency in the depressing effect of 2-alkylamino-1,1-diphenylpropanol derivatives on cough induced by electric stimulation of the superior

(13) (a) E. L. May, in "Medicinal Chemistry," A. Burger, ed., Interscience Publishers Inc., New York, N. Y., 1960, p. 321; (b) E. C. Dodds, *Brit. Med. Bull.*, **4**, 88 (1946).

(14) K. Ogiu, H. Fujimura, and K. Yamakawa, *Yakugaku Zasshi*, **80**, 283, 286, 289, 292, 295, 298 (1960).

(15) M. Nakanishi, unpublished.

(16) Z. Horii, J. Tsuji, and T. Inoi, *ibid.*, **77**, 248, 256, 1095 (1957); **78**, (1958).

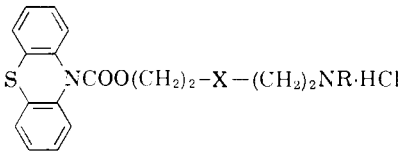
(17) K. Takatori, *ibid.*, **80**, 1759 (1960).

(18) M. Nakanishi, *ibid.*, **79**, 1359, 1363, 1367, 1371 (1959).

(19) E. Lindner and L. Stein, *Arzneimittel-Forsch.*, **9**, 94 (1959); E. Lindner, personal communication (1960).

TABLE VII

SERIES 2. ANTITUSSIVE TYPES IN THE PHENOTHIAZINE SERIES. 2-*tert*-AMINOETHOXYETHYL AND 2-*tert*-AMINOETHYLTHIOETHYL PHENOTHIAZINE-N-CARBOXYLATE HYDROCHLORIDES[a]

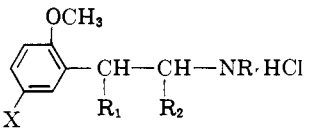


				Antitussive activity			
Compd.	X	NR	M.p., °C.	Animals used	AtD_{50} (mg./kg.) dog i.v.	Animals used	AtD_{50} (mg./kg.) cat i.v.
XLV	O	$N(CH_3)_2$	165.5	20	5.2 (4.4–6.1)	20	7.5 (6.2–9.0)
XLVI	O	Piperidino	158	24	4.8 (3.9–5.9)	25	4.5 (3.9–5.2)
XLVII	S	$N(CH_3)_2$	145	24	8.2 (7.5–9.0)	20	7.7 (6.1–9.8)
XLVIII	S	$N(C_2H_5)_2$	128	20	12.5 (11.1–14.1)	20	10.0 (7.8–12.8)
XLIX	S	Piperidino	174.6	30	4.6 (3.7–5.2)	20	4.0 (3.2–5.0)

[a] Synthesized and supplied by Dr. M. Nakanishi.[15]

TABLE VIII

SERIES 3.[a] ADRENERGIC AMINE TYPES. 2-(2-*tert*-AMINOETHYL)-ANISOLE HYDROCHLORIDES

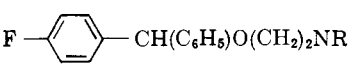


						Antitussive activity			
Compd.	X	R_1	R_2	NR	M.p., °C.	Animals used	AtD_{50} (mg./kg.) dog i.v.	Animals used	AtD_{50} (mg./kg.) cat i.v.
L	H	H	CH_3	$NHCH_3$	129–131	2	Ineffective at 20.0	2	Ineffective at 20.0
LI	H	H	CH_3	$N(CH_3)_2$	157–158	2	20.0[b,c]	2	15.0[b]
LII	H	H	CH_3	Morpholino	178	20	6.4 (5.4–7.6)	20	4.4 (3.6–5.2)
LIII	H	H	CH_3	Piperidino	197	24	3.6 (3.0–4.3)	25	2.4 (2.0–2.9)
LIV	H	CH_3	H	Morpholino	195–196		....	2	Ineffective at 20.0
LV	H	CH_3	H	Piperidino	165–167		....	20	11.3 (10.0–13.7)
LVI	CH_3	H	CH_3	$NHCH_3$	136–137	1	Ineffective at 20.0	2	20.0[b]
LVII	CH_3	H	CH_3	$N(CH_3)_2$	184	20	5.3 (4.2–6.8)[d]	25	4.9 (3.9–6.0)
LVIII	CH_3	H	CH_3	Piperidino	188	25	4.8 (3.7–6.5)[e]	36	1.6 (1.3–1.9)

[a] Synthesized and supplied by Z. Horii, J. Tsuji, and T. Inoi.[16] [b] Minimal effective dose (MED). [c] Convulsion with MED. [d] Excitation. [e] Marked excitation.

TABLE IX

SERIES 4.[a] ANTIHISTAMINIC TYPES. PHENYL-(4-FLUOROPHENYL)-METHYL β-*tert*-AMINOETHYL ETHER HYDROCHLORIDES



				Antitussive activity			
Compd.	NR	Salt	M.p., °C.	Animals used	AtD_{50} (mg./kg.) Dog i.v.	Animals used	AtD_{50} (mg./kg.) Cat i.v.
LIX	$N(CH_3)_2$	Citrate	140	25	6.25 (5.38–7.19)	20	3.68 (3.12–4.27)
LX	$N(C_2H_5)_2$	Citrate	119	20	12.2 (10.2–14.5)	20	7.40 (6.12–8.81)
LXI	Morpholino	HCl	151–155	20	5.84 (4.98–6.83)	20	5.23 (4.46–6.11)
LXII	Pyrrolidino	HCl	142–144	25	2.90 (2.59–3.25)	20	2.58 (2.32–3.01)
LXIII	Piperidino	HCl	162	25	3.20 (2.83–3.62)	24	2.85 (2.52–3.23)

[a] Synthesized and kindly supplied by Dr. K. Takatori.[17]

laryngeal nerve of cats. Recently, Takagi, *et al.*,[20] reported that antitussive potency of antihistaminics of the type $C_6H_5CHRO(CH_2)_{2-3}NR_2$ decreased from piperidino, *via* dimethylamino, to morpholino, when tested by mechanical and chemical (SO_2) stimulations on the tracheal mucosa of the guinea pig. We found a greater effect for piperidino derivatives in spite of differences of stimulation or species used for the experiment. Pyrrolidino groups increased antitussive activity more potently than piperidino groups in both an analgesic and an antihistaminic type tested. If this should hold more generally, it could be assumed that five- and six-membered nitrogenous rings are necessary for the production or strengthening of antitussive activity.

