Oxygen Heterocycles by the Parham Cyclialkylation[1]

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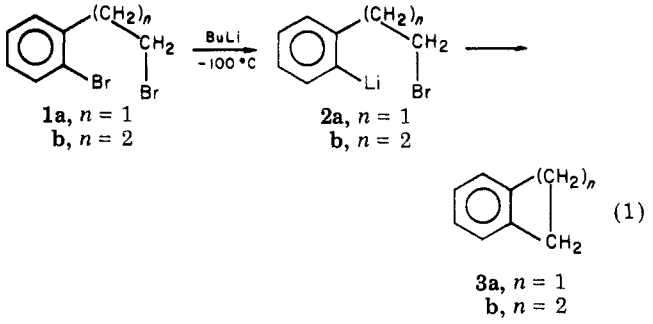
Received October 27, 1980

The addition of butyllithium at −100 °C to ω-bromoalkyl ethers of o-bromophenol (and its congeners) led to preferential exchange of the aryl bromine at position 2. The resulting organolithium reagents, under suitable conditions, cyclized to afford 2,3-dihydrobenzofurans (**6**), 3,4-dihydro-2*H*-1-benzopyrans (**13**), or 2,3,4,5-tetrahydro-1-benzoxepins (**16**) in good yields, but less satisfactory results were obtained with the intermediate expected to produce 8-methyl-3,4,5,6-tetrahydro-2*H*-1-benzoxocin (**19**). ω-Bromoethyl and ω-bromopropyl ethers of suitable dibromophenols were treated successively with 2 equiv of butyllithium and an electrophile to yield derivatives of **6** and **13**.

As part of a systematic study of the effect of butyllithium at −100 °C on (bromophenyl)alkyl halides, Parham et al.[2] discovered what has been called the Parham cyclialkylation reaction.[3,4] The first such cyclization was encountered when 2,β-dibromoethylbenzene (**1a**, eq 1) was



1a, $n = 1$
b, $n = 2$

2a, $n = 1$
b, $n = 2$

(1)

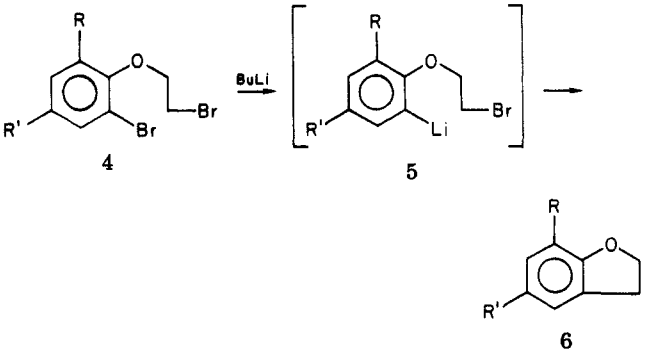
3a, $n = 1$
b, $n = 2$

allowed to exchange with butyllithium and the resulting 2-lithio(β-bromoethyl)benzene (**2a**) was warmed to 25 °C, affording a 68% yield of benzocyclobutene (**3a**). Through use of suitable derivatives of **1a**, substituted benzocyclobutenes may be prepared conveniently[3,5] in good yield. Parham et al.[2] also demonstrated that indan (**3b**) may be prepared in 78% yield by starting with 3-(2-bromophenyl)-1-bromopropane (**1b**).

The purpose of the present work was to determine whether the Parham cyclialkylation could be extended to the formation of rings containing oxygen atoms, and if so, how yields might vary with ring size.

2-(o-Bromophenoxy)ethyl bromides **4** are readily available[6] by the action of ethylene dibromide on a suitable phenol in the presence of alkali. Treatment of these bromides (**4**) with butyllithium at −100 °C led to halogen–metal exchange to yield **5** (Table I) which rapidly eliminated lithium bromide.[7] As may be seen in Table I, good yields (69–79%) of the expected 2,3-dihydrobenzofurans **6** were obtained. The phenoxyethyl bromides **4e** and **4f**, which have a second bromine in the aromatic ring, are of special interest in that each offers the possi-

Table I. Cyclization of 2-(o-Bromophenoxy)ethyl Bromides 4 to 2,3-Dihydrobenzofurans 6



4 **5** **6**

	R	R'	ethyl bromides 4, bp, °C (torr)	2,3-dihydrobenzofurans 6 yield, %	2,3-dihydrobenzofurans 6 bp, °C (torr)
a	H	H	92-97 (0.27-0.40)[a]	69	67.5-70 (8.0)[b]
b	H	Me	86-87 (0.08-0.09)[d]	73	71-74 (3.8)[d]
c	H	MeO	*e, f*	77	90-91 (2.5)[g]
d	H	Cl	136-137 (0.05-0.06)[f,h]	71	51-53 (0.05)[f]
e	H	Br	*f, j*	79[k]	*f, l*
f	Br	Me	122-134 (0.08-0.12)[f,m]	78	65-70 (0.04)[n]

