The Preparation of 3,4-Dihydro-1-benzoxepin-5(2*H*)-ones

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Several methods for the preparation of 3,4-dihydro-1-benzoxepin-5(2*H*)-ones are described. In addition to the desired ketones, a variety of novel by-products have been isolated.

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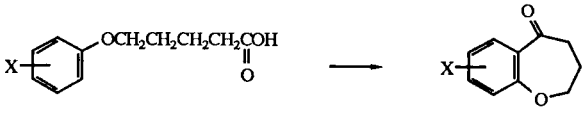
For a series of compounds containing a benzoxepin nucleus [1,2], we required a variety of aryl ring substituted 3,4-dihydro-1-benzoxepin-5(2*H*)-ones **2** [3]. This paper summarizes our experiences in this area.

The earliest reported member of this series **2a** was prepared in low yield by heating phenoxybutanoic acid **1a** with phosphorus pentoxide in benzene [4], (Scheme I) [5]. In recent years, cyclization of **1** with polyphosphoric acid neat [6-20] or diluted with xylene [11,14,21,22] has become the method of choice; hydrofluoric acid has sometimes been used [6]. Less frequently, the corresponding aryloxybutanoic acid chlorides have been cyclized with either aluminum chloride [6,9] or stannic chloride [6,8,23].

Scheme I

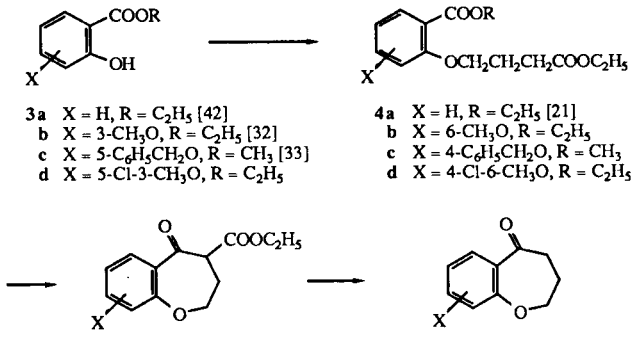


1 **2**

X		X
1a	H [41]	**2a** H [4]
b	3-F	**b** 8-F
c	4-Br [34]	**c** 7-Br [40]
d	2,4-F_2	**d** 7,9-F_2
e	3,4-Cl_2 [12]	**e** 7,8-Cl_2 [12]
f	2-CF_3	**f** 9-CF_3
g	3-CF_3	**g** 8-CF_3
h	2-CH_3O [35]	**h** 9-CH_3O
i	3-CH_3O [6]	**i** 8-CH_3O [6]
j	4-CH_3S	**j** 7-CH_3S
k	4-n-C_3H_7O	**k** 7-n-C_3H_7O
l	2,5-$(CH_3O)_2$	**l** 6,9-$(CH_3O)_2$
m	3,4-$(CH_3O)_2$	**m** 7,8-$(CH_3O)_2$
n	3,4,-(OCH_2O)	**n** 7,8-(OCH_2O)
o	3,4,5-$(CH_3O)_3$	**o** 6,7,8-$(CH_3O)_3$
p	4-Cl-2-CH_3O	**p** 7-Cl-9-CH_3O
q	3-CH_3O-4-NO_2	**q** 8-CH_3O-7-NO_2
r	3-F-4-CH_3O	**r** 8-F-7-CH_3O
s	4-t-C_4H_9 [36]	**s** 7-t-C_4H_9
t	4-NO_2 [37]	

The Dieckmann reaction (Scheme II) [5] has been explored [21] as a route to these ketones, but the conditions employed provided only a very low yield of the cyclization product **5a**.

Scheme II



3a X = H, R = C_2H_5 [42]
b X = 3-CH_3O, R = C_2H_5 [32]
c X = 5-$C_6H_5CH_2O$, R = CH_3 [33]
d X = 5-Cl-3-CH_3O, R = C_2H_5

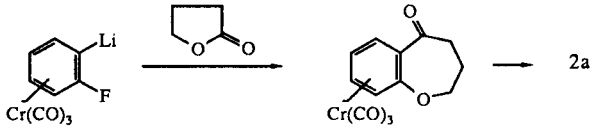
4a X = H, R = C_2H_5 [21]
b X = 6-CH_3O, R = C_2H_5
c X = 4-$C_6H_5CH_2O$, R = CH_3
d X = 4-Cl-6-CH_3O, R = C_2H_5

5a X = H [21]
b X = 9-CH_3O
c X = 7-$C_6H_5CH_2O$
d X = 7-Cl-9-CH_3O

2a X = H [21]
h X = 9-CH_3O
t X = 7-OH
p X = 7-Cl-9-CH_3O

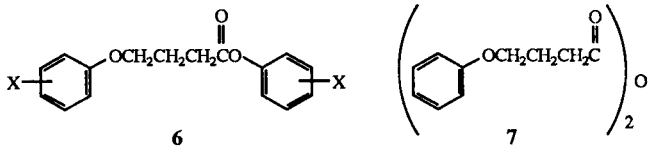
Finally, an intramolecular anionic displacement using π-(*o*-lithiofluorobenzene)chromium tricarbonyl and butyrolactone (Scheme III) has been utilized to prepare **2a** [23].