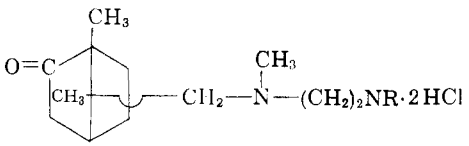
The piperidino group does not always increase other

(20) K. Takagi, H. Fukuda, K. Fujie, K. Matsui, and M. Sato, *Nippon Yakurigaku Zasshi*, **56**, 180§ (1960); *Yakugaku Zasshi*, **81**, 261 (1961).

pharmacological activities such as toxicity, analgesia,[1] general CNS depressant and local anesthetic action in connection with cough depression resulting from stretch receptor anesthesia,[21] although it definitely increases antitussive activity. It appears that piperidino compounds depress predominantly the central respiratory mechanisms[22,23] and definitely inhibit the respiration of brain tissue slices in a glucose medium when tested by Warburg's manometric technique. More detailed mechanisms are now under investigation and will be reported in the near future.

TABLE X

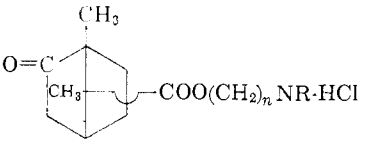
SERIES 5.[a] CAMPHOR DERIVATIVES. α-9-(N-*tert*-AMINOETHYL-N-METHYLAMINO)-CAMPHOR DIHYDROCHLORIDES

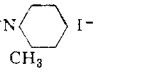
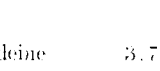


Compd.	NR	M.p., °C.	Antitussive activity: Animals used	Antitussive activity: AtD_{50} (mg./kg.) cat i.v.
LXIV	$N(C_2H_5)_2$	165	3	Ineffective at 20.0
LXV	Piperidino	220.4	5	10.7[b]

TABLE X (*continued*)

dl-bet-AMINOALKYL ISOKETOPINATE HYDROCHLORIDES



Compd.	n	NR	M.p., °C.	Antitussive activity: Animals used	Antitussive activity: AtD_{50} (mg./kg.) cat i.v.
LXVI	2	$N(CH_3)_2$	191	3	Ineffective at 20.0
LXVII	2	$N(CH_3)_3 \cdot I^-$	208	3	Ineffective at 20.0
LXVIII	2	Piperidino	247	20	5.2 (4.4–6.2)
LXIX	2		208	2	Ineffective at 20.0
LXX	3	$N(CH_3)_2$	162	2	Ineffective at 20.0
LXXI	3	$N(CH_3)_3 \cdot I^-$	181	2	Ineffective at 20.0
LXXII	3	Piperidino	203	20	10.5 (8.8–11.6)
LXXIII	3		190	2	Ineffective at 20.0
Control	Codeine phosphate		Dog: 3.76 (3.38–4.19)	Cat: 2.53 (2.24–2.86)	

[a] Synthesized and supplied by Dr. M. Nakanishi.[18] [b] Minimal effective dose (MED).

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Antihypertensive Agents. I. Non-diuretic 2H-1,2,4-Benzothiadiazine 1,1-Dioxides

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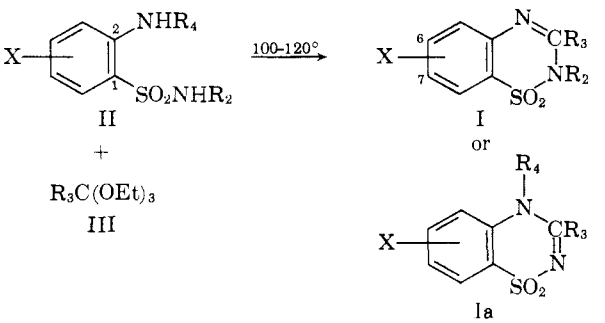
Certain substituted 2H-1,2,4-benzothiadiazine 1,1-dioxides have been synthesized which show antihypertensive but not diuretic activity. The effect on activity of some structural modifications in this series has been examined.

Sulfamoyl substituted 2H-1,2,4-benzothiadiazine 1,1-dioxides, including the 3,4-dihydro compounds, are a well known class of orally effective diuretic agents.[1] Many of them also show an antihypertensive effect and are used clinically in the treatment of mild hypertension.[2] Although the precise mechanism of this action is not known, it has generally been assumed to be related to the diuretic and natriuretic properties of the compounds.[3] However, it has been shown recently that the non-diuretic 7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide[4] (I, X = 7-Cl, R_2 = H R_3 = CH_3) exerts a pronounced antihypertensive effect which is thought to be due to the direct action of the compound at the vascular level.[5] This paper reports the synthesis of I (X = 7-Cl, R_2 = H, R_3 = CH_3) and of related compounds as part of a study to determine the effect of certain structural modifications in this series on biological activity.

The synthesis of the 2H-1,2,4-benzothiadiazine 1,1-dioxides (I) was accomplished by the condensation of a substituted *o*-aminobenzenesulfonamide (II) with the appropriate orthoester (III).[6]



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