1,4-Benzodioxepins and 1,4-Benzazepines from 3-Phenyl-2-benzofuranones

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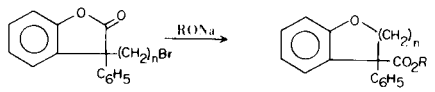
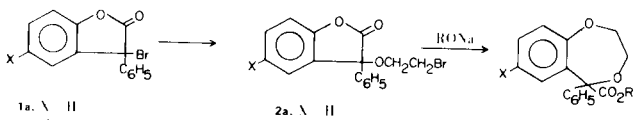
The first reports (1) in a series of papers on neighboring group reactions (2) described the alkoxide-induced rearrangement of three homologous benzofuranones to the corresponding esters.



This reaction provides convenient access to many benzoheterocycles containing one oxygen atom in 5,6, or 7-membered rings (*i.e.*, n = 1,2,3) (3). This note reports the extension of this method to the construction of analogous bicyclic systems with the benzene ring fused to 7-membered rings containing two hetero-atoms.

The key intermediates are the easily accessible 3-bromo-3-phenyl-2-benzofuranones **1**, which are readily solvolyzed in 2-bromoethanol to the bromo-ethoxy derivatives **2** (70-80% yields). In the presence of alkoxide these bromides rearrange to the 2,3-dihydro-5-phenyl-5*H*-1,4-benzodioxepine-5-carboxylic acid derivatives **3**.

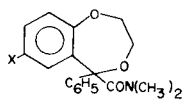


1a, X = H
1b, X = Cl

2a, X = H
2b, X = Cl

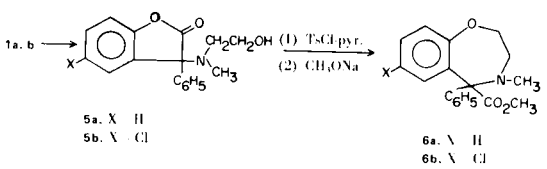
3

Results are summarized in Table I. Whereas the reaction with methoxide ion in methanol gave good yields of **3**, only moderate to poor yields of the aminoalkyl esters were obtainable. To procure even these amounts it was found necessary to use dimethylformamide as a solvent. Curiously, this medium is not inert under the reaction conditions, and appreciable amounts (15-34%) of the carboxamides **4** were isolated from all reactions utilizing this solvent. Presumably dimethylamine (or the anion derived from it) is formed from the solvent and competes with alkoxide ion in the rearrangement reaction. Other dipolar aprotic solvents (*e.g.*, dimethylsulfoxide of hexamethylphosphoramide) may provide a more inert environment for this process, but none was tried. In the event that improved results would not arise from such a solvent change, best over-all yields of the basic esters **3** b, c, e, f) would possibly be obtainable indirectly from the corresponding acid **3g**.



4

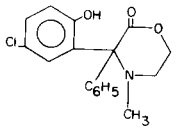
Attempts to effect reaction of the bromo compound **1a** with 2-mercaptoethanol or its sodium salt failed to give the desired 2-hydroxyethylsulfide from which a benzoxathiepin could be made. However, reaction of **1a** and **1b** with *N*-methylethanolamine led to good yields (70-80%) of the hydroxyethylamines **5**; and treatment of their tosylates with sodium methoxide in methanol effected smooth rearrangement (> 80%) to the target tetrahydro-1,4-benzoxazepines **6**.



5a, X = H
5b, X = Cl

6a, X = H
6b, X = Cl

Curiously unlike the parent compound **5a**, the chloro derivative **5b**, in chloroform solution, equilibrates with a predominant amount (60%) of the isomeric lactone A. Fortunately, this does not interfere appreciably with the progress of the desired reaction sequence.



A

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. Ir spectra were obtained using a Perkin-Elmer Model 521 spectrophotometer. Pmr spectra were recorded on a Varian T-60 (60 MHz) spectrometer. Chemical shifts are reported as δ relative to TMS (δ = 0.00 ppm), using the following abbreviations: s = singlet; t = triplet; m = multiplet.

3-(2-Bromoethoxy)-3-phenyl-2-benzofuranone (**2a**).