Scheme III

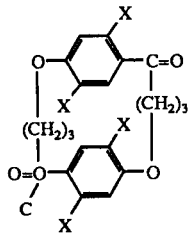


Cyclization of aryloxybutanoic acids **1** using acid catalysis often leads to any of four types of by-products, **6-9**. The most common side reaction leads to aryl esters **6** [7,14, 21,22,25], ostensibly by cleavage of the ether linkage and subsequent esterification [7]. The reaction is most often associated with the presence of electronegative substituents on the aryl ring [7].

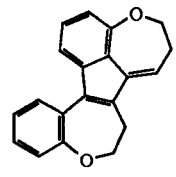
Less commonly, side products which have been isolated were the aryloxybutanoic anhydride **7** [11,21] and dimers such as **8a** [10] and **9** [14,25]. The formation of polycondensation products using hydrofluoric acid has also been claimed [6].



6 **7**



8a, X = H
b, X = CH_3O



9

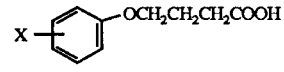
Results and Discussion.

The majority of the 3,4-dihydro-1-benzoxepin-5(2*H*)-ones were prepared by polyphosphoric acid-mediated cyclization of the corresponding aryloxybutanoic acids. A variety of unoptimized times and temperatures were utilized (Table II). In certain cases where no product could be obtained by this method, modest yields were obtained using trifluoroacetic anhydride in trifluoroacetic acid.

The most common by-product was the aryl ester **6** and new examples are summarized in Table III. Examination of this Table supports the view that, in general, there is a positive correlation between substituent electronegativity and yields of **6**.

Formation of **6** may be rationalized via acid cleavage of **1** to the corresponding phenol followed by esterification with a second molecule of **1**. Phenols have been isolated from such reaction mixtures [7] and these can be con-

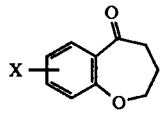
Table I



Compound	X	Reaction Time (hours)	Yield %	MP (°C)	Recrystallization Solvent [a]	Formula Mol. wt.	Analysis % Calcd./Found C	H
1b	3-F	18	83	51-53	A	$C_{10}H_{11}FO_3$ 198.19	60.60 60.66	5.59 5.65
1d	2,4-F_2	72	86	74-75	A	$C_{10}H_{10}F_2O_3$ 216.18	55.56 55.62	4.66 4.86
1f	2-CF_3	48	86	85-87	B	$C_{10}H_{11}F_3O_3$ 248.20	53.23 53.06	4.47 4.50
1g	3-CF_3	48	76	54-55	B	$C_{10}H_{11}F_3O_3$ 248.20	53.23 53.18	4.47 4.32
1j	4-CH_3S	48	80	104-106	C	$C_{11}H_{14}O_3S$ 226.29	58.38 58.44	6.24 [b] 6.12
1k	4-*n*-C_3H_7O	70	70	81-83	A	$C_{13}H_{18}O_4$ 238.27	65.53 65.66	7.61 7.79
1l	2,5-$(CH_3O)_2$	84	77	101-102	A	$C_{12}H_{16}O_5$ 240.25	59.99 60.16	6.71 6.75
1m	3,4-$(CH_3O)_2$	48	72	89-91	D	$C_{12}H_{16}O_5$ 240.25	59.99 59.72	6.71 6.86
1n	3,4-OCH_2O	18	79	118-120	C	$C_{11}H_{12}O_5$ 224.21	58.92 59.18	5.40 5.33
1o	3,4,5-$(CH_3O)_3$	60	75	86-88	E	$C_{13}H_{15}O_4$ 270.27	57.77 57.93	6.71 6.66
1p	4-Cl-2-CH_3O	48	86	77-81	A	$C_{11}H_{13}ClO_4$ 244.67	53.99 53.65	5.36 5.39
1q	3-CH_3O-4-NO_2	168	86	162-164	C	$C_{11}H_{13}NO_6$ 252.22	51.76 51.48	5.13 [c] 5.16
1r	3-F-4-CH_3O	48	84	108-109	A	$C_{11}H_{13}FO_4$ 228.21	57.89 57.44	5.74 5.79

[a] A, Cyclohexane; B, Heptane; C, Nitromethane; D, Carbon Tetrachloride; E, Toluene. [b] Calcd: S; 14.17; Found: S, 14.20. [c] Calcd. N, 5.49; Found: N, 5.71.

