The Synthesis of 1-Haloalkyl-1,3,4,5-tetrahydro-2-benzoxepins

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Short, efficient routes to several 7,8-dimethoxy-1-haloalkyl-1,3,4,5-tetrahydro-2-benzoxepins were developed. These benzoxepins were prepared by the Lewis acid catalyzed condensation of the acetals of chloropropionaldehyde or bromoacetaldehyde with 3-(3,4-dimethoxyphenyl)-1-propanol. This condensation was facilitated by methyl substitution on the propanol. In an alternate route, ethyl 3-(3,4-dimethoxyphenyl)propanoate was acylated with 3-chloropropionyl chloride. The adduct was reduced with lithium aluminum hydride. The resultant 3-[2-(3-chloro-1-hydroxypropyl)-4,5-dimethoxyphenyl]propanol was dehydrated to the corresponding tetrahydrobenzoxepin. By these two general routes, 7,8-dimethoxy-1,3,4,5-tetrahydro-2-benzoxepins were produced which were substituted by hydrogen or methyl at benzoxepin C-4 and chloroethyl or bromomethyl at benzoxepin C-1.

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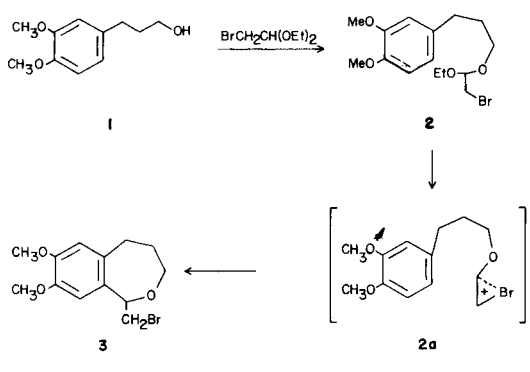
The chemistry and biological activity of the 1,3,4,5-tetrahydro-2-benzoxepin ring system have not been extensively explored (1). We now report several short, efficient routes to 1-haloalkyl-1,3,4,5-tetrahydro-2-benzoxepines. These haloalkyl benzoxepins serve as novel alkylating agents for a variety of amines. The biologically most interesting amine adducts link the electron rich dimethoxyphenyl ring of the benzoxepin with aryl piperazines *via* an alkyl chain at benzoxepin C-1 (2a,b). Many of these adducts are potent hypotensives. For example, 1-(4-fluorophenyl)-4-[2-(1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin-1-yl)ethyl]piperazine is a post synaptic alpha blocker with both central and peripheral activities on blood pressure (2a).

Humber has reported that 6,7-dimethoxy-1-haloalkylisochromans are efficiently and conveniently prepared by reaction of various halo substituted aldehydes and ketones with 2-(3,4-dimethoxyphenyl)ethanol (3). This method for the 6-membered isochroman has not been applied to the synthesis of the analogous 7-membered tetrahydrobenzoxepin ring system. Indeed, such 1-haloalkyl-1,3,4,5-tetrahydro-2-benzoxepins have not been reported in the literature. We have developed two routes for the synthesis of 7,8-dimethoxy-1-haloalkyl-1,3,4,5-tetrahydro-2-benzoxepins.

Scheme I

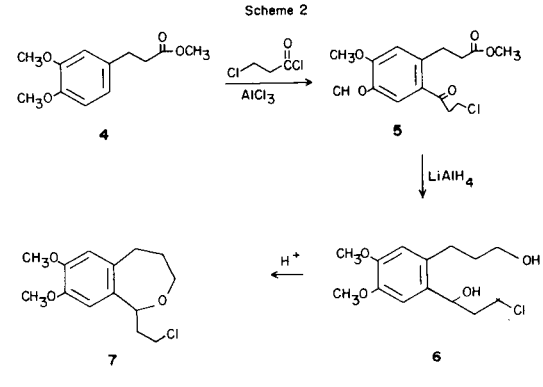


Results and Discussion.

1-Bromomethyl-1,3,4,5-tetrahydro-2-benzoxepin was synthesized by the route shown in Scheme I (2b). Reduction of 3-(3,4-dimethoxyphenyl)propanoic acid with borane-methyl sulfide gave alcohol **1**. Benzoxepin **3** was formed from an electrophilic cyclization with bromoacetaldehyde diethyl acetal and alcohol **1**. A similar cyclization has been reported for the synthesis of 1-bromomethyl-6,7-dimethoxyisochroman (3). Whereas the reported cyclization to the analogous six-membered isochroman system proceeds rapidly and in high yield under mild conditions, the benzoxepin ring of **3** formed with considerably more reluctance. Even with a full equivalent of trifluoroacetic acid, the mixed actal intermediate (**2**) can be isolated in significant yield. In the case of the isochroman ring, a mixed acetal intermediate is not observed.

