Synthesis of 2-Dialkylaminomethyl-1,4-benzoxathians

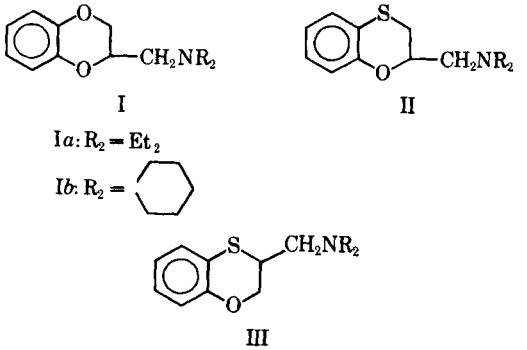
C. S. TSAI, U. S. SHAH, H. B. BHARGAVA, R. G. ZAYLSKIE*, and W. H. SHELVER▲

Abstract □ Some sulfur analogs of 2-dialkylaminomethyl-1,4-benzodioxans were synthesized and evaluated as α-adrenergic blocking agents to observe the effect of substitution of sulfur for oxygen on adrenolytic activity. Reaction of 2-hydroxybenzenethiol with dialkyl-2,3-dibromopropylamines resulted in the formation of 2-dialkylaminomethyl-1,4-benzoxathians. The structure of these compounds was proven by the use of NMR spectroscopy. In an effort to explore other synthetic routes, 2-hydroxybenzenethiol was reacted with ethyl 2,3-dibromopropionate to give an ethyl 1,4-benzoxathiancarboxylate, which was reduced to the corresponding alcohol and converted *via* the tosylate to various dialkylaminomethyl-1,4-benzoxathians. A study of the NMR spectra indicated these compounds were 2-dialkylaminomethyl-1,4-benzoxathians. Pharmacological evaluations using the rat vas deferens preparation demonstrated that the benzoxathians are partial agonists revealing a fundamental difference from the corresponding oxygen analogs, the benzodioxans, which are competitive antagonists to epinephrine.

Keyphrases □ 2-Dialkylaminomethyl-1,4-benzoxathians—synthesis, evaluation as α-adrenergic blocking agents (rat vas deferens) □ α-Adrenergic blocking agents, potential—evaluation of 2-dialkylaminomethyl-1,4-benzoxathians □ 2-Hydroxybenzenethiol—reactant in the formation of 2-dialkylaminomethyl-1,4-benzoxathians □ NMR spectroscopy—identification, 2-dialkylaminomethyl-1,4-benzoxathians

Fourneau and Bovet (1) synthesized the first benzodioxan derivatives with pronounced α-adrenergic blocking activity nearly 40 years ago. However, little progress has been made in determining the mechanism by which these compounds exert their action. The subsequent synthesis of many benzodioxan derivatives has not revealed any compounds with significantly greater activity than 2-diethylaminomethyl-1,4-benzodioxan (*Ia*)[1] or 2-piperidinomethyl-1,4-benzodioxan (*Ib*)[2] found in the original study. Modifications of the nitrogen substituents, the dioxan ring, or the aromatic ring generally led to compounds with decreased adrenolytic activity (2).

The lack of progress in preparation of more active compounds coupled with a lack of knowledge concerning the mechanism of action of these compounds indicates the need for a more thorough examination of structure–activity relationships. To elucidate the role of the oxygen atoms of the dialkylaminomethyl-1,4-benzodioxans, it was proposed to examine the effect of substitution of sulfur for the oxygen atom on the adrenolytic activity of the compounds. The two possible monosulfur analogs of the benzodioxans are the 2-dialkylaminomethyl-1,4-benzoxathians (II) and the 3-dialkylaminomethyl-1,4-benzoxathians (III). This paper describes the synthesis and proof of structure of some 2-dialkylaminomethyl-1,4-benzoxathians (II).

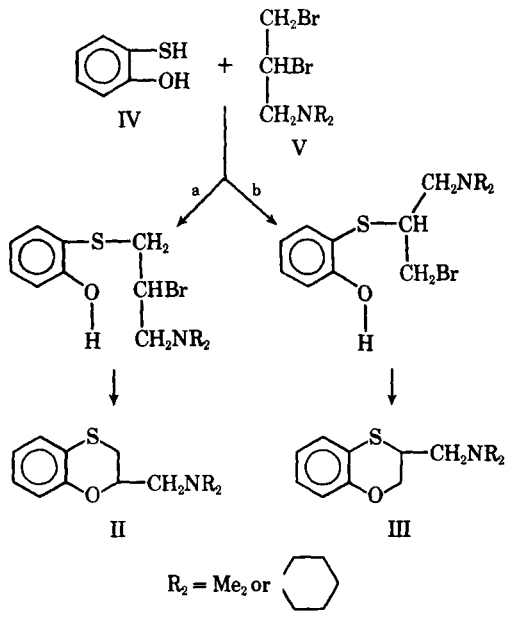


[1] Prosympal, 833 F.
[2] Piperoxan, 933 F.