A stirred mixture of 3-bromo-3-phenyl-2-benzofuranone (**1a**) (4) (41.2 g., 0.143 mole), powdered calcium carbonate (15 g., 0.15 mole), and 40 ml. (0.56 mole) of 2-bromoethanol was heated on the steam bath for 3 hours and allowed to stand at room temperature overnight. The solidified reaction mixture was triturated

Table I

2,3-Dihydro-5-phenyl-5*H*-1,4-benzodioxepins

No.	X	Y	M.p., °C	Yield %	Purification Solvent	Formula	Carbon % Calcd.	Carbon % Found	Analyses Hydrogen % Calcd.	Analyses Hydrogen % Found	Nitrogen % Calcd.	Nitrogen % Found
3a	H	CO_2CH_3	107-109	99	CH_3OH	$C_{17}H_{16}O_4$ (a)	71.82	71.88	5.68	5.58		
3b	H	$CO_2(CH_2)_2N(CH_3)_2 \cdot HCl$	198-200	40	C_2H_5OH	$C_{20}H_{24}ClNO_4$ (b)	63.58	63.40	6.41	6.52	3.71	3.55
3c	H	$CO_2(CH_2)_2N(C_2H_5)_2 \cdot HCl$	153-155	49	$C_2H_5COCH_3$-ether	$C_{22}H_{28}ClNO_4$ (c)	65.10	65.12	6.95	7.03	3.45	3.42
3d	Cl	CO_2CH_3	110-111	76	CH_3OH	$C_{17}H_{15}ClO_4$ (d)	64.06	64.21	4.74	4.82		
3e	Cl	$CO_2(CH_2)_2N(CH_3)_2 \cdot (CO_2H)_2$	170-172	28	$C_2H_5COCH_3$	$C_{22}H_{24}ClNO_8$	56.72	56.41	5.19	5.23	3.01	2.86
3f	Cl	$CO_2(CH_2)_2N(C_2H_5)_2 \cdot (CO_2H)_2$	120-121	36	$C_2H_5COCH_3$	$C_{24}H_{28}ClNO_8$	58.36	58.16	5.71	5.79	2.83	2.79
3g	Cl	CO_2H	174-175	88 (e)	C_2H_5OH-H_2O	$C_{16}H_{13}ClO_4$	63.06	62.72	4.30	4.33		
4a	H	$CON(CH_3)_2$	148-150	15-18	C_2H_5OH	$C_{18}H_{19}NO_3$ (f)	72.72	72.84	6.44	6.55		
4b	Cl	$CON(CH_3)_2$	142-144	20-34	Ether	$C_{18}H_{18}ClNO_3$	65.16	65.54	5.47	5.45	4.22	4.28

(a) *Anal.* Calcd. for O: 22.52. Found: 22.55; (b) *Anal.* Calcd. for Cl: 9.39. Found: 9.44; (c) *Anal.* Calcd. for Cl: 8.74. Found: 8.54; (d) *Anal.* Calcd. for Cl: 11.12. Found: 10.95; (e) By saponification of **3d** in hot 10% aqueous-alcoholic potassium hydroxide (18 hours reflux); (f) *Anal.* Calcd. for O: 16.14. Found: 16.34.

with hot benzene and collected at the filter. The filtrate was taken up in chloroform, washed with water, and concentrated to dryness *in vacuo* in a rotating evaporator. The residual amber oil (15 g.) crystallized, was slurried in cold ether, collected at the filter, and dried to give 9.93 g., m.p. 111-115°. The wet filter cake from the reaction mixture was stirred with boiling chloroform, filtered from insoluble material (12 g.), and concentrated to dryness in a rotating evaporator. The residual oil (34.8 g.) crystallized, was triturated with cold ether, collected at the filter and dried to give 29.32 g., m.p. 114-117° (total yield: 39.25 g., 82%). Recrystallization of a sample from ether gave pure **2a**, m.p. 116-118°; ir (chloroform): 1820 (ν C=O); pmr (deuteriochloroform): δ 3.3-3.8 (m, 4H, OCH_2CH_2Br), δ 7.2-7.7 (m, 9H, ArH).

Anal. Calcd. for $C_{16}H_{13}BrO_3$: C, 57.67; H, 3.94; Br, 23.99. Found: C, 57.51; H, 4.04; Br, 23.59.

3-(2-Bromoethoxy)-5-chloro-3-phenyl-2-benzofuranone (**2b**).

Application of the foregoing procedure to crude **1b**, prepared by bromination of 5-chloro-3-phenyl-2-benzofuranone (5) in the usual way (4), gave a 70% yield of **2b**, m.p. 100-105°. Recrystallization from benzene-pentane gave pure **2b**, m.p. 110-111°.