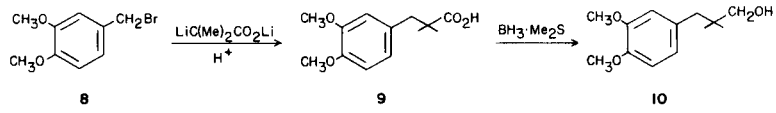
The above condensation reaction was next extended to the two carbon chain case. The diethyl acetal of chloropropionaldehyde was substituted for the diethyl acetal of bromoacetaldehyde. These acetals, which are both commercially available, were selected because of convenience. However, only a 5-10% yield of 1-chloroethyl-1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin **7** and a small amount of starting material were isolated when dimethoxyphenyl-

Scheme 2



0022-152X/81/040821-04$02.25

Scheme 3



propanol **1** and the diethyl acetal of chloropropionaldehyde were reacted under our standard cyclization conditions. The difference between the bromomethyl and chloroethyl compounds may be explained by the intermediacy of the 3-membered bromonium ion **2a** (Scheme 1) in the reaction of **1** and bromoacetaldehyde acetal. A similar stabilized intermediate like **2a** can not be formed from the mixed acetal which is formed from dimethoxypropanol **1** and chloropropionaldehyde diethyl acetal. Both the chlorine atom which is less effective than bromine in distributing charge and a four-membered chloronium intermediate discourage participation of chlorine in the transition state to **7**. Because our standard conditions were poor with chloropropionaldehyde diethyl acetal, we developed an alternate route to the 1-chloroethyltetrahydro-benzoxepin **7**. This route is shown in Scheme 2.

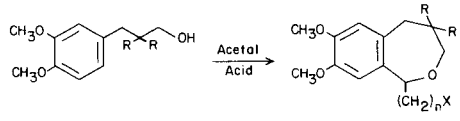
Friedel-Crafts acylation of methyl 3-(3,4-dimethoxyphenyl)propanoate **4** with 3-chloropropionyl chloride and aluminum chloride yielded **5** and established the necessary ring substitution pattern. Reduction of **5** with lithium aluminum hydride gave the diol **6**. Dehydration of 6 with *p*-toluenesulfonic acid gave 1-chloroethyl-1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin **7**. The overall yield, starting from 3-(3,4-dimethoxyphenyl)propanoic acid, is 50-60%. This entire sequence requires only a clean-up chromatography of the final product.

With the one and two carbon haloalkyl benzoxepins in hand, we next turned our attention to the synthesis of 4,4-dimethylbenzoxepins. With these alkylated benzoxepins, we planned to investigate the influence of ring alkylation on the biological activity of benzoxepin derivatives (2). The logical precursor of these methylated systems is 2,2-dimethyl-3-(3,4-dimethoxyphenyl)-1-propanol **10**. The synthesis of propanol **10** is shown in Scheme 3. Carboxylic acid **9** which was obtained from 3,4-dimethoxybenzyl bromide and the dianion of isobutyric acid (4) was reduced with borane methyl sulfide to alcohol **10** in excellent yield. The successful conversion of propanol **10** to the 1-bromomethyl and 1-chloroethyl benzoxepins is summarized in Table 1. Propanol **10** cyclized readily with chloropropionaldehyde diethyl acetal to give benzoxepin **11** in 61% yield, compared to 5-10% yield for the analogous reaction of the acetal with **1**. Correspondingly, cyclization of **10** with bromoacetaldehyde diethyl acetal gave **12** in 88% yield, compared with 37% for the cyclization of **1** to **3**. The success of the direct cyclization in the dialkylated series must be due at least in part to the *gem*-dialkyl effect. According to Allinger and Zalkow, ring closure reactions are enhanced by geminal alkyl substitution by a reduction in gauche interactions in the alkylated system and by a reduction in internal rotations in the open chain dialkylated starting material (5).

In summary, we have reported novel synthesis of 1-haloalkyl-1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepins. The biological activity of these benzoxepins and their adducts with aryl piperazines has been reported elsewhere (2).