RESULTS AND DISCUSSION

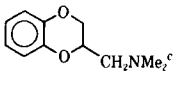
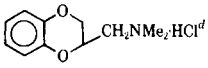
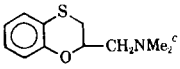
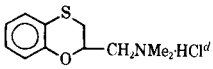
The 2-hydroxybenzenethiol (IV) required as a starting material was synthesized by an alternative procedure to the one described in the literature (3). The thiol group of *o*-aminobenzenethiol was protected with an *n*-butyl group, the protected compound was diazotized and converted to the phenol, and the protecting *n*-butyl group was removed by reduction with sodium in liquid ammonia. All the reactions were routinely carried out with high yields.

An examination of the route in Scheme I reveals either one or both of the two isomeric benzoxathians could be formed when IV is reacted with the appropriate dialkyl-2,3-dibromopropylamine (V). Of the two nucleophilic groups of IV, the sulfur would initiate reaction because of its greater nucleophilicity. The nucleophilic attack of the sulfur atom on the primary carbon atom (carbon 3) would result in formation of the 2-dialkylaminomethyl-1,4-benzoxathian (II) (path a), whereas attack of the sulfur on the secondary carbon atom (carbon 2) would result in formation of III (path b). Attack on the secondary carbon atom (carbon 2) would be favored by anchimeric assistance of the dialkylamino group, a factor responsible for the high reactivity of the β-haloethylamines. Attack of the primary carbon atom (carbon 3) would be favored if the reaction proceeded by an S_N2 mechanism. The reaction of 2,3-dibromopropyl-1-piperidine and *N*,*N*-diethyl-2,3-dibromopropylamine with IV was carried out previously by Bovet and Benoit (5). At that time, no instrumental



Scheme I

Table I—Chemical Shifts of 2-Dimethylaminomethyl-1,4-benzodioxan and 2-Dimethylaminomethyl-1,4-benzoxathian[a]

Structure	NCH_3	CH_2N	$X^b—CH_2—CH$	CH	Aromatic
	2.28	2.52	3.70	4.33	6.83
	2.95	3.32	3.65	4.41	6.80
	2.31	2.60	3.01	4.30	6.90
	3.08	3.58	3.23	—[e]	7.10

[a] All spectra were run on a Varian A-60A NMR spectrometer. [b] X is either oxygen or sulfur. [c] The shifts are relative to tetramethylsilane using deuterated chloroform as the solvent. [d] The shifts are relative to the sodium salt of 3-(trimethylsilyl)propanesulfonic acid. [e] This peak was obscured by the HDO peak at 4.61.

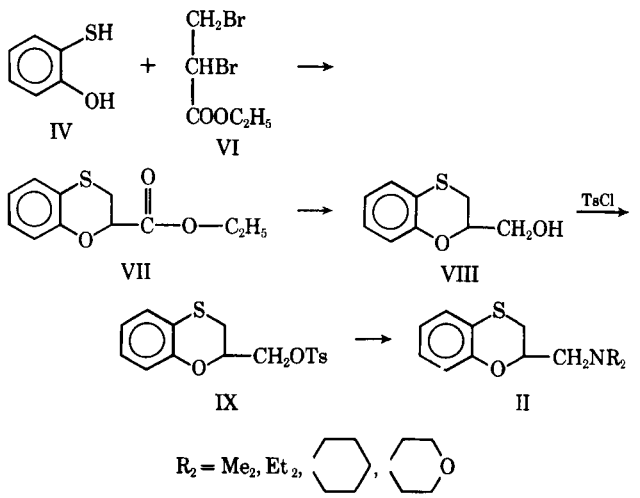
methods were capable of establishing the position of the side chain on the benzoxathian, and these workers indicated that their compounds could be either 2- or 3-substituted benzoxathians. It was found that the reaction of IV with *N,N*-dimethyl-2,3-dibromopropylamine gave predominately 2-dimethylaminomethyl-1,4-benzoxathian and thus proceeded by path a. Examination of the reaction product by GC indicated the formation of less than 10% of other products.