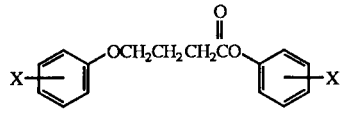
Table II



Compound	X	Method	Temp °C/ Time, hr	Yield %	Mp °C (Bp °C/mm Hg)	IR (C=O) ν cm^{-1}	Formula Mol. wt.	Analysis % Calcd./Found C	H
2b	8-F	A	65/1	75	53-55 [a]	1681	$C_{10}H_9FO_2$ 180.17	66.66 66.41	5.04 5.05
2c	7-Br	A	70/1	61	(104-109/0.3)	1688	$C_{10}H_9BrO_2$ 241.09	49.82 49.97	3.76 3.76
2d	7,9-F_2	A	85/1	6	78-80 [b]	1698	$C_{10}H_8F_2O_2$ 198.16	60.61 60.32	4.07 4.13
2e	7,8-Cl_2	A	70/5	65	71-72 [c] (120.125/0.3)	1682	$C_{10}H_8Cl_2O_2$ 231.08	51.97 52.05	3.49 3.44
2f	9-CF_3	A	65/2	5	(85-87/0.1)	1690	$C_{11}H_9F_3O_2$ 230.18	57.39 57.30	3.94 4.02
2g	8-CF_3	A	85/1	10	(75-80/0.05)	1688	$C_{11}H_9F_3O_2$ 230.18	57.39 57.07	3.94 3.92
2h	9-CH_3O	A,C	50/1	10 55 [g]	(120-125/1.0)	1683	$C_{11}H_{12}O_3$ 192.21	68.73 68.46	6.29 6.21
2i	8-CH_3O	A	60/0.5	71 [h]	(108-111/0.3)	1674	$C_{11}H_{12}O_3$ 192.21	68.73 68.83	6.29 6.22
2j	7-CH_3S	A	25/18	23	(112-115/0.3)	1681	$C_{11}H_{12}O_2S$ 208.27	63.43 63.50	5.81 5.92
2k	7-*n*-C_3H_7O	A	75/1.5	64	(134-136/0.4)	1680	$C_{13}H_{16}O_3$ 220.26	70.88 70.64	7.32 7.12
2l	6,9-$(CH_3O)_2$	A	60/1.5	5	79-80 [c]	1690	$C_{12}H_{14}O_4$ 222.25	64.85 64.60	6.36 6.34
2m	7,8-$(CH_3O)_2$	A	60/1	70	77-79 [c]	1672	$C_{12}H_{14}O_4$ 222.25	64.85 64.67	6.36 6.41
2n	7,8-OCH_2O	B		18	101-104 [c]	1653	$C_{11}H_{10}O_4$ 206.19	64.07 64.18	4.59 4.68
2o	6,7,8-$(CH_3O)_3$	B		42	(130-132/0.3)	1687	$C_{13}H_{16}O_5$ 252.26	61.89 62.22	6.39 6.13
2p	7-Cl-9-CH_3O	A,C	70/.75	18 46 [g]	64-66 [c] (125-128/0.3)	1688	$C_{11}H_{11}ClO_3$ 226.65	58.29 58.58	4.89 4.97
2q	8-CH_3O-7-NO_2	A	75/0.5	72	121-123 [c]	1677	$C_{11}H_{11}NO_5$ 237.21	55.69 55.70	4.67 [f] 4.75
2r	8-F-7-CH_3O	A	80/1	86	77-79 [c]	1669	$C_{11}H_{11}FO_3$ 210.20	62.85 62.78	5.28 5.39
2s	7-t-C_4H_9	A	80/1	78	(105-112/0.2)	1682	$C_{14}H_{18}O_2$ 218.28	77.03 77.32	8.31 8.21
2t	7-HO	C		22 [g]	(155-160/0.1)	1676	$C_{10}H_{10}O_3$ 178.18	67.40 67.73	5.66 5.77
2u	7-$C_6H_5CH_2O$	D		71	61-62 [c] (140-150/0.4)	1682	$C_{17}H_{16}O_3$ 268.30	76.10 75.93	6.02 6.15
2v	8-$C_6H_5CH_2O$	E		66	58-59 [e]	1677	$C_{17}H_{16}O_3$ 268.30	76.10 75.80	6.02 6.07

[a] From hexane. [b] by sublimation. [c] from cyclohexane. [d] from methanol. [e] from cyclohexane/hexane. [f] Calcd. N, 5.91; Found: N, 6.07. [g] Yield by Method C from diester. [h] The nmr and gas chromatographic analyses indicated the presence of 10-12% of the 6-methoxy isomer.

Table III



Compound	X	Yield %	BP °C (mm Hg)	MP °C	IR (C=O) ν cm^{-1}	Formula Mol Wt	Analysis % Calcd./Found C	H
6a	4-Br	8	177-180 (0.3)	82-84 [a]	1758	$C_{16}H_{14}Br_2O_3$ 414.11	46.40 44.36	3.41 3.42
6b	3-CF_3	67	144-152 (0.05)		1763	$C_{18}H_{14}F_6O_3$ 392.29	55.11 55.36	3.60 3.78
6c	4-NO_2	20		99-101 [a]	1758	$C_{16}H_{14}N_2O_7$ 346.29	55.45 55.48	4.08 [b] 4.23
6d	2-CH_3O	7	165-170 (0.3)		1768	$C_{18}H_{20}O_5$ 316.34	68.34 68.65	6.37 6.71
6e	2,4-F_2	56	155-158 (0.5)		1767	$C_{16}H_{12}F_4O_3$ 388.25	58.84 58.62	3.68 3.76
6f	3,4-Cl_2	15	175-183 (0.3)	60-63 [a]	1770	$C_{16}H_{12}Cl_4O_3$ 394.08	48.76 48.98	3.07 3.07
6g	4-Cl-2-CH_3O	52	190-194 (0.3)	85-88 [a]	1771	$C_{18}H_{18}Cl_2O_5$ 385.25	56.12 55.89	4.71 4.72