[a] Lit.[8] bp 110-111 °C (1-2 torr). [b] Lit.[9] bp 88-90 °C (18 torr). [c] Lit.[10] bp 172-173 °C (15 torr). [d] Lit.[11] bp 97 °C (15 torr). [e] Recrystallized from CH_2Cl_2-hexane; 47% yield; mp 63-64.5 °C. [f] Analysis for C, H, and halogen (if present) was ±0.35% of theoretical. [g] Lit.[12] bp 63-64 °C (0.20 torr). [h] Prepared (47% yield) by the general method. Total halogen analysis calculated as Cl. [i] Melting point of 35-40 °C. The analytical sample was prepared by preparative GLC on 60/80 Chromosorb W. [j] Prepared by the general method (59% yield) and crystallized from hexane; mp 65.5-67 °C. [k] Yield determined by GLC. [l] Purified by recrystallization from ethanol-water as colorless needles, mp 45-48 °C [lit.[13] bp 135 °C (20 torr)]. Our analytical sample was prepared by GLC. [m] Prepared in 54% yield. Analytical sample, bp 122-125 °C (0.08 torr). [n] Lit.[11] bp 153 °C (15 torr).

(1) This research was supported in part by the U.S. Army Research Office through Grant DAAG29-77-G-0170.

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(7) Samples withdrawn, quenched, and examined by ^1H NMR revealed through disappearance of signals due to CH_2Br and appearance of signals due to $ArCH_2$ that exchange was usually complete after only 15 min.

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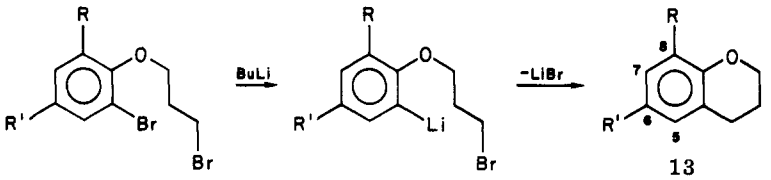
Table II. Cyclizations of 3-(*o*-Bromophenoxy)propyl Bromides 11 to 3,4-Dihydro-2*H*-benzopyrans 13

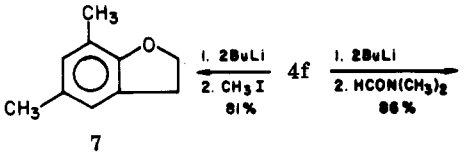


11 12 13

	R	R'	propyl bromides 11, bp, °C (torr)	3,4-dihydro-2*H*-1-benzopyrans 13 time,[a] h	yield, %	bp, °C (torr)
a	H	H	116-117 (0.25-0.27)[b]		80	67-70 (2.6-3.0)[c]
b	H	Me	92.5-96 (0.03-0.04)[d]		71	52-53 (0.37-0.38)[e]
c	H	MeO	118-123 (0.03-0.04)[d,f]	4	72	70-75 (0.25-0.30)[g]
d	H	Cl	133-137 (0.05-0.06)[h]	4[i]	75	89-93 (2.1-2.2)[j]
e	Br	Me	153-161 (0.18-0.20)[d,k]	4	79	91-95 (0.18-0.22)[d]

[a] Cyclization time needed at −78 °C after the initial exchange **11** → **12**, which is complete after 30 min at −100 °C. [b] Lit.[17] bp 110-115 °C (1-2 torr). [c] Lit.[18] bp 98-99 °C (18 torr). [d] Analysis for C, H, and Br was ±0.35%. [e] Lit.[19] bp 111-112 °C (18 torr). [f] An analytical sample (mp 52-54 °C) was crystallized from hexane. [g] Lit.[20] bp 92 °C (10 torr). [h] Analysis for C, H, and halogen (as Cl) was ±0.30% (analytical sample was prepared by GLC). [i] An experiment in which the 4-h period at −78 °C was omitted afforded only a 34% yield of the cyclized product (**13d**), the major product (61%) being 3-(4-chlorophenoxy)propyl bromide. [j] Lit.[21] bp 86-89 °C (1.0 torr). [k] Melting point of 32-33 °C observed for a solidified sample.

bility for a one-pot synthesis of more complex dihydrobenzofuran derivatives. After cyclization is achieved, a second equivalent of butyllithium may be added and a further transformation brought about. For example, the addition of 2 equiv of butyllithium successively to **4f** followed by addition of methyl iodide afforded 5,7-dimethyl-2,3-dihydrobenzofuran (**7**) in 81% overall yield (eq 2). A similar transformation in which the added elec-



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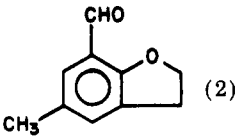
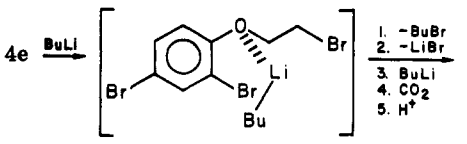