The assignment of the 2-dialkylaminomethyl-1,4-benzoxathian structure to the products was based on the comparison (Table I) of the NMR spectra of the free base and the hydrochloride of the dimethylaminomethylbenzoxathian from the reaction depicted in Scheme I with the NMR spectra of the free base and the hydrochloride of 2-dimethylaminomethyl-1,4-benzodioxan. Compounds with the dimethylamino group were utilized in the initial NMR studies because of the simplicity of their spectra. Groups adjacent to the nitrogen are expected to show large changes in absorption frequency upon protonation of the nitrogen. The assignment of group frequencies in 2-dimethylaminomethyl-1,4-benzodioxan was confirmed by comparing the spectrum of the free base with the spectrum of the hydrochloride. The absorption due to the methyl group was easily identified as a strong singlet occurring at δ 2.28 for in the free base and at δ 2.95 for the hydrochloride. The methylene adjacent to the nitrogen can be assigned an absorption at δ 2.52 for the free base which moves to δ 3.32 in the spectrum of the hydrochloride. The remaining methylene and methine protons of the dioxan ring give rise to an absorption as a complex multiplet from δ 3.70 to δ 4.33 in the spectrum of the free base and from δ 3.65 to δ 4.41 in the spectrum of the hydrochloride. Finally, the aromatic protons occur at δ 6.83 for the free base and at δ 6.80 for the hydrochloride.

The spectrum of the dimethylaminomethyl-1,4-benzoxathians was analyzed in a similar fashion. The signal due to the methyl groups is easily identified as a singlet occurring at δ 2.31 for the free base and at δ 3.08 for the hydrochloride. The methylene group adjacent to the nitrogen gives a doublet at δ 2.60 for the free base and a multiplet at δ 3.58 for the hydrochloride. The methine of the oxathian ring absorbs at approximately δ 4.3, the same range of the benzodioxan methine, which indicates that the benzoxathian isolated is 2-dimethylaminomethyl-1,4-benzoxathian (II) since the similar frequencies indicate that the methine in both compounds are in the same environment, *i.e.*, adjacent to oxygen. The remaining methylene group of the benzoxathian absorbs at δ 3.01 for the free base and δ 3.23 for the hydrochloride. Since these protons are substantially upfield from the corresponding protons for the methylene of 2-dimethylaminomethyl-1,4-benzodioxan, the methylene protons responsible for this absorption must be adjacent to the sulfur atom. The identification of the product of the reaction described in Scheme I is thus confirmed to be 2-dimethylaminomethyl-1,4-benzoxathian (II).

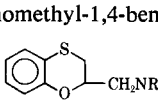
When IV was reacted with 2,3-dibromopropyl-1-piperidine, the product had an NMR spectrum compatible with that expected from 2-piperidinomethyl-1,4-benzoxathian. Conversion of the free base to the corresponding hydrochloride gave a compound melting lower than at the melting point reported by Bovet and Benoit (5); at present, no explanation exists for this difference [observed m.p. 212–214°; lit. (5) m.p. 238°]. The compound was identical to the compound obtained by the alternate route described below.

To examine alternate synthetic procedures, the sequence shown in Scheme II was explored. The reaction of ethyl 2,3-dibromopropionate (VI) with IV resulted in the formation of ethyl 1,4-benzoxathian-2-carboxylate (VII). Comparison of the NMR spectrum of this compound with the NMR spectrum of the corresponding benzodioxan established that the carboethoxy group was in the 2-position. The triplet for the methine (—CH_2CH—COOEt)



Scheme II

Table II—2-Dialkylaminomethyl-1,4-benzoxathian[a]



NR_2	Boiling Point/mm.	Yield, %	Formula	Analysis, % Calc.	Found
NMe_2	140–145°/0.3	55	$C_{11}H_{15}NOS$	C 63.12	63.00
				H 7.22	7.36
				N 6.69	6.46
NEt_2	150–153°/0.3	52	$C_{13}H_{19}NOS$	C 65.80	65.60
				H 8.01	7.82
				N 5.91	5.90
	160–163°/0.3	49	$C_{14}H_{19}NOS$	C 67.43	67.43
				H 7.68	7.60
				N 5.61	5.43
	165–170°/0.3	40	$C_{13}H_{17}NO_2S$	C 62.12	62.10
				H 6.81	6.98
				N 5.57	5.37

[a] All analyses were made on free bases purified by preparative GC.

occurred at δ 4.66 (J = 4 Hz.) for the benzoxathian ester and at δ 4.50 (J = 4 Hz.) for the corresponding benzodioxan ester. The —S—CH_2—CH of the benzoxathian ester gave a doublet at δ 3.03 (J = 4 Hz.), and the O—CH_2—CH of the benzodioxan gave a doublet at δ 4.06 (J = 4 Hz.). The similarity of the methine chemical shift and the difference of the methylene peaks indicate that the methine hydrogen of the benzoxathian is adjacent to the oxygen while the methylene group is adjacent to sulfur, possible only if the carboethoxy group is in the 2-position of the benzoxathian ring.