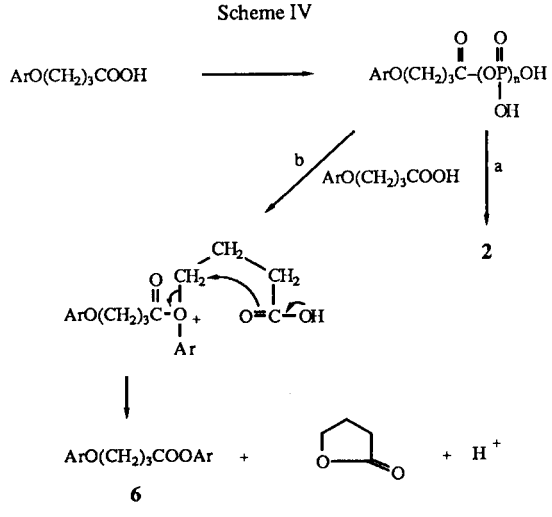
[a] From cyclohexane. [b] Calcd: N, 8.09; Found: N, 8.16.

verted to aryl esters by carboxylic acids in the presence of polyphosphoric acid [26,27].

However, we also found that while acids **1g** and **1p** readily generate high yields of aryl esters (**6b** and **6g**, respectively), the latter esters, when heated further in polyphosphoric acid, are perfectly stable and completely recoverable. There is no *a priori* reason why **6b** and **6g** should not undergo acid-catalyzed cleavage as readily as the corresponding acids.

An alternate pathway that accounts for the latter observation is outlined in Scheme IV.

Scheme IV

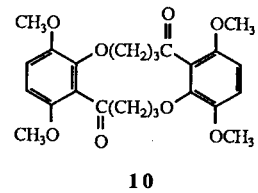


The putative mixed anhydride of the acid **1** and polyphosphoric acid or an equivalent intermediate [28] can either cyclize (route a) or attack the ether linkage of a molecule of **1** (route b). In the presence of sufficiently electronegative substitution, route b might become favored, leading to the formation of aryl ester and, presumably, butyrolactone. Ether cleavage by anhydrides or acid chlorides is accounted for by an analogous pathway [29].

Dimeric by-products, as established by mass spectra, were formed from the 2,5-dimethoxy (**1l**)- and 3,4,5-trimethoxy (**1o**)-acids.

The nmr spectral data established the product from **1l** as structure **8b** and not structure **10** by the lack of *ortho* coupling of the aromatic protons. This is in contrast to the spectrum of the monomer **2l** which shows the aromatic protons coupled with J = 9.0 Hz.

On the other hand, the dimeric product from acid **1o** must possess structure **11** in that, due to its symmetrical nature, only one position is available for acylation. This structure represents a hitherto undescribed ring system.



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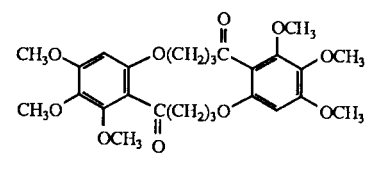
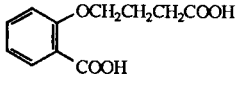


11

Worthy of note is the contrast in behavior of the 3- and 2-trifluoromethyl acids **1g** and **1f**, respectively, on warming in polyphosphoric acid. While the major product from the former is the aryl ester **6b**, the major product in the latter case is the dicarboxylic acid **12**.

Polyphosphoric acid-catalyzed hydrolysis of a trifluoromethyl group has been previously noted [30] and the distinction might be expected via facilitation of the rate of hydrolysis by the electron-donating *o*-alkoxy group [31].



12

We have found the Dieckmann reaction (Scheme II) to be a useful alternative. Cyclization occurs in good yield when the reaction is carried out at room temperature in dimethylformamide using sodium hydride as the base. Conversion of the keto esters **5** to the desired ketones could be accomplished under acid or basic conditions. Under acid conditions, the benzyl ether function of **5c** is concomitantly cleaved generating the phenolic ketone **2t**. This is a useful intermediate for the synthesis of a variety of ether-containing derivatives such as **2u** (Table II).

Finally, the 8-benzyloxy ketone **2v** (Table II) was obtained by benzyloxide displacement of the activated 8-fluorine in **2b** using benzyl alcohol and potassium carbonate in refluxing dimethylformamide. We could not effect an analogous displacement with the isomeric, less activated 7-fluoro analog [11].

EXPERIMENTAL

Melting points were determined in open capillaries on a Thomas Hoover apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on Varian FT 80A and VXR 300 spectrometers. Chemical shifts are recorded in parts per million from tetramethylsilane as an internal standard. Mass spectra were recorded on a Finnigan MAT 4600 spectrometer. Infrared spectra were recorded on Perkin Elmer models 180 and 1800 spectrometers. Spectra of solid samples were obtained as potassium bromide pellets; liquids were recorded as films.

In this section, we have presented the nmr spectra of representative examples of aryloxybutanoic acids **1**, their aryl esters **6** and the 3,4-dihydro-1-benzoxepin-5(2*H*)-ones **2**. The spectra of all other such compounds are in accordance with the stated structure.

General Procedure for the Preparation of Aryloxybutanoic Acids. (Table I).

4-(3-Fluorophenoxy)butanoic Acid (**1b**).

