Bridged 1,4-Benzoxazocines from 5-Hydroxy-3-phenyl-2-benzofuranone

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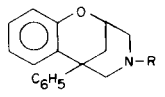
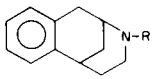
A previously described neighboring group reaction has been extended to the synthesis of hydroxy-substituted bridged 1,4-benzoxazocines (*i.e.*, **7**, **8**) bearing a structural analogy to potent analgetics of the hydroxy-6,7-benzomorphan series. In contrast to the latter, the presence of a hydroxyl group in the aromatic ring of the present series destroys all analgesic activity possessed by the unsubstituted system.

A preceding report (1) described the synthesis and moderate analgesic activity of a new bridged heterocyclic system, A, resembling the 6,7-benzomorphan structure B.



A

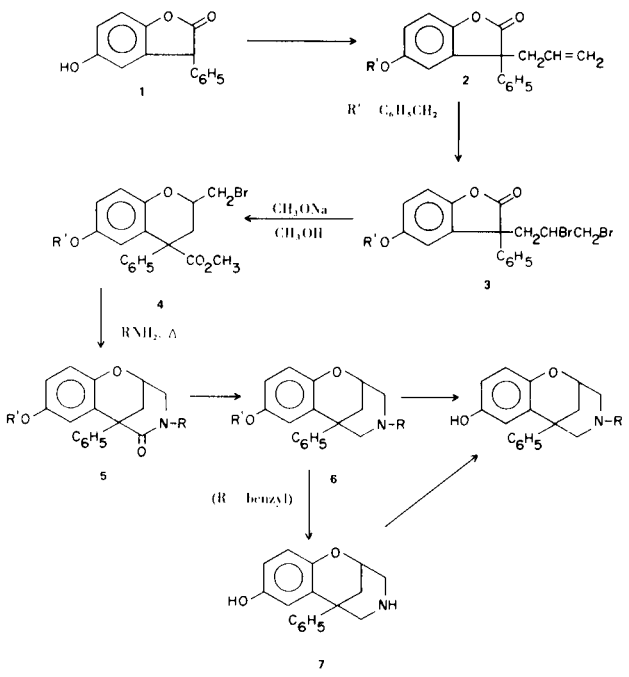


B

Maximal potency in the benzomorphans is known (2) to occur in phenolic derivatives. The present paper (3) describes the logical extension of the synthesis of type A compounds to include analogous phenols. Unfortunately, such substitution in A essentially destroyed whatever analgesic activity was present in the parent compounds.

The starting material for the present study was 5-hydroxy-3-phenyl-2-benzofuranone (**1**) (4). In accord with previous work (5), it was found that the anion of **1** could be allylated at carbon and then benzylated at oxygen to give **2** in a 60% yield without isolating the product of the first alkylation. Addition of bromine to the allyl group gave **3** (92% yield) as a mixture of solid enantiomers which was not resolved into its components as had been done previously for the parent system. Instead, this mixture was treated directly with sodium methoxide in methanol to obtain a non-crystalline mixture of *cis* and *trans* bromo esters **4** (92% yield). Heating this mixture with primary amines gave neutral lactams **5** which could easily be separated, albeit in poor yields (15-26%), from basic products derived from the *trans* bromo ester. Data for the six examples of this type synthesized are summarized in Table I. Hydride reduction of these lactams gave the corresponding benzyloxyamines **6** (see Table II), three of which (**6a**, **d**, **f**) could be catalytically hydrogenolyzed to the target hydroxyamines **8**.

Similar catalytic hydrogenation of the dibenzyl derivative **6b** gave the expected secondary amine **7** which could be alkylated selectively at nitrogen under a variety of conditions (Procedures D-H in the experimental section). The compound **8a** obtained by methylation of **7** was identical with the product derived from the *N*-methyllactam **5a** by hydride reduction followed by hydrogenolysis.



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). Chemical shifts are reported as δ related to TMS (δ = 0.00 ppm), using the following abbreviations: s = singlet;

Table I

4-Substituted-8-benzyloxy-5-oxo-6-phenyl-3,4,5,6-tetrahydro-2,6-methano-2*H*-1,4-benzoxazocines (**5**)

No.	R	M.p., °C	Yield (a) Purified, %	Purification Solvent	Formula	Analyses Carbon % Calcd.	Found	Hydrogen % Calcd.	Found	Nitrogen % Calcd.	Found
5a	CH_3	179-180	21	CH_3OH	$C_{25}H_{23}NO_3$	77.9	78.0	6.0	6.2	3.6	3.7
5b	$C_6H_5CH_2$	186-187	26	$CH_3COC_2H_5$	$C_{31}H_{27}NO_3$	80.7	80.6	5.9	6.0	3.0	3.0
5c	$C_6H_5CH_2CH_2$	131-132	23	CH_3OH	$C_{32}H_{29}NO_3$	80.8	80.8	6.2	6.2	2.9	2.9
5d	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2$	105-106	15	CH_3OH	$C_{34}H_{33}NO_5$	76.2	76.1	6.2	6.2	2.6	2.7
5e	Cyclopropyl	182-183	16	CH_3OH	$C_{27}H_{25}NO_3$	78.8	79.2	6.1	6.3	3.4	3.4
5f	Cyclopropylmethyl	158-159	25	CH_3OH	$C_{28}H_{27}NO_3$	79.0	79.2	6.4	6.6	3.3	3.4

(a) By procedure A from a mixture of *cis* and *trans* bromoester **4**.

d = doublet; m = multiplet. Thin-layer chromatograms (tlc) were obtained using Silic AR-7GF silica gel to a distance of 15 cm. Spots were detected by visual examination and by development in iodine vapor.