8 (2)

trophile was dimethylformanide afforded 5-methyl-2,3-dihydro-7-benzofurancarboxaldehyde (**8**) in 86% yield. The aryl bromine atoms of β-(2,4-dibromophenoxy)ethyl bromide (**4e**) are not equivalent, and it is the bromine ortho to the oxygen atom which is exchanged selectively by the butyllithium. Doubtless this result is due to a directing effect exhibited by the lone pairs on oxygen as in **9** (eq 3). With the addition of 2 equiv of butyllithium



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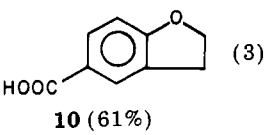

10 (61%) (3)

followed by carbonation, the previously unknown 2,3-dihydro-5-benzofurancarboxylic acid (**10**) may be prepared conveniently.

Parham cyclialkylation provides a useful addition to the methods now available for the synthesis of 2,3-dihydrobenzofurans since the regiochemistry of cyclization is controlled by the location of the ortho bromine atom, and cyclization should not be impeded by the presence of meta-directing groups. The new method compliments classical approaches[14] most of which involve acid-catalyzed cyclizations and more frequently lead to derivatives having substituents in the furan ring.

Although there were no published examples of the formation of a six-membered ring via the Parham cyclialkylation, such a cyclization seemed promising as a 6-Exo-Tet process, favored according to the Baldwin rules for ring closure.[15] The requisite 3-(*o*-bromophenoxy)propyl bromides were prepared[6] from 1,3-dibromopropane and the appropriate phenol.

As in the case of the 2-(*o*-bromophenoxy)ethyl bromides **4** the halogen–lithium exchange of the aryl bromine in the propyl analogues (**11**) was complete after only 30 min at −100 °C. Also, for the simplest member of the propyl series **4a** (and for its homologue **4b**), cyclization occurred in good yield during the exchange period (Table II). A significant difference in rate was observed when the aromatic ring had a methoxyl group (**11a**), chlorine atom (**11d**), or bromine atom (**11e**) meta to the bromine to be exchanged. Although bromine–lithium exchange took place as expected, cyclization of the organolithium product (**12c–e**) proceeded very slowly at −100 °C.[16] It appears significant that methoxyl and halogen substituents are inductively electron-attracting and, when located meta to the anionic center, should serve to stabilize it. Fortunately, when the temperature is raised to and maintained at −78 °C for 4

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(16) Failure to observe such rate differences in the dihydrobenzofuran systems may be attributed to the formation of all five-membered rings with such rapidity that even the slowest of the reactions is complete at the time of the first test.
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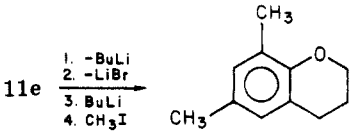
h, good yields of the expected dihydrobenzopyrans **13** could be obtained.

As would be predicted from experiments in the phenoxyethyl series (**4f–8**), it was possible to carry out a one-pot double lithiation sequence in which 3-(2,6-dibromo-4-methylphenoxy)propyl bromide (**11e**) was converted to 3,4-dihydro-6,8-dimethyl-2*H*-1-benzopyran (**14**) in 64% yield (eq 4).



(4)

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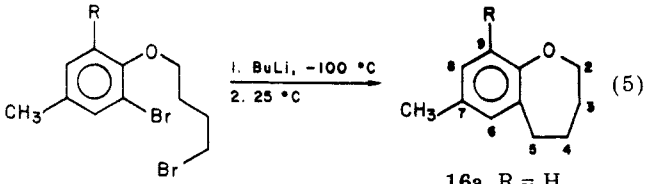
The usual approach to the synthesis of 3,4-dihydro-2*H*-1-benzopyrans (chromans) without substituents in the oxygen-containing ring has been via the zinc chloride catalyzed cyclization of 3-(aryloxy)-1-propanols or 3-(aryloxy)-1-halopropanes.[21] Although the intermediates (**11**) used in the Parham cyclialkylation method are slightly more difficult to obtain, cyclization may be accomplished in a regiospecific manner and in the presence of acid-sensitive groups.

Although the Parham cyclialkylation had never been extended to the formation of seven-membered rings, the system involved is 7-Exo-Tet,[15] giving promise of success. 4-(2-Bromo-4-methylphenoxy)butyl bromide (**15a**), readily available by the reaction of 1,4-dibromobutane with the appropriate phenol, exchanged rapidly at −100 °C with butyllithium (eq 5), but even at −78 °C the reaction cy-



(5)

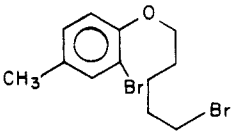
15a, R = H
b, R = Br

16a, R = H
b, R = Br

clization was too slow for preparative work. When the reaction mixture was allowed to warm to 25 °C, 2,3,4,5-tetrahydro-7-methyl-1-benzoxepin (**16a**) was obtained in 73% yield. The related tetrahydrobenzoxepin **16b**, having a bromine at position 9, was obtained in 65% yield by the same general procedure. When the preparation of the bromo derivative **16b** was repeated and the reaction mixture cooled once more to −100 °C followed by the addition of another equivalent of butyllithium, exchange of the bromine atom of **16b** was rapid, and carbonation of the resulting organolithium reagent (**16**, R = Li) afforded 7-methyl-2,3,4,5-tetrahydro-1-benzoxepincarboxylic acid (**16**, R = COOH) in 48% overall yield.