A mixture of 3-fluorophenol (11.2 g, 0.1 mole), 95% ethyl 4-bromobutanoate (22.6 g, 0.11 mole), potassium carbonate (15 g, 0.11 mole) and potassium iodide (0.2 g) was refluxed in 250 ml of acetone for 18 hours. The mixture was filtered and the solvent removed from the filtrate at reduced pressure. The residue, in ether, was extracted with cold 5% sodium hydroxide and the ether was removed at reduced pressure. The residual ester was hydrolyzed by heating on a steam bath with a solution of 10 g of sodium hydroxide in 25 ml of ethanol and 200 ml of water until a clear solution formed. The cooled solution was acidified with hydrochloric acid and the solids which formed were filtered and dried. Recrystallization from cyclohexane gave 16.4 g (83%) of 4-(3-fluorophenoxy)butanoic acid, mp 51-53°; ^{1}H nmr (deuteriochloroform): δ 1.90-2.25 (m, 2H), 2.41-3.71 (m, 2H), 3.95 (t, 2H, J = 6.3 Hz), 6.98-7.35 (m, 4H), 10.99 (broad s, 1H).

Preparation of 3,4-Dihydro-1-benzoxepin-5(2*H*)-ones (Table II).

Procedure A.

A mixture of the aryloxybutanoic acid and 15 parts by weight of polyphosphoric acid was stirred and heated in an oil bath for the indicated time/temperature. The cooled mixture was poured into ice water and, when the polyphosphoric acid had decomposed, the product was extracted into ether. The ether solution was washed with water, 5% sodium hydroxide, and saturated sodium chloride solution. After drying over magnesium sulfate, the ether was removed to leave the crude product. The ketones and by-products were isolated by distillation and/or recrystallization.

3,4-Dihydro-6,9-dimethoxy-1-benzoxepin-5(2*H*)-one (**21**, Table II).

Using Procedure A and acid **11**, the ketone **21** was isolated in 5% yield; ^{1}H nmr (deuteriochloroform): δ 2.11-2.20 (m, 2H), 2.81-2.85 (m, 2H), 3.82 (s, 3H), 3.87 (s, 3H), 4.27 (t, 2H, J = 6.2 Hz), 6.61 (d, 1H, J = 9.0 Hz), 6.95 (d, 1H, J = 9.0 Hz).

8,17,19,22-Tetramethoxy-2,11-dioxatricyclo[14,2,2,27,10]-docosa-7,9,16,18,19,21-hexane-6,15-dione (**8b**).

In addition to **21**, there was also isolated a water- and ether-insoluble solid which was recrystallized from boiling dimethylacetamide to give a 53% yield of **8b**, mp 229-230°; ir: 1660 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform/trifluoroacetic acid): δ 2.22-2.28 (m, 4H), 3.18-3.29 (m, 4H), 3.88 (s, 6H), 3.94 (s, 6H), 4.21 (t, 4H, J = 6.2 Hz), 6.56 (s, 2H), 7.43 (s, 2H); ms: (CI-CH_4) m/e 445 (MH^+).

Anal. Calcd. for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35. Found: C, 64.56; H, 6.40.

4-(4-Nitrophenoxy)butanoic Acid 4-Nitrophenyl Ester (**6c**, Table III).

Using Procedure A and the 4-nitro acid **1t**, the solid, water-insoluble ester was the only product isolated. The compound had ^{1}H nmr (deuteriochloroform): δ 2.10-2.47 (m, 2H), 2.87 (t, 2H, J = 6.7 Hz), 4.17 (t, 2H, J = 6.7 Hz), 6.82-7.02 (m, 2H), 7.13-7.25 (m, 2H), 8.06-8.32 (m, 4H).

4-(2-Carboxyphenoxy)butanoic Acid (**12**).

Acidification of the basic extracts in the reaction of **1f** gave a 48% yield of this acid, mp 103-110°. Recrystallization from acetonitrile raised the mp to 117-119°; ir: 1670, 1721 (C=O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.92-2.01 (m, 2H), 2.46-2.53 (m, 2H), 4.08 (t, 2H, J = 6.2 Hz), 6.98-7.68 (m, 4H), 12.34 (broad s, 1H); ms: (CI-CH_4) m/e 225 (MH^+), m/e 207 (MH^+-H_2O), ^{13}C nmr (dimethyl sulfoxide-d_6): 24.2, 29.9, 67.2, 113.3, 120.0, 121.6, 130.6, 132.8, 157.2, 167.4, 174.2 ppm.

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 58.60; H, 5.32.

Procedure B.

3,4-Dihydro-6,7,8-trimethoxy-1-benzoxepin-5(2*H*)-one (**2o**, Table II).

A solution of 13.5 g (0.05 mole) of 4-(3,4,5-trimethoxyphenoxy)-butanoic acid (**1o**) in 50 ml of trifluoroacetic acid was stirred in an ice bath and 20 ml of trifluoroacetic anhydride was added dropwise. The bath was removed and stirring continued at room temperature for 18 hours. Volatile material was removed at reduced pressure and the residue was stirred with 100 ml of ether. Insoluble solids were filtered (see below) and the filtrate was washed with water, 5% sodium carbonate and saturated sodium chloride. Removal of the ether gave an oil which was distilled to give 5.3 g (42%) bp 130-132°/0.3 mm; ^1H nmr (deuteriochloroform): δ 1.90-2.19 (m, 2H), 2.76 (t, 2H, J = 7.4 Hz), 3.76 (s, 3H), 3.82 (s, 3H), 3.89 (s, 3H), 4.09 (t, 2H, J = 7.4 Hz), 6.32 (s, 1H).