Anal. Calcd. for $C_{16}H_{12}BrClO_3$: C, 52.27; H, 3.29; Br, 21.13; Cl, 9.64. Found: C, 52.56; H, 3.41; Br, 21.03; Cl, 9.65.

Methyl 2,3-Dihydro-5-phenyl-5*H*-1,4-benzodioxepin-5-carboxylate (**3a**).

To a stirred solution of 0.015 mole of sodium methoxide in methanol (50 ml.) was added in portions 5 g. (0.015 mole) of solid **2a**. The solution was stirred over a week-end at room temperature and concentrated to dryness *in vacuo*. The solid residue was stirred in water, collected at the filter, washed and dried. There was obtained 4.23 g. (99%) of **3a**, m.p. 105-108°. Recrystallization from methanol gave pure **3a** (3.66 g.) m.p. 107-109°; ir (chloroform): 1750 (ν C=O); pmr (deuteriochloroform): δ 3.80 (s, 3H, OCH_3), δ 3.9-4.5 (m, 4H, OCH_2CH_2O), δ 6.7-7.7 (m, 9H, ArH).

The methyl ester **3d** (see Table I) also was prepared from the bromide **2b** by the foregoing procedure.

2-Dimethylaminoethyl 2,3-Dihydro-5-phenyl-5*H*-1,4-benzodioxepin-5-carboxylate Hydrochloride (**3b**) and *N*,*N*-Dimethyl 2,3-dihydro-5-phenyl-5*H*-1,4-benzodioxepin-5-carboxamide (**4a**).

To a stirred suspension of 0.72 g. (0.03 mole) of sodium hydride in 30 ml. of dimethylformamide (DMF) was added 2.67 g. (0.03 mole) of 2-dimethylaminoethanol, and stirring was continued for 1 hour at room temperature. Then a solution of 6.67 g. (0.02 mole) of the bromo compound **2a** in 30 ml. of DMF was added and stirring was continued at room temperature overnight. The reaction mixture was poured into cold water, the precipitated oil was taken up in ether and extracted with 10% hydrochloric acid. The ether layer containing neutral product was dried over anhydrous magnesium sulfate, while the aqueous acidic extract was made alkaline with 25% sodium hydroxide. The precipitated basic oil was taken up in ether, washed with water and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave an amber oil (3.07 g.) that was taken up in dry ether and treated with a slight excess of ethereal hydrogen chloride. The crude salt (3.02 g., 40%, m.p. 193-196°) was recrystallized once from ethanol to give 2.68 g. of pure **3b**, m.p. 198-200°; ir (chloroform): 1760 (ν C=O).

The neutral ethereal extract was filtered and concentrated to dryness. The solid residue (1.68 g.) was recrystallized once from ethanol to give pure **4a**, m.p. 148-150°; ir (deuteriochloroform):

1640 (ν C=O); pmr (deuteriochloroform): δ 2.92 (s, 3H, NCH_3), δ 3.03 (s, 3H, NCH_3), δ 4.0-4.3 (m, 4H, OCH_2CH_2O), δ 6.5-7.5 (m, 9H, ArH).

The foregoing procedure also was used to prepare the other basic esters **3c**, **3e**, and **3f**, except that the last two were isolated as bioxalates rather than as hydrochlorides (see Table I). In all cases, the amides (**4a** or **4b**) were isolated as neutral by-products.

3-(2-Hydroxyethyl)methylamino-3-phenyl-2-benzofuranone (**5a**).

To a stirred suspension of the bromo compound **2a** (8.67 g., 0.03 mole) in 6 ml. of tetrahydrofuran (THF), cooled to 10°, was added dropwise 4.50 g. (0.06 mole) of *N*-methylethanolamine while maintaining the temperature below 35°. The mixture was stirred at room temperature for 44 hours and then was taken up in a mixture of ether (400 ml.) and water (75 ml.). The ether layer was separated, washed with water to neutrality, and dried over anhydrous magnesium sulfate. Filtration, concentration to a volume of 25-30 ml., and cooling in ice gave 6.92 g. (81%) of **5a**, m.p. 107-108°. Recrystallization of a sample from THF gave pure **5a**, m.p. 110-111°; ir (deuteriochloroform): 1810 (ν C=O of benzofuranone), 3400-3700 (ν OH); pmr (deuteriochloroform): δ 2.33 (s, 3H, CH_3N), δ 2.67 [t, 2H, $C(H_2)CH_2N$], δ 3.5-3.9 [m, 2H, $C(H_2)CH_2OH$], δ 7.0-7.7 (m, 9H, ArH), δ OH not directly observable.