For the synthesis of 2,3,4,5-tetrahydro-1-benzoxepins without substituents in the nonaromatic ring, the new method is more convenient than those hiterto employed[23] and makes use of commercially available starting materials.

In general, eight-membered rings are more difficult to form than seven-membered rings, not only because of the increase in reaction entropy as the chain is lengthened but also because of the nonclassical strain which is significantly greater in the eight-membered ring.[24] Treatment of 1-bromo-5-(2-bromo-4-methylphenoxy)pentane (**17**) with



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butyllithium in the usual way afforded a mixture which on vapor-phase chromatography–mass spectroscopy appeared to contain no more than 21% of 8-methyl-3,4,5,6-tetrahydro-2*H*-benzoxocin. Another experiment, using 2.2 equiv[25] of *tert*-butyllithium, was only slightly less disappointing.

Although it appears that, at best, the Parham cyclialkylation will afford only poor yields of 3,4,5,6-tetrahydro-2*H*-benzoxocins, it does provide a new and efficient synthesis of analogues having five- to seven-membered rings.[26]

Experimental Section

General Methods. All reactions involving organolithium reagents were conducted under an atmosphere of dry nitrogen. Tetrahydrofuran (THF) was dried by distillation from lithium aluminum hydride or calcium hydride and was stored over molecular sieves (4 Å) until used. Hexane (practical) was dried by storage over molecular sieves (4 Å). Gas–liquid chromatography (GLC) was carried out on a Varian Model 910 gas chromatograph with a thermal-conductivity detector. Analysis of mixtures by gas chromatography–mass spectroscopy was accomplished with a Hewlett-Packard 5992A GC/MS system with the assistance of Mr. Joachim Wolfram. Elemental analyses were performed by MHW Laboratories. Melting points were determined on a Mel-Temp heating block apparatus and (like boiling points) are not corrected.

Phenoxyethyl Bromides 4. These were prepared in yields of 47–61% by refluxing and stirring for 6–22 h a mixture containing 0.120 mol of the phenol, 30.1 g (0.160 mol) of the ethylene bromide, 5.20 g of sodum hydroxide, and 90 mL of water essentially as described by Marvel and Tannenbaum.[6]

2,3-Dihydrobenzofurans 6. 2-(2-Bromophenoxy)ethyl bromide (or a suitable congener **4**, 30 mmol) was dissolved in 200 mL of dry THF to which 50 mL of dry hexane was added. The solution was placed in a 500-mL flask equipped for low-temperature lithiation[2] and was cooled to −100 °C. Butyllithium (33 mmol) in hexane solution was added at such a rate that the temperature did not rise above −95 °C. After 30 min[27] at −100 °C the reaction mixture was poured into water (200 mL). The layers were separated, and the aqueous phase was extracted with ether (3 × 150 mL). The organic material was dried and concentrated and the crude product distilled under reduced pressure. Yields and physical constants are shown in Table I.

Double Lithiation Experiments. (a) 5,7-Dimethyl-2,3-dihydrobenzofuran (7). 2-(2,6-Dibromo-4-methylphenoxy)ethyl bromide (**4f**; 5.59 g, 15 mmol) was dissolved in dry THF (100 mL) and hexane (25 mL) and the solution transferred to a 250-mL flask equipped for low-temperature lithiation. The solution was cooled to −100 °C and butyllithium (17 mmol) added at such a rate that the temperature never rose more than 5 °C. After 30 min at −100 °C an additional equivalent (17 mmol) of butyllithium was added at such a rate that the temperature rose no more than 5 °C. Thirty minutes after the second addition, analysis of a quenched sample by ^{1}H NMR indicated that exchange was complete.[28]

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(24) Eliel, E. L. "Stereochemistry of Carbon Compounds"; McGraw Hill: New York, 1962; p 198.
(25) The second equivalent was added to dehydrohalogenate the *tert*-butyl bromide produced by exchange. Cf.: Seebach, D.; Neumann, H. *Chem. Ber.* **1974**, *107*, 847.
(26) Since this paper was submitted for publication, A. S. Myers, M. Reuman, and R. A. Gabel [*J. Org. Chem.*, in press] described the synthesis of 2,3-dihydrofuran-, chroman-, and 2,3,4,5-tetrahydro-1-benzoxepincarboxylic acids by a new regiospecific cyclization.
(27) A sample withdrawn after only 15 min and examined by ^{1}H NMR showed that cyclization was already complete.