7,8,16,17-Tetrahydro-1,2,3,10,11,12-hexamethoxydibenzo[*b*,*i*]-[1,8]dioxacyclotetradecin-9,18-(8*H*,17*H*)dione (**11**).

From the above reaction, an ether-insoluble solid was isolated which could be recrystallized from ethyl acetate to afford a 26% yield of **11**, mp 232-234°; ir: 1701 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.98-2.30 (m, 4H), 2.84-3.23 (m, 4H), 3.75 (s, 6H), 3.86 (s, 12H), 3.90-4.12 (m, 4H), 6.19 (s, 2H), 7.19 (s, 2H); ms: (CI-CH_2) m/e 505 (MH^+).

Anal. Calcd. for $C_{26}H_{32}O_{10}$: C, 61.89; H, 6.39. Found: C, 62.11; H, 6.43.

General Procedure for the Preparation of the 2-Carboxyphenoxybutanoic Acid Esters **4b-d** (Scheme II).

The procedure utilized was essentially the same as described for the alkylation of the phenols in the general procedure for the preparation of the aryloxybutanoic acids. The crude ester, rather than being subjected to hydrolysis, was purified by distillation.

The following hydroxybenzoates **3b-d** were utilized: ethyl 2-hydroxy-3-methoxybenzoate [32], methyl 2-hydroxy-5-phenylmethoxybenzoate [33] and ethyl 5-chloro-2-hydroxy-3-methoxybenzoate **3d** (preparation described below).

4-(2-Carboxy-6-methoxyphenoxy)butanoic Acid Diethyl Ester (**4b**).

This ester was isolated in 96% yield, bp 140-145°/0.05 mm: ir: 1725 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.28 (t, 3H, J = 7.5 Hz), 1.42 (t, 3H, J = 7.5 Hz), 1.94-2.27 (m, 2H), 2.53-2.73 (m, 2H), 3.82 (s, 3H), 3.96-4.50 (m, 6H), 6.97-7.36 (m, 4H).

Anal. Calcd. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.77; H, 7.13.

4-(2-Carboxy-4-phenylmethoxyphenoxy)butanoic Acid Ethyl Methyl Ester (**4c**).

This ester was isolated in 89% yield, bp 210-218°/0.4 mm; ir: 1732 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.25 (t, 3H, J = 7.5 Hz), 1.94-2.28 (m, 2H), 2.59 (t, 2H, J = 6.4 Hz), 3.92 (s, 3H), 4.02 (t, 3H, J = 6.6 Hz), 4.10 (q, 2H, J = 7.5 Hz), 5.02 (s, 2H), 6.78-7.49 (m, 8H).

Anal. Calcd. for $C_{21}H_{24}O_6$: C, 67.73; H, 6.47. Found: C, 67.47; H, 6.48.

4-(2-Carboxy-4-chloro-6-methoxyphenoxy)butanoic Acid Diethyl Ester (**4d**).

This ester was isolated in 91% yield, bp 145-155°/0.25 mm; ir: 1736 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.29 (t, 3H, J = 7.5 Hz), 1.42 (t, 3H, J = 7.5 Hz), 1.93-2.25 (m, 2H), 2.60, 2.61 (overlapping t, 2H, J = 6.0 and 6.0 Hz), 3.82 (s, 3H), 3.95-4.23 (m, 6H), 6.98 (d, 1H, J = 2.8 Hz), 7.28 (d, 1H, J = 2.8 Hz).

Anal. Calcd. for $C_{16}H_{21}ClO_6$: C, 55.73; H, 6.14. Found: C, 55.38; H, 6.08.

Procedure C.

General Procedure for the Preparation of the 2,3,4,5-Tetrahydro-5-oxo-1-benzoxepin-4-carboxylic Acid Ethyl Esters **5b-d** (Scheme II).

A mixture of the diester, **4b-d**, (0.1 mole), 8.8 g (0.22 mole) of a 60% sodium hydride-oil suspension and 250 ml of dry dimethylformamide containing a few drops of ethanol was stirred at room temperature for 18-24 hours. The reaction was mildly exothermic and there was a slow gas evolution. The mixture was then heated on a steam bath for 0.5 hours, cooled and poured slowly into 2 ℓ of cold 1% hydrochloric acid. The oily product was extracted into chloroform and the extracts were washed with several portions of water, then saturated sodium chloride solution. Removal of the chloroform left an oil which was taken up in a mixture of 200 ml acetonitrile and 25 ml of heptane. The acetonitrile layer was separated and the solvent removed at reduced pressure leaving the keto ester which was purified by distillation or recrystallization.

2,3,4,5-Tetrahydro-9-methoxy-5-oxo-1-benzoxepin-4-carboxylic Acid Ethyl Ester (**5b**).