Reduction of the ester (VII) to the corresponding alcohol (VIII) proceeded in good yield. Conversion of the alcohol to the tosylate (IX) and to the various amines proceeded smoothly, and the compounds listed in Tables II and III were prepared and characterized.

Evaluation of the pharmacological activity (Table IV) of these benzoxathians revealed that they act as partial agonists rather than as competitive antagonists. The difference between an antagonist and an agonist is the value of the intrinsic activity: zero for an antagonist and one for an agonist. Partial agonists have intrinsic activities greater than zero but less than one. Under certain conditions, partial agonists can antagonize agonists, which would explain the previously observed pharmacological effects of 2-piperidinomethyl-1,4-benzoxathian (5). This compound was reported to antagonize the effect of norepinephrine on blood pressure. While the molecular details of the α-adrenergic receptor remain somewhat speculatory, it is apparent that the area surrounding the nitrogen of either an agonist or an antagonist is of prime importance. Indeed, the substitution of the nitrogen of norepinephrine with groups of increasing size transforms the compound from an agonist to a partial agonist to a competitive antagonist (6). In the present case, the substitution of a sulfur for an oxygen relatively distant from the nitrogen of the benzodioxan abolished the antagonist activity and converted the compound into a partial agonist.

The reason for the delicate balance between agonist and antagonist is a matter of conjecture at the present time, but Ariens *et al.* (7) suggested a possible explanation. They proposed that there are two receptors: one for agonist action and one for antagonist action, with both the receptors sharing a common area surrounding the nitrogen of the drug molecule. Whatever the reason, the presence of a sulfur in the 4-position of the benzodioxan nucleus eliminates the antagonistic activity. The relatively low affinity (pD_2) of the benzoxathian (100 times lower than epinephrine) indicates that the sulfur either interferes with receptor fit or prevents the drug from reaching the receptor.

EXPERIMENTAL[3]

2-*n*-Butylmercaptoaniline—A mixture of 200 g. (1.6 moles) of 2-aminobenzenethiol, 2250 ml. of aqueous potassium hydroxide and 400 ml. of ethanol was placed in a 5-l. three-necked flask. Two hundred and sixteen grams (1.6 moles) of 1-bromobutane was added dropwise. Refluxing was continued for 10–12 hr. After the reaction mixture was cooled to room temperature, it was extracted four times with 200-ml. portions of ether. The ether extract was dried over anhydrous sodium sulfate. The ether then was removed, and the residue was distilled at 110–112°/1.5 mm., giving 240 g. (80%) of product. The IR spectrum did not show an SH peak (SH anticipated 2500 cm.$^{-1}$).

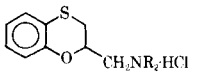
2-Hydroxybutylbenzenethiol—A mixture of 271.1 g. (1.5 moles) of 2-*n*-butylmercaptoaniline, 295 g. of sulfuric acid in 1000 ml. of water, 1500 ml. of water, and 100 g. of crushed ice was placed in a 5-l. beaker. A solution of 105 g. (1.52 moles) of sodium nitrite in 250 ml. of water was rapidly added while the reaction mixture was kept between 0 and 5°. While the diazotization was in progress, 1 l. of sulfuric acid in 750 ml. of water was placed in a 5-l. flask and heated to 120–140°. The diazotized mixture was added to the hot sulfuric acid at such a rate that the reaction mixture boiled vigorously. After the addition, the reaction mixture was cooled to room temperature and extracted four times with 200-ml. portions of ether. The ether was dried over anhydrous sodium sulfate. Evaporation of the ether gave a crude product which was distilled at 85°/0.3 mm., giving 182 g. (70%) of product. The IR spectrum showed an OH peak at 3400 cm.$^{-1}$.