One hour after the addition of the second equivalent of butyllithium, a solution of methyl iodide (4.26 g, 30 mmol) in THF (20 mL) was added quickly to the reaction mixture (temperature <-92 °C), and the mixture was maintained at -100 °C for 30 min before being allowed to warm to room temperature. After 1 h at room temperature the mixture was poured into 150 mL of water and worked up in the usual way to afford 1.80 g (81%) of **7**: bp 72–75.5 °C (1.75–1.80 torr) [lit.[11] bp 110 °C (15 torr)]; ^{1}H NMR δ 2.14 (s, 3, CH_3), 2.20 (s, 3, CH_3), 3.08 (t, J = 7 Hz, 2, Ar CH_2), 4.40 (t, J = 7 Hz, 2, OCH_2), 6.66 (br s, 1, Ar H), 6.75 (br s, 1, Ar H).

(b) 5-Methyl-2,3-dihydro-2-benzofurancarboxyaldehyde (8). Two successive equivalents of butyllithium were added to **4f** at -100 °C as described in the preceding experiment. Thirty minutes after the addition of the second equivalent of butyllithium, a solution of 1.61 g (22 mmol) of dimethylformamide was added over 3 min. The solution was held at -100 °C for 30 min and was then allowed to warm slowly to room temperature. Stirring of the suspension at room temperature was continued for 1 h. The reaction mixture was poured into 5% hydrochloric acid, the phases were separated, and the aqueous phase was extracted with ether (3 × 150 mL). The organic materials were dried, concentrated, and distilled under reduced pressure. The yield of aldehyde **8** was 1.80 g (81%): bp 72–75.5 °C (0.08 torr) [lit.[11] bp 161–162 °C (10 torr)]; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3, CH_3), 3.29 (t, J = 9 Hz, 2, Ar CH_2), 4.78 (t, J = 9 Hz, 2, OCH_2), 7.36 (br s, 1, Ar H), 7.48 (br s, 1, Ar H), 10.30 (s, 1, CHO); IR (neat 2770, 2735 (O=CH), 1670 cm^{-1} (C=O).

(c) 2,3-Dihydro-5-benzofurancarboxylic Acid (10). (2,4-Dibromophenoxy)ethyl bromide (**4e**; 8.97 g, 25 mmol) was dissolved in dry THF (165 mL) and hexane (40 mL). The solution was placed in a 500-mL flask equipped for low-temperature lithiation and was cooled to -100 °C. Butyllithium (27 mmol) was added at such a rate that the temperature did not rise above -93 °C. The solution was stirred at -100 °C for 30 min, and then 27 mmol of butyllithium was added at -100 °C. A sample was taken after 30 min and processed, and examination by ^{1}H NMR showed exchange to be complete. One hour (at -100 °C) after the second addition of butyllithium, the mixture was poured into a slurry of solid CO_2 in ether (150 mL). After the mixture had come to room temperature, the layers were separated. The organic phase was extracted with saturated sodium bicarbonate solution (3 × 150 mL). The combined bicarbonate solutions were washed once with ether and then acidified with hydrochloric acid. The resulting precipitate was recrystallized from ethanol, giving 2.50 g (61%) of **7** as shiny colorless plates: mp 184–188 °C; mp (pure) 186–189 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 3.14 (t, J = 9 Hz, 2, Ar CH_2), 4.64 (t, J = 9 Hz, 2, OCH_2), 6.10 (br s, 1, OH), 6.74–7.90 (m, 3, Ar H); IR (KBr) 2650 (OH), 1670 cm^{-1} (CO).

Anal. Calcd for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.93; H, 4.94.

Phenoxypropyl Bromides (11). These were prepared by the reaction of 1,3-dibromopropane and a suitable phenol, following the general procedure of Marvel and Tannenbaum[6] (yields 50–74%). Physical constants are reported in Table II.

3,4-Dihydro-2*H*-1-benzopyrans (Chromans) 13. 3-(*o*-Bromophenoxy)propyl bromides **11** were treated at -100 °C with 1 equiv of butyllithium as in the preparation of the dihydrobenzofurans **6**, the progress of the exchange and cyclization being monitored by ^{1}H NMR examination of quenched samples. While halogen–lithium exchange appeared in every instance to be complete within 30 min at -100 °C, cyclization of a few of the lithium reagents (**12**) was so slow as to require an extended period at -78 °C for completion. Results are summarized in Table II.