This ester was isolated in 71% yield, mp 84-90°. A sample recrystallized from cyclohexane had mp 92-94°; ir: 1680, 1740 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.25 (t, 3H, J = 7.0 Hz), 2.41-2.70 (m, 2H), 3.81 (s, 3H), 4.06-4.75 (m, 5H), 7.04 (d, 2H, J = 5.4 Hz), 7.34 (d, 1H, J = 5.4 Hz).

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.52; H, 6.13.

2,3,4,5-Tetrahydro-5-oxo-7-phenylmethoxy-1-benzoxepin-4-carboxylic Acid Ethyl Ester (**5c**).

This ester was isolated in 49% yield, bp 183-195°/0.6 mm, ir: 1680, 1742 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.25 (t, 3H, J = 7.0 Hz), 2.38-2.71 (m, 2H), 3.98-4.48 (m, 5H), 5.05 (s, 2H), 6.96-7.50 (m, 8H).

Anal. Calcd. for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.87; H, 5.84.

7-Chloro-2,3,4,5-tetrahydro-9-methoxy-5-oxo-1-benzoxepin-4-carboxylic Acid Ethyl Ester (**5d**).

This ester was isolated in 84% yield, mp 89-93°. A sample recrystallized from pentane had mp 93-95°; ir: 1675, 1723 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.24 (t, 3H, J = 7.2 Hz), 2.37-2.69 (m, 2H), 3.86 (s, 3H), 3.98-4.68 (m, 5H), 6.97 (d, J = 2.2 Hz), 7.32 (d, J = 2.2 Hz).

Anal. Calcd. for $C_{14}H_{15}ClO_5$: C, 56.29; H, 5.06. Found: C, 56.27; H, 5.10.

Hydrolysis of the Keto Esters **5b-d** (Scheme II).

a) Basic Hydrolysis: The keto ester **5b** or **5d** (0.1 mole) was heated for 0.5 hours on a steam bath with 800 ml of 1*N* sodium hydroxide. A solution formed initially but an oil soon separated. After cooling, the oil was extracted into ether and the extracts were washed with saturated sodium chloride and dried over magnesium sulfate. Removal of the solvent gave the respective ketones **2h** and **2p** which were purified by distillation.

3,4-Dihydro-9-methoxy-1-benzoxepin-5(2*H*)-one (**2h**).

This ketone was isolated in 77% yield, bp 101-103°/0.5 mm; ir: 1683 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.04-2.25 (m, 2H), 2.88 (t, 2H, J = 6.7 Hz), 3.87 (s, 3H), 4.25 (t, 2H, J = 6.7 Hz), 6.94-7.37 (m, 3H).

7-Chloro-3,4-dihydro-9-methoxy-1-benzoxepin-5(2*H*)-one (**2p**).

This ketone was isolated in 55% yield, mp 64-66° after recrystallization from cyclohexane. The compound had ir: 1688 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.18-2.27 (m, 2H), 2.87-2.92 (m, 2H), 3.90 (s, 3H), 4.29 (t, 2H, J = 6.6 Hz), 6.90 (d, 1H, J = 2.4 Hz), 7.30 (d, 1H, J = 2.4 Hz).

In both of the above examples, the ir and nmr spectra were identical to those of the ketone prepared by Procedure A.

b) Acid Hydrolysis: The keto ester **5c** (0.1 mole) was heated with a mixture of 100 ml of ethanol, 300 ml of acetic acid and 50 ml of concentrated hydrochloric acid on a steam bath for 7 hours. The mixture was concentrated and the oil which separated was extracted into toluene. After washing with water, dilute sodium bicarbonate and saturated sodium chloride, the solvent was removed and the residue purified by distillation.

3,4-Dihydro-7-hydroxy-1-benzoxepin-5(2*H*)-one (**2t**).

The ketone was isolated in 44% yield, bp 155-160°/0.1 mm; ^1H nmr (deuteriochloroform): δ 1.93-2.26 (m, 2H), 2.84 (t, 2H, 7.4 Hz), 4.11 (t, 2H, J = 7.4 Hz), 6.58 (broad s, 0.9H), 6.90-7.38 (m, 3H).

Procedure D.

3,4-Dihydro-7-phenylmethoxy-1-benzoxepin-5(2*H*)-one **2u** (Table II).

A mixture of 17.8 g (0.1 mole) of ketone **2t**, 13.9 g (0.11 mole) of benzyl chloride, 15 g (0.11 mole) of potassium carbonate, 0.1 g of potassium iodide and 250 ml of acetone was refluxed for 24 hours. The solids were filtered and the solvent removed at reduced pressure. The residual oil was purified by distillation to give 19.0 g (71%) bp 140-150°/0.4 mm. The distillate solidified on standing and a sample, recrystallized from methanol, had mp 61-62°; ^1H nmr (deuteriochloroform): δ 1.97-2.31 (m, 2H), 2.88 (t, 2H, J = 7.2 Hz), 4.16 (t, 2H, J = 7.2 Hz), 5.05 (s, 2H), 6.90-7.45 (m, 8H).

Procedure E.

3,4-Dihydro-8-phenylmethoxy-1-benzoxepin-5(2*H*)-one **2v**, (Table II).