Table 1

Direct Cyclization of Dimethoxyphenylpropanol Substrates to Benzoxepins



Substrate	R	Acid	n	Acetal	Product	Isolated Yield, %
1	H, H	trifluoroacetic acid	1	bromoacetaldehyde diethyl acetal	**3**	37
10	CH_3, CH_3	boron trifluoride etherate	1	bromoacetaldehyde diethyl acetal	**12**	88
1	H, H	*p*-toluenesulfonic acid monohydrate	2	chloropropionaldehyde diethyl acetal	**7**	5-10
10	CH_3, CH_3	boron trifluoride etherate	2	chloropropionaldehyde diethyl acetal	**11**	61

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Nuclear magnetic resonance (nmr) spectra were taken on a Varian HFT-80 spectrometer. Medium pressure chromatographies were done on EM Silica Gel 60. Microanalyses were performed by the Physical and Analytical Chemistry Department, The Upjohn Company. All reactions were done under a nitrogen atmosphere. Skelly Solve B is a product of the Skelly Oil Company. 3-(3,4-Dimethoxyphenyl)propanoic acid was purchased from the Aldrich Chemical Company.

3-(3,4-Dimethoxyphenyl)propanol (**1**) (6).

To 50.0 g (0.28 mole) of 3-(3,4-dimethoxyphenyl)propanoic acid in 300 ml of methylene chloride was added dropwise 38 ml (0.38 mole) of 10*M* borane methyl sulfide (Aldrich). The reaction mixture was stirred for 1 hour and then washed with aqueous bicarbonate and brine. The organic layer was dried over sodium sulfate and taken to dryness to give 47.1 g (87%) of **1** as a colorless liquid; nmr (deuteriochloroform): δ 1.84 (m, 2H), 2.09 (broad s, 1H), 2.65 (t, 2H), 3.65 (t, 2H), 2.81 (s, 6H), 6.71 (s, 3H).

1-Bromomethyl-1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin (**3**) and mixed acetal (**2**).

A mixture of 5.00 g (0.026 mole) of **1**, 9.76 ml (0.065 mole) of bromoacetaldehyde diethyl acetal, and 2.0 ml (0.026 moles) of trifluoroacetic acid (TFA) in 125 ml of nitromethane was heated at 65° for 2.5 hours. The mixture was then partitioned with methylene chloride and aqueous sodium bicarbonate. The organic phase was filtered through sodium sulfate and taken to dryness. The residue was chromatographed on a short silica gel column (methylene chloride) to remove baseline tars and the product fractions were re-chromatographed on silica gel (10% ethyl acetate/Skelly Solve B) to give 1.67 g of the mixed acetal **2** (more mobile) and 2.00 g (38%) of **3** as a colorless oil.

Compound **3**.

Compound **3** had nmr (deuteriochloroform): δ 1.80 (m, 2H), 2.85 (m, 2H), 3.78 (m, 4H), 3.85 (s, 6H), 4.83 (t, 1H), 6.62 (s, 2H).

Anal. Calcd. for $C_{13}H_{17}BrO_3$: C, 51.84; H, 5.69; Br, 26.53. Found: C, 51.60; H, 5.76; Br, 26.36.

Mixed Acetal **2**.

This compound had nmr (deuteriochloroform): δ 1.22 (t, 3H), 1.90 (m, 2H), 2.68 (t, 2H), 3.38 (d, 2H), 3.60 (m, 2H), 3.82 (2s, 6H), 4.67 (t, 1H), 6.78 (s, 3H). Mixed acetal **2**, an oil, was not analyzed.

Methyl 3-[2-(3-chloro-1-oxopropyl)-4,5-dimethoxyphenyl]propanoate (**5**).

Methyl 3,4-dimethoxyphenylpropanoate **4** was prepared from 3,4-dimethoxyphenylpropanoic acid and methanolic hydrogen chloride (m.p. 40.5-41.5).

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.25; H, 7.19.

To 53.0 g (0.236 mole) of 3,4-dimethoxyphenylpropanoic acid methyl ester, 33.8 ml (0.355 mole) of 3-chloropropionyl chloride, and 1 l of methylene chloride was added 47.3 g (0.355 mole) of aluminum chloride. After stirring for 3 hours, 3.5 ml of 3-chloropropionyl chloride and 3.8 g of aluminum chloride were added and the mixture was stirred for an additional 2 hours. The mixture was then cooled in an ice bath and water was slowly added. The mixture was shaken with 10% hydrochloric acid and the organic layer dried over sodium sulfate. The organic phase was concentrated. Ether was added and the material crystallized. Recrystallization from methylene chloride, ethyl ether and petroleum ether gave 54.0 g (73%) of **5**, mp 88-89°; ir: 1733, 1669 cm^{-1}.