6,8-Dimethyl-3,4-dihydro-2*H*-1-benzopyran (14) by a Double Lithiation. A solution of 5.8 g (15 mmol) of 3-(4-methyl-2,6-dibromophenoxy)propyl bromide (**11e**) in 100 mL of dry THF and 25 mL of dry hexane was cooled to -100 °C and 17 mmol of butyllithium added at such a rate that the temperature did not rise above -92 °C. The solution was stirred for 30 min at -100 °C and then for 4 h at -78 °C. The mixture was once more cooled to -100 °C and 17 mmol of butyllithium added at such a rate that the temperature did not rise above -92 °C. The solution was stirred for 30 min at -100 °C and then for 4 h at -78 °C. The mixture was once more cooled to -100 °C and 17 mmol of butyllithium added. One hour[29] later a solution of 4.26 g (30 mmol) of methyl iodide in 10 mL of dry THF was added. The solution was stirred at -100 °C for 30 min and then warmed to 25 °C (~1.5 h required). Workup in the usual way gave **14**: 64% yield; oil; bp 86–89 °C (2.1–2.2 torr); ^{1}H NMR ($CDCl_3$) δ 1.96 (m, 2, $OCH_2CH_2CH_2$), 2.14 (s, 3, CH_3), 2.20 (s, 3, CH_3), 2.72 (t, J = 6 Hz, 2, Ar CH_2), 4.16 (t, J = 6 Hz, 2, OCH_2), 6.68 (s, 1, Ar H), 7.14 (s, 1, Ar H).

Examination of the above product by GLC (20% SE-30 on 60/80 Chromosorb W) indicated that the product contained ~6% of 3,4-dihydro-6-methyl-2*H*-1-benzopyran (**13b**) as determined by peak matching. The analytical sample was collected by preparative gas–liquid chromatography.

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.76; H, 8.59.

1-Bromo-4-(2-bromo-4-methylphenoxy)butane (15a). This was prepared in 67% yield by the general method of Marvel and Tannenbaum[6] starting with 2-bromo-4-methylphenol and 1,4-dibromobutane: bp 119–122.5 °C (0.04–0.05 torr); ^{1}H NMR ($CDCl_3$) δ 2.00 (m, 4, $OCH_2CH_2CH_2CH_2$), 2.24 (s, 3, CH_3), 3.48 (t, J = 6 Hz, 2, CH_2Br), 3.98 (t, J = 6 Hz, 2, OCH_2), 6.63–7.40 (m, 3, Ar H).

Anal. Calcd for $C_{11}H_{14}Br_2O$: C, 41.02; H, 4.38; Br, 49.63. Found: C, 40.93; H, 4.46; Br, 49.61.

1-Bromo-4-(2,3-dibromo-4-methylphenoxy)butane (15b). This was prepared in 71% yield essentially as in the preparation of **15a**, except that the phenol employed was 2,6-dibromo-4-methylphenol: bp 143–145 °C (0.05–0.06 torr); ^{1}H NMR ($CDCl_3$) δ 2.05 (m, 4, $OCH_2CH_2CH_2CH_2$), 2.24 (s, 3, CH_3), 3.54 (t, J = 6 Hz, 2, CH_2Br), 3.97 (t, J = 6 Hz, 2, OCH_2), 7.25 (s, 2, Ar H). The analytical sample was obtained by preparative GLC.

Anal. Calcd for $C_{11}H_{14}Br_3O$: C, 32.95; H, 3.27; Br, 59.79. Found: C, 33.16; H, 3.30; Br, 59.62.

7-Methyl-2,3,4,5-tetrahydro-1-benzoxepin (16a). A solution of 9.66 g (30 mmol) of **15a** in 200 mL of dry THF and 50 mL of dry hexane was cooled to -100 °C and 33 mmol of butyllithium in hexane added slowly (maximum temperature -98 °C). After 30 min at -100 °C[30] the mixture was allowed to warm to 25 °C (~1.5 h) and allowed to remain at that temperature for an additional 6 h. When worked up in the usual way, the reaction afforded 3.53 g (73%) of **16a** as a clear colorless oil: bp 91–97 °C (3.5–3.7 torr) [lit.[31] bp 88–90 °C (2.0–3.0 torr)]; ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 4, $OCH_2CH_2CH_2CH_2$), 2.20 (s, 3, CH_3), 2.70 (m, 2, Ar CH_2), 3.84 (m, 2, OCH_2), 6.60–6.80 (m, 3, Ar H).[32]

9-Bromo-7-methyl-2,3,4,5-tetrahydro-1-benzoxepin (16b). A sample of **15b** was subjected to halogen–lithium exchange and cyclized essentially as was **15a**, affording a 53% yield of **16b**: bp 85–89 °C (0.09–0.11 torr); ^{1}H NMR ($CDCl_3$) δ 1.82 (m, 4, $OCH_2CH_2CH_2CH_2$), 2.25 (s, 3, CH_3), 2.76 (m, 2, Ar CH_2), 4.02 (m, 2, OCH_2), 6.92 (br s, 1, Ar H, position 6), 7.20 (br s, 1, Ar H, position 8).

Anal. Calcd for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43; Br 33.14. Found: C, 55.07; H, 5.32; Br, 33.37.