2-Hydroxybenzenethiol (IV)—This compound was obtained by a reductive procedure, adopted from Ferretti (8), for the preparation of *o*-benzenedithiol. To 2.5 l. of liquid ammonia condensed in a 5-l. three-necked flask was added 206 g. (1.13 moles) of 2-hydroxybutylbenzenethiol. Sixty grams (2.6 moles) of sodium was added in small pieces. The excess sodium was destroyed by the cautious addition of 21.4 g. (0.4 mole) of ammonium chloride. The ammonia was allowed to evaporate, and the solid residue was dissolved in 400 ml. of water. The aqueous layer was extracted with ether and the ether layer was discarded. Then the aqueous layer was made acidic with 20% hydrochloric acid and extracted with ether. After drying over anhydrous sodium sulfate, the ether was evaporated and IV was distilled at 50–60°/0.5 mm. [lit. (3) 40–44°/0.1 mm.], giving 115 g. (80%) of product. The IR spectrum showed a broad OH peak (3400 cm.$^{-1}$) and an SH peak (2560, 2510 cm.$^{-1}$).

Ethyl 1,4-Benzoxathian-2-carboxylate (VII)—A mixture of 88.2 g. of IV, 1 l. of acetone, and 70 g. (0.5 mole) of anhydrous potassium carbonate was placed in a three-necked flask. Then 50 g. (0.21 mole) of ethyl 2,3-dibromopropionate was added dropwise, and the mixture was heated to reflux. The addition was repeated three times using a total of 280 g. (2.0 moles) of potassium carbonate and 200 g.

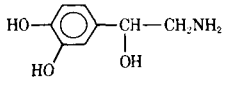
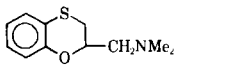
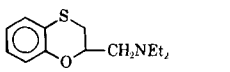
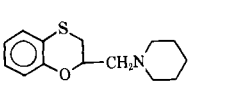
[3] All melting points were determined on a Thomas-Hoover melting-point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer grating IR spectrophotometer, model 337. Solid samples were run as KBr disks, and liquid samples were run neat. The NMR spectra were recorded on a Varian Associates A-60A spectrometer in deuterated chloroform using tetramethylsilane or in deuterium oxide using the sodium salt of 3-(trimethylsilyl)propanesulfonic acid as an internal standard. The NMR spectra given are in terms of δ and show the multiplicity (s = singlet, d = doublet, t = triplet, and m = multiplet), integration, and type of proton. The carbon–hydrogen–nitrogen analyses were carried out by The Alfred Bernhardt Mikroanalytiches Laboratorium, West Germany.

Table III—2-Dialkylaminomethyl-1,4-benzoxathian Hydrochlorides



NR_2	Melting Point	Formula	Analysis, % Calc.	Found
NMe_2	204–206°	$C_{11}H_{16}ClNOS$	C 53.78	53.78
			H 6.57	6.70
			N 5.70	5.60
NEt_2	127–128°	$C_{13}H_{20}ClNOS$	C 57.07	56.92
			H 7.31	7.26
			N 5.12	5.22
	212–214°	$C_{14}H_{20}ClNOS$	C 58.82	57.74
			H 7.02	7.01
			N 4.89	5.05
	194–195°	$C_{13}H_{18}ClNO_2S$	C 54.20	54.07
			H 6.31	6.15
			N 4.87	4.81

Table IV—Intrinsic Activity and Affinity of 2-Dialkylaminomethyl-1,4-benzoxathians Tested on the Rat Vas Deferens[a]

Structure	Intrinsic Activity[b]	pD_2[c]
	1.00	5.40
	0.47	3.48
	0.91	3.99
	0.85	4.02

[a] The values represent the average of two experiments per determination. [b] The ratio of the height of contraction produced by the drug to the height of contraction produced by (−)-norepinephrine. [c] The negative logarithm of the concentration of the drug needed to produce 50% of the maximum contraction produced by the drug.

(0.84 mole) of ethyl 2,3-dibromopropionate. The refluxing was continued for 36 hr. After filtering, the reaction mixture was concentrated to 200 ml. and diluted with 400 ml. of water. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were dried over anhydrous sodium sulfate and the ether was removed. The residue was distilled at 130°/0.5 mm., giving 100 g. (47%) of product. The IR spectrum showed a carbonyl peak (1770, 1750 cm.$^{-1}$); NMR ($CDCl_3$): 1.2 (t, 3, CH_3CH_3), 3.1 (d, 2, S—CH_2), 4.0 (q, 2, CH_2CH_3), 4.8 (t, 1, O—C*H*), and 6.5 (m, 4, Ar—*H*).