Anal. Calcd. for $C_{15}H_{19}ClO_5$: C, 57.23; H, 6.08. Found: C, 57.41; H, 6.07.

2-(3-Chloro-1-hydroxypropyl)-4,5-dimethoxybenzenepropanol (**6**).

To 54.0 g (0.172 mole) of **5** in 1500 ml of ether was added 6.4 g. of lithium aluminum hydride. The mixture was stirred overnight and then was quenched with 6.4 ml water, 6.4 ml of 15% sodium hydroxide and 19.2 ml of water. The resulting slurry was filtered through a Celite and sand plug and the filtrate was washed with brine. The organic layer was filtered through sodium sulfate and taken to dryness *in vacuo* to give **6**. The chlorodiol **6** was fairly pure by tlc. Because it was not stable, the isolated product was used in the next step without further purification; nmr (deuteriochloroform): δ 1.85 (m, 2H), 2.10 (m, 2H), 2.33 (broad s, 2H), 2.70 (m, 2H), 3.60 (m, 4H), 3.87 (s, 6H), 5.15 (m, 1H), 6.63 (s, 1H), 6.93 (s, 1H).

1-Chloroethyl-1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin (**7**).

To 40 g of crude **6** in 500 ml of methylene chloride was added 13 g of *p*-toluene sulfonic acid monohydrate. After stirring for 10 minutes the solution was washed with aqueous sodium bicarbonate and brine. The organic layer was filtered through sodium sulfate and taken to dryness. Chromatography on silica gel (20% ethyl acetate in Skelly Solve B) gave 14.7 g of product (56% overall from 4) as an oil; nmr (deuteriochloroform): δ 1.80 (m, 2H), 2.32 (m, 2H), 2.95 (m, 2H), 3.75 (m, 2H), 3.86 (s, 6H), 4.20 (m, 2H), 4.78 (q, 1H), 6.70 (s, 2H).

Anal. Calcd. for $C_{14}H_{19}ClO_3$: C, 62.10; H, 7.07; Cl, 13.10. Found: C, 61.79; H, 7.09; Cl, 12.81.

3,4-Dimethoxybenzyl Bromide (**8**).

The literature procedure (**8**) was modified. To an ice-cooled solution of 96 g (0.57 mole) of 3,4-dimethoxybenzyl alcohol in 800 ml of toluene and 3000 ml of hexane was added 175 ml of 48% hydrogen bromide. After 2 hours the mixture was filtered through sodium sulfate and concentrated to approximately 1 l. The concentrated solution was allowed to stand overnight in the refrigerator, after which 7.72 g of a solid with an nmr spectrum which was consistent with 1-(2-bromomethyl-4,5-dimethoxyphenyl)-1-(3,4-dimethoxyphenyl)methane was collected (mp 104-105.5°) and discarded. The filtrate was taken to dryness, the oil was taken up in ether, and Skelly Solve B was added until a slight cloudiness persisted. After standing in the refrigerator, 51.6 g of 3,4-dimethoxybenzyl bromide were collected (mp 47-50°). Second and third crops were collected for a total of 89.2 g (68%); nmr (deuteriochloroform): δ 3.87 (2s, 6H), 4.49 (s, 2H), 6.85 (m, 3H).

3-(3,4-Dimethoxyphenyl)-2,2-dimethylpropanoic Acid (**9**).

To 66.8 ml (0.476 mole) of diisopropylamine in 1500 ml of THF cooled in an ice-brine bath was added 300 ml of 1.6*M* *n*-butyllithium. After stirring for 10 minutes, 20.0 ml (0.216 mole) of isobutyric acid was added (4), followed by 37.7 ml (0.216 mole) of hexamethylphosphoramide. The mixture was stirred for 5 hours, after which 50.0 g (0.216 mole) of 3,4-dimethoxybenzyl bromide was added. After 16 hours, a small amount of saturated aqueous ammonium chloride was added and the mixture was washed with 7% aqueous sodium hydroxide, backwashing with ether. The aqueous layers were made acidic with concentrated hydrochloric acid and extracted with methylene chloride. The organic layers were filtered through sodium sulfate and taken to dryness. The crude solid was taken on to the next step without further purification. A small sample was crystallized from ether: Skelly Solve B, mp 102-108°; nmr (deuteriochloroform): δ 1.20 (s, 6H), 2.82 (s, 2H), 3.82, 3.84 (6H), 6.72 (m, 3H), 8.0 (broad s, 1H).