7-Methyl-2,3,4,5-tetrahydro-1-benzoxepin-9-carboxylic Acid (16, R = COOH). Bromine–lithium exchange was carried out on 12.03 g (30 mmol) of **15b**, and after cyclization at 25 °C was complete, the solution was again cooled to -100 °C and another equivalent (33 mmol) of butyllithium added. After 1 h[29] at the same temperature, the reaction mixture was poured onto a slurry of crushed solid carbon dioxide in ether (150 mL). After the solution reached room temperature, it was extracted with saturated sodium bicarbonate solution (3 × 150 mL). The bicarbonate extracts were acidified (HCl) and the organic acid (**16**, R = COOH) was taken up in dichloromethane (3 × 150 mL). The extracts were dried and concentrated, and the resulting oil was

(28) Comparison of the spectrum with that of an authentic sample showed **6b** to be the major component.

(29) After only 30 min ^{1}H NMR examination of a quenched sample showed that halogen–lithium exchange was complete.

(30) In a preliminary experiment it was shown by ^{1}H NMR of quenched samples that although halogen–lithium exchange was complete after only 15 min at -100 °C, there was no indication of cyclization even after 2 h at -78 °C.

(31) Newman, M. S.; Mekler, A. B. *J. Org. Chem.* **1961**, *26*, 3361.

(32) Similar ^{1}H NMR data have been reported by Christenson.[33]

crystallized from hexane–CCl_4, affording 2.95 g (48%) of stout prisms: mp 89–92.5 °C (lit.[33] mp 94–95 °C); ^1H NMR ($CDCl_3$) δ 1.80 (m, 4, $OCH_2CH_2CH_2CH_2$), 2.30 (s, 3, CH_3), 2.85 (m, 2, Ar CH_2), 4.24 (m, 2, OCH_2), 7.27 (d, J = 2 Hz, 1, Ar H, position 6), 7.85 (d, J = 2 Hz, 1, Ar H, position 8), 11.20[32] (br s, 1, OH); IR ($CHCl_3$) 1730 cm^{-1} (C=O); analytical sample, mp 91.5–93 °C.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.82; H, 6.95.

1-Bromo-5-(2-bromo-4-methylphenoxy)pentane (17). This was prepared in 72% yield from 2-bromo-4-methylphenol and 1,5-dibromopentane by the method[6] used for the lower homologues: bp 152–155 °C (0.03 torr); ^1H NMR ($CDCl_3$) δ 1.80 (m, 6, $OCH_2CH_2CH_2CH_2CH_2$), 2.23 (s, 3, CH_3), 3.40 (t, J = 7 Hz, 2, CH_2Br), 3.94 (t, J = 6 Hz, 2, OCH_2), 6.60–7.35 (AMX m, 3, Ar H).

Anal. Calcd for $C_{12}H_{16}Br_2O$: C, 42.89; H, 4.80; Br, 47.55. Found: C, 42.88; H, 4.98; Br 47.49.

Results of Bromine–Lithium Exchange of 17. (a) Using Butyllithium. A solution of **17** (10.08 g, 30 mmol) in 200 mL of THF and 50 mL of hexane was cooled to −100 °C and treated in the usual way with 33 mmol of butyllithium. After 30 min[34] at −100 °C the mixture was allowed to warm slowly (~1.5 h) to 25 °C and then stirred an additional 6 h. The mixture was poured into water, and the organic materials were extracted with ether (3 × 150 mL). The dried solution was concentrated to afford 7.4 g of yellow oil which was analyzed by gas chromatography/mass spectroscopy (2% OV-1 column, 3 ft × 0.125 in.) programmed from 150 to 230 °C at 10 °C/min (flow rate 30 mL He/min). The major components, identified only by interpretation of the fragmentation patterns, were as follows. 4-(4-Methylphenoxy)-1-pentene: 34% yield; retention time 3.2 min; mass spectrum, m/e (relative intensity) 176 (M^+, 22), 108 (100), 107 (28), 41 (24). 8-Methyl-3,4,5,6-tetrahydro-2*H*-1-benzoxocin: 21% yield; retention time 4.1 min; mass spectrum, m/e (relative intensity) 176 (M^+, 36), 147 (17), 121 (100), 91 (23). 1-Bromo-5-(4-methylphenoxy)pentane: 10% yield; retention time 8.4 min; mass spectrum, m/e (relative intensity) 256, 258 (M^+ isotopes, 6, 5), 151 (15), 149 (16), 108 (100), 107 (27), 69 (30). 1-Bromo-5-(2-butyl-4-methylphenoxy)pentane: 36% yield; retention time 11.5 min; mass spectrum, m/e (relative intensity) 312, 314 (M^+ isotopes, 7, 8), 165 (44), 151 (23), 149 (25), 121 (100), 69 (64). No further effort was made to separate the mixture.