A mixture of 1.80 g (0.01 mole) of ketone **2b**, 1.20 g (0.011 mole) of benzyl alcohol, 1.5 g (0.011 mole) of potassium carbonate and 25 ml of dimethylformamide was refluxed in a nitrogen atmosphere for 18 hours. The mixture was cooled and diluted with water. The product was isolated by extraction with chloroform and purified by flash chromatography on silica gel. Elution with 4:1 toluene-chloroform gave 1.77 g (66%) of **2v**, mp 58-59° after recrystallization from 1:1 cyclohexane-hexane; ^1H nmr (deuteriochloroform): δ 2.14-2.23 (m, 2H), 2.87 (t, 2H, J = 6.9 Hz), 4.23 (t, 2H, J = 6.8 Hz), 5.09 (s, 2H), 6.64 (d, 1H, J = 2.5 Hz), 6.73 (dd, 1H, J = 2.5, 8.8 Hz), 7.31-7.42 (m, 5H), 7.77 (d, 1H, J = 8.8 Hz).

Ethyl 5-Chloro-2-hydroxy-3-methoxybenzoate (**3d**) and Ethyl 2,3-Dichloro-6-hydroxy-5-methoxybenzoate.

A solution of 88.8 g (0.45 mole) of ethyl 2-hydroxy-3-methoxybenzoate (**3b**) in 250 ml of benzene was stirred at room temperature while adding dropwise a solution of 69.4 g (0.5 mole) of 97% sulfuryl chloride in 50 ml of benzene over one hour. The mixture was stirred for 6 hours, cooled in ice and treated with 60 ml of water added slowly dropwise. The water layer was separated and the benzene solution washed with water, 5% sodium carbonate and water. After drying with magnesium sulfate, the solvent was removed and the residue treated with 200 ml of cyclohexane. Insoluble solids were filtered to give 79.8 g (76%) of **3d**, mp 72-75°. A sample recrystallized from cyclohexane had mp 79-81°; ir: 1675 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.43 (t, 3H, J = 7.1 Hz), 3.88 (s, 3H), 4.39 (q, 2H, J = 7.1 Hz), 6.95 (d, 1H, J = 2.6 Hz), 7.38 (d, 1H, J = 2.6 Hz), 11.01 (s, 1H).

Anal. Calcd. for $C_{10}H_{11}ClO_4$: C, 52.07; H, 4.81. Found: C, 51.97; H, 4.76.

Concentration of the cyclohexane filtrate gave 4.3 g of solid. Recrystallization of this material from cyclohexane gave 3.2 g (5%) of ethyl 2,3-dichloro-6-hydroxy-5-methoxybenzoate, mp 97-98°; ir: 1708 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.43 (t, 3H, J = 7.2 Hz), 3.82 (s, 3H), 4.44 (q, 2H, J = 7.2 Hz), 6.98 (s, 1H), 9.43 (s, 1H); ^{13}C nmr (deuteriochloroform): 13.8, 56.3, 62.5, 114.9, 116.0, 122.0, 123.8, 147.0, 148.6, 167.4 ppm.

Anal. Calcd. for $C_{10}H_{10}Cl_2O_4$: C, 45.31; H, 3.80. Found: C, 45.15; H, 3.89.

3-Fluoro-4-Methoxyphenol.

A mixture of 98.3 g (0.58 mole) of 3-fluoro-4-methoxyacetophenone and 148 g (0.73 mole) of 85% 3-chloroperoxybenzoic acid in 2.5 ℓ of methylene chloride was refluxed for 48 hours, cooled and extracted with 5% potassium carbonate solution until the extracts remained clear on acidification. The solvent was evaporated and the residue dissolved in 300 ml of ethanol. Sodium hydroxide (100 g, 50%) was added slowly and the mixture was stirred for 3 hours. Most of the ethanol was removed at reduced pressure and 750 ml of water was added to the remainder. The aqueous solution was washed with ether and acidified with dilute hydrochloric acid. The oil which separated was extracted into ether and the extracts dried with magnesium sulfate. Removal of the solvent left a solid residue which was slurried in cyclohexane and filtered to give 78.3 g (94%), mp 51-54°. Recrystallization from cyclohexane raised the mp to 54-55°; ir: 3405 (OH) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.83 (s, 3H), 5.59 (broad s, 1H), 6.41-6.93 (m, 3H).

Anal. Calcd. for $C_7H_7FO_2$: C, 59.15; H, 4.96. Found: C, 59.03; H, 5.07.

3-Methoxy-4-Nitrophenol.

A mixture of 195.7 g (1.14 mole) of 4-fluoro-2-methoxy-1-nitrobenzene [38], 500 ml of dimethylsulfoxide and 185 g of 50% sodium hydroxide was heated in an oil bath. At a bath temperature of 100°, there was a mildly exothermic reaction (internal

temperature to 135°) and the oil bath was removed. When the exotherm had subsided, the bath was replaced and heating continued at 120-125° for 15 minutes. The mixture was then cooled, diluted with water and acidified with dilute hydrochloric acid. The solids were filtered and dried. Additional material was obtained by extraction of the filtrate with chloroform. The combined solids were recrystallized from toluene to give 132.8 g (68%), mp 138-140°. The reported mp is 142-144° [39]. The phenol was utilized for the preparation of **1q**.

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