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.19; H, 7.58.

3-(3,4-Dimethoxyphenyl)-2,2-dimethyl-1-propanol (**10**).

To an ice-cooled solution of crude acid **9** (75 g) in 1 l of methylene chloride was added 35 ml of 10*M* borane methyl sulfide complex. The ice bath was removed and the solution was stirred for 2.5 hours. Aqueous sodium bicarbonate was then slowly added until no more effervesence occurred. The aqueous layer was decanted and the organic phase was washed with water and aqueous sodium bicarbonate. The organic layer was filtered through sodium sulfate and taken to dryness. Chromatography on silica gel (20% ethyl acetate in Skelly Solve B) gave 39.2 g of **10** (81% overall yeild from 3,4-dimethoxybenzyl bromide) which crystallized upon standing (mp 48.5-50.0°).

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.78. Found: C, 69.64; H, 8.78.

1-(2-Chloroethyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-4,4-dimethyl-2-benzoxepin (**11**).

To 4.93 g (0.022 mole) of **10** and 5.52 ml (0.033 mole) of 3-chloropropionaldehyde diethyl acetal in 250 ml of nitromethane was added 2.70 ml (0.022 mole) of boron trifluoride etherate. The mixture was stirred at room temperature for 1.25 hours, after which methylene chloride was added and the solution was washed with aqueous sodium bicarbonate and water. The organic layer was filtered through sodium sulfate and concentrated. Ether was added to the residue and the resulting solids were removed by filtration. The filtrate was concentrated and the residue chromatographed on silica gel (20% ethyl acetate in Skelly Solve B) to give 4.2 g (64%) of **11** as a solid, mp 66-67°; nmr (deuteriochloroform): δ 0.83 (2s, 6H), 2.25 (m, 2H), 2.69 (d, 2H), 3.55 (d, 2H), 3.75 (t, 2H), 3.85 (2s, 7H), 4.72 (q, 1H), 6.63 (2s, 2H).

Anal. Calcd. for $C_{16}H_{23}ClO_3$: C, 64.31; H, 7.76. Found: C, 64.49; H, 7.61.

1-Bromomethyl-1,3,4,5-tetrahydro-7,8-dimethoxy-4,4-dimethyl-2-benzoxepin (**12**).

To 10.0 g (0.045 mole) of **10** and 13.6 ml (0.091 mole) of bromoacetaldehyde diethyl acetal in 300 ml of nitromethane was added 4.4 ml (0.036 mole) of boron trifluoride etherate. The mixture was stirred for 3.5 hours. The mixture was worked up in the manner of compound **11** to give 13.08 g (88%) of crystalline **12** after chromatography (mp 50-54°); nmr (deuteriochloroform): δ 0.86 (2s, 6H), 2.67 (q, 2H), 3.48 (d, 2H), 3.68 (d, 2H), 3.86 (s, 6H), 4.80 (t, 1H), 6.60 (2s, 2H).

Anal. Calcd. for $C_{15}H_{21}BrO_3$: C, 54.62; H, 6.43; Br, 24.27. Found: C, 54.64; H, 6.41; Br, 24.03.

REFERENCES AND NOTES

(1) For a review, see "The Chemistry of Heterocyclic Compounds," Vol. 26, A. Rosowsky, Ed., Wiley Interscience, New York, N. Y., 1972, pp. 86-89.

(2a) J. M. McCall, R. E. TenBrink, D. T. Pals, R. B. McCall, J. Orley, S. J. Humphrey and M. G. Wendling, *J. Med. Chem.*, **24**, 64 (1981); (b) R. E. TenBrink, J. M. McCall and H. G. Johnson, *J. Med. Chem.*, **23**, 1058 (1980).

(3) T. A. Dobson and L. J. Humber, *J. Heterocyclic Chem.*, **12**, 591 (1975).

(4) P. E. Pfeffer, L. S. Silbert and J. M. Chirinko, Jr., *J. Org. Chem.*, **37**, 451 (1972).

(5) N. L. Allinger and V. Zalkow, *J. Org. Chem.*, **25**, 701 (1960).

(6) D. Nasipuri, J. Roy and U. Rakshit, *J. Indian Chem. Soc.*, **37**, 369 (1960).

(7) We have reported this preparation elsewhere (reference 2b). We include it here for ready comparison to the synthesis of the other benzoxepins.

(8) R. D. Haworth, W. H. Perkin and J. Rankin, *J. Chem. Soc.*, **127**, 1444 (1925).