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 72.23; H, 6.05; N, 4.94.

5-Chloro-3-(2-hydroxyethyl)methylamino-3-phenyl-2-benzofuranone (**5b**).

Application of the above procedure to the bromo compound **2b** gave a 73% yield of **5b**, m.p. 109-110°. Recrystallization of a sample from THF-hexane gave pure **5b**, m.p. 113-114°; the ir and pmr spectra indicated that **5b** (in deuteriochloroform solution) exists in equilibrium with the isomeric lactone (*i.e.*, structure A); ir (deuteriochloroform): 1740 (ν C=O of structure A), 1810 (ν C=O of structure **5b**); pmr (deuteriochloroform): δ 2.20 (s, 1.8 H, 0.6 CH_3N of structure A), δ 2.32 (s, 1.2 H, 0.4 CH_3N of structure **5b**), δ 2.5-2.9 [m, 2H, $C(H_2)CH_2N$], δ 3.4-3.8 [m, 0.4 $C(H_2)$-CH_2OH of structure **5b**], δ 4.3-4.9 (m, 0.6 $C(H_2)CH_2OC$=O of structure A], δ 6.7-7.7 (m, 8H, ArH), δ 11.3-12.0 [m (very broad), 1H, OH].

Anal. Calcd. for $C_{17}H_{16}ClNO_3$: C, 64.25; H, 5.07; N, 4.41. Found: C, 64.55; H, 5.13; N, 4.44.

Methyl 5-Phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxylate (**6a**).

To an ice-cooled, stirred solution of 6.80 g. (0.024 mole) of **5a** in 45 ml. of dry pyridine was added in portions 9.20 g. (0.048 mole) of *p*-toluenesulfonyl chloride. The reaction mixture was refrigerated (+ 4°) for 44 hours and then poured into ice water (600 ml.). The precipitated oil was taken up in chloroform (300 ml.), washed with water (3 x 200 ml.), and concentrated to dryness in a rotary evaporator *in vacuo*. The residual oil was dissolved in 80 ml. of cold, dry methanol and treated with a solution of sodium methoxide (from 0.6 g., 0.026 g.-atom of sodium) in 25 ml. of methanol. After stirring at room temperature overnight, the reaction mixture was heated under reflux for 2 hours and then concentrated to dryness. The residue was taken up in a mixture of ether and water, the ether was washed to neutrality with water and then dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave 5.90 g. (83% yield from **5a**) of an amber glass that crystallized (m.p. 78-81°) upon trituration with pentane. Recrystallization of a sample from hexane gave pure **6a**, m.p. 80-82°; ir (deuteriochloroform): 1730 (ν ester C=O); pmr (deuteriochloroform): δ 2.33 (s, 3H, NCH_3), δ 3.0-3.6 [m, 2H, $C(H_2)CH_2N$], δ 3.67 (s, 3H, OCH_3), δ 3.8-4.2 [m, 2H, $C(H_2)CH_2O$], δ 6.9-7.7 (m, 9H, ArH).

Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 73.07; H, 6.62; N, 4.73.

Methyl 7-Chloro-5-phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxylate (**6b**).

When the compound **5b** was submitted to the above procedure an 84% yield of **6b**, m.p. 88-92°, was obtained. Two recrystallizations of a sample from hexane gave pure **6b**, m.p. 92-94°; pmr (deuteriochloroform): essentially the same as that of **5a**.

Anal. Calcd. for $C_{18}H_{18}ClNO_3$: C, 65.16; H, 5.47; N, 4.22. Found: C, 65.24; H, 5.59; N, 4.19.

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(2) The present note is No. XVI in the series, "Neighboring Group Reactions." For paper XV, see H. E. Zaugg, J. E. Leonard, R. W. De Net, and D. L. Arendsen, *J. Heterocyclic Chem.*, **11**, 797 (1974).

(3) For other synthetic applications of this rearrangement see, H. E. Zaugg *et al.*, *J. Am. Chem. Soc.*, **86**, 1399 (1964; *ibid.*, **84**, 4567 (1962); *J. Org. Chem.*, **35**, 3567 (1970); *ibid.*, **28**, 1795 (1963); *J. Med. Chem.*, **5**, 430 (1962).

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