(b) Using *tert*-Butyllithium. The halogen–metal exchange experiment was repeated except that 10.08 g (30 mmol) of **17** was treated with 66 mmol (2.2 equiv[29]) of *tert*-butyllithium. At the conclusion of the experiment, the product consisted of 6.17 g of yellow oil which was analyzed in the same way by GC/MS. The major components appeared to be 5-(4-methylphenoxy)-1-pentene (33%), 1-(4-methylphenoxy)pentane [35%; retention time 3.4 min; mass spectrum, m/e (relative intensity) 178 (M^+, 16), 108 (100), 107 (18), 91 (5)], and 8-methyl-3,4,5,6-tetrahydro-2*H*-1-benzoxocin (29%).[35]

Registry No. 4a, 18800-28-7; **4b**, 76429-63-5; **4c**, 76429-64-6; **4d**, 76429-65-7; **4e**, 76429-66-8; **4f**, 76429-67-9; **6a**, 496-16-2; **6b**, 76429-68-0; **6c**, 13391-30-5; **6d**, 76429-69-1; **6e**, 66826-78-6; **6f**, 76429-70-4; **7**, 76429-71-5; **8**, 76429-72-6; **10**, 76429-73-7; **11a**, 37136-84-8; **11b**, 66246-12-6; **11c**, 76429-74-8; **11d**, 76429-75-9; **11e**, 76429-76-0; **13a**, 493-08-3; **13b**, 3722-74-5; **13c**, 3722-76-7; **13d**, 3722-71-2; **13e**, 76429-77-1; **14**, 76429-78-2; **15a**, 76429-79-3; **15b**, 76429-80-6; **16a**, 41177-64-4; **16b**, 76429-81-7; **16** (R = COOH), 35700-37-9; **17**, 76429-82-8; ethylene bromide, 106-93-4; 2-bromophenol, 95-56-7; 4-methyl-2-bromophenol, 6627-55-0; 4-methoxy-2-bromophenol, 17332-11-5; 4-chloro-2-bromophenol, 695-96-5; 2,4-dibromophenol, 615-58-7; 4-methyl-2,6-dibromophenol, 2432-14-6; dimethylformamide, 68-12-2; 1,3-dibromopropane, 109-64-8; 1,4-dibromobutane, 110-52-1; 1,5-dibromopentane, 111-24-0; 4-(4-methylphenoxy)-1-pentene, 6793-72-2; 8-methyl-3,4,5,6-tetrahydro-2*H*-1-benzoxocin, 76429-84-0; 1-bromo-5-(4-methylphenoxy)pentane, 53178-42-0; 1-bromo-5-(2-butyl-4-methylphenoxy)pentane, 76446-90-7; 5-(4-methylphenoxy)-1-pentene, 76429-83-9; 1-(4-methylphenoxy)pentane, 33426-70-9.

Supplementary Material Available: Augmented forms of Tables I and II giving ^1H NMR data for both cyclization products and precursors (2 pages). Ordering information is given on any current masthead page.

(33) Christenson, H. *Synth. Commun.* **1974**, *4*, 1.

(34) A preliminary experiment showed that exchange of the aryl bromine was complete after only 15 min at −100 °C (AA'MM' pattern in ^1H NMR of a quenched sample). There was no further change observed after an additional 2 h at −100 °C.

(35) The retention time and mass spectroscopic fragmentation pattern were as described in part a.

Heteroadamantanes. 2. Synthesis of 3-Heterodiamantanes[1a,b]

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Received October 14, 1980

Diamantane (1) has been converted into the unsaturated ketone 8, which is the common precursor in syntheses of 3-azadiamantane (16), 3-oxadiamantane (9), and 3-thiadiamantane (19). An oxaprotodiamantane also has been synthesized and shown to rearrange to 3-oxadiamantane upon treatment with aqueous sulfuric acid.

Numerous heteroadamantanes have been prepared[2] and give evidence of interesting chemistry dependent upon the stereochemically defined interaction of the heteroatom with various reactive sites in the molecule.[2-6] Furthermore, the physical properties of the solid phase of these substances, which are indicative of considerable orientational disorder,[7,8] also contribute to the current interest in heteroadamantanes.

(1) (a) Abstracted from the Ph.D. dissertation of V.V.K., Kent State University, Dec 1980. (b) Presented in part at the Northeast Regional Meeting of the American Chemical Society, Potsdam, NY, June 1980, Abstract 240.

(2) (a) R. C. Fort, Jr. "Adamantane: The Chemistry of Diamond Molecules", Marcel Dekker, New York, 1976, Chapter 6; (b) C. Ganter, *Fortschr. Chem. Forsch.*, **67**, 15 (1976).

(3) R. C. Fort, Jr., and T. A. Flood, Abstracts, Northeast Regional Meeting of the American Chemical Society, Potsdam, NY, June 1980, No. 239.

(4) J. G. Henkel and W. C. Faith, Abstracts, Second Chemical Congress of North American Continent, Las Vegas, NV, Aug 1980, No. 0-326.

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(6) P. M. Starewicz, E. A. Hill, P. Kovacic, and A. R. Gagneux, *J. Org. Chem.* **44**, 3707 (1979).

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(8) J. T. S. Andrews, R. E. Carpenter, T. M. Martinko, R. C. Fort, Jr., T. A. Flood, and M. G. Adlington, *Mol. Cryst. Liq. Cryst. Lett.*, **41**, 257 (1978).

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