2-Hydroxymethyl-1,4-benzoxathian (VIII)—A mixture of 280 g. (0.98 mole) of 70% sodium bis(2-methoxyethoxy)aluminum hydride in benzene and 500 ml. of tetrahydrofuran was placed in a three-necked flask and 100 g. (0.49 mole) of VII was added dropwise with stirring and refluxing. The refluxing was continued for 8–9 hr. After cooling the reaction mixture, 300 ml. of 10% hydrochloric acid was added and the mixture was filtered. The filtrate was concentrated to approximately 200 ml. and diluted with 600 ml. of water. The aqueous layer was extracted with ether. After the ether extract was dried over anhydrous sodium sulfate, the ether was evaporated, giving 61 g. (78%) of crude product. The IR spectrum showed an OH peak (3400 cm.$^{-1}$); NMR ($CDCl_3$): 2.25 (s, 1, O*H*), 2.90 (two d, 2, S—CH_2), 3.7 (d, 2, CH_2OH), 4.2 (m, 1, O—C*H*), and 6.5 (m, 4, Ar—*H*).

2-Hydroxymethyl-1,4-benzoxathian *p*-Toluenesulfonate (IX)—A mixture of 60 g. (0.3 mole) of VIII and 107 ml. of anhydrous pyridine was placed in a 500-ml. flask; 60 g. (0.3 mole) of *p*-toluenesulfonyl chloride (TsCl) was added at such a rate that the temperature did not exceed 20°. After the mixture was stored in a refrigerator for 48 hr., it was poured into 500 ml. of cold water. The aqueous layer was extracted with chloroform. After drying over anhydrous sodium sulfate, the chloroform layer was evaporated, giving 99 g. (98%) of product. The IR spectrum did not show an OH peak; NMR ($CDCl_3$): 2.41 (s, 3, CH_3), 2.96 (d, 2, S—CH_2), 4.30 (m, 3, O—C*H* and CH_2OTs), and 6.93–7.71 (m, 8, Ar—*H*).

2-Dialkylaminomethyl-1,4-benzoxathian (Method A)—The amines were obtained by following Scheme II. A mixture of 150 ml. of dimethyl sulfoxide and 25 g. (0.08 mole) of the tosylate was placed in a 500-ml. flask, and 0.35 mole of the amine was added. The reaction mixture was heated at 50–60° for 60 hr. After this period the reaction mixture was poured into 500 ml. of water and extracted with ether. The ether layer was extracted with 10% hydrochloric acid, and the aqueous layer was made alkaline with 40% sodium hydroxide. The aqueous layer was extracted with ether and the ether extract was dried over anhydrous sodium sulfate. The ether was evaporated and the crude product was distilled under reduced pressure. The free base was dissolved in anhydrous ether and dry hydrogen chloride gas was bubbled through the solution, and the crude hydrochloride was recrystallized from methanol and diethyl ether. The yields, boiling points, and analyses of the free bases are given in Table II. The melting points and analyses of the hydrochlorides are given in Table III.

2-Dialkylaminomethyl-1,4-benzoxathian (Method B)—A mixture of 12.6 g. (0.1 mole) and 50 g. (0.5 mole) of anhydrous potassium carbonate and 80 ml. of acetone was placed in a 500-ml. three-necked flask. An acetone solution of 33.2 g. (0.1 mole) of 1-piperidine-2,3-dibromopropylamine hydrochloride was added, and the reaction mixture was allowed to reflux for 8–10 hr. After the reaction mixture was cooled to room temperature, it was diluted to 400 ml. with water and extracted with ether. The ether layer was extracted with 10% hydrochloric acid, and the aqueous layer was made alkaline with 40% sodium hydroxide. The aqueous layer was extracted with ether, and the ether extract was dried over anhydrous sodium sulfate. The ether was evaporated and the crude product was distilled, giving 1.0 g. (10%) of product. The free base was dissolved in anhydrous diethyl ether and dry hydrogen chloride gas was bubbled through the solution, and the crude hydrochloride was recrystallized from methanol and diethyl ether, m.p. 212–214° [lit. (5) m.p. 238°]. The same method was used to prepare the 2-dimethylaminomethyl-1,4-benzoxathian, m.p. 203–205°. The melting points, IR spectra, and NMR spectra of these compounds were identical to those obtained by Method A.

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* U. S. Department of Agriculture, Agricultural Research Service, Entomology Research Division, Metabolism and Radiation Research Laboratory, Fargo, N. Dak.

▲ To whom inquiries should be directed.