3-Allyl-5-benzyloxy-3-phenyl-2-benzofuranone (**2**).

To a cooled (5-10°), stirred solution of 113 g. (0.5 mole) of 5-hydroxy-3-phenyl-2-benzofuranone (**1**) (4) and 62 g. (0.51 mole) of allyl bromide in 800 ml. of dry dimethylformamide was added, portionwise under an atmosphere of dry nitrogen, 12 g. (0.50 mole) of sodium hydride (from 21 g. of 57% mineral oil dispersion previously washed with dry benzene). After stirring overnight at room temperature, the mixture became neutral. It was then cooled once again in ice and a solution of 85.6 g. (0.5 mole) of benzyl bromide in 300 ml. of dry dimethylformamide was added followed by the portionwise addition of another 0.5 mole of washed sodium hydride. After stirring overnight at room temperature, the dark reaction mixture became neutral once again. It was divided into two equal portions, each half was poured into 3 l. of ice water and stirred at room temperature over a weekend. The oil that had precipitated initially mostly crystallized. The water was decanted from the oily solid which was triturated and washed by decantation with several more portions of water. The crude product (165 g.) was collected at the filter and air-dried. It was taken up in 900 ml. of hot methanol, decolorized with charcoal, and allowed to cool slowly in the presence of seed crystals. The crystallized product was collected at the filter, washed with cold methanol and dried to give 108 g. (60% yield) of **2**, m.p. 66-68°, of suitable purity for use in the next step. Recrystallization of a sample from methanol gave pure **2**, m.p. 70-71°; ir (deuteriochloroform): 1800 (ν C = O).

Anal. Calcd. for $C_{24}H_{20}O_3$: C, 80.9; H, 5.7. Found: C, 81.2; H, 5.6.

5-Benzyloxy-3-(2,3-dibromopropyl)-3-phenyl-2-benzofuranone (**3**).

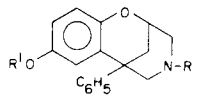
To a cooled (5-10°), stirred solution of 98 g. (0.275 mole) of **2** in 500 ml. of chloroform was added dropwise over a period of 3 hours, a solution of 44 g. of bromine in 150 ml. of chloroform. After stirring at room temperature overnight, the solvent was removed *in vacuo* using a rotary evaporator. The solid residue was triturated with methanol, collected at the filter, and dried, to give 131 g. (92%) of **3**, as a mixture of diastereomers, m.p. 110-120°; tlc (developed with a 50:50 mixture of cyclohexane-benzene) Rf = 0.18 and 0.28; ir (deuteriochloroform): 1800 (ν C=O); pmr (deuterichloroform): δ 2.5-4.2 (m, 5H, $CH_2CHBrCH_2Br$), δ 5.10 (s, 2H, $ArCH_2O$), δ 6.8-7.7 (m,~13H, ArH). This mixture was used in the next step.

Methyl 6-Benzyloxy-2-bromomethyl-4-phenyl-4-chromancarboxylate (**4**).

To a solution of sodium methoxide in methanol prepared from 2.9 g. (0.126 g. -atom) of sodium and 500 ml. of dry methanol was added in one portion 65 g. (0.126 mole) of the mixture of dibromides **3**. After stirring for 2 hours at room temperature, most of the dibromide had dissolved. The portion remaining out of solution formed a gummy ball. After standing overnight at room temperature, the stirred mixture was heated under reflux for 3 hours, during which time a completely homogenous solution formed. The strongly alkaline solution was concentrated to dryness, the residue was taken up in a mixture of ether and water, and the ether extract was washed to neutrality with water and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave a thick amber colored oil (54.6 g., 92% yield) that could not be made to crystallize; ir (deuterio-

Table II

4,8-Disubstituted-6-phenyl-3,4,5,6-tetrahydro-2,6-methano-2*H*-1,4-benzoxazocines



R^1	R	Salt	Solvate	M.p., °C	Procedure	Yield Purified, %	Purification Solvent	Formula	Analyses Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found	Nitrogen % Calcd.	Nitrogen % Found
$C_6H_5CH_2$	CH_3		-	113-115	B	86	$(C_2H_5)_2O$	$C_{25}H_{25}NO_2$	80.8	81.0	6.8	6.9	3.8	3.8
$C_6H_5CH_2$	$C_6H_5CH_2$	HCl		215-216 (dec)	B	90	C_2H_5OH	$C_{31}H_{30}ClNO_2$	76.9	77.1	6.3	6.3	2.9	2.9
$C_6H_5CH_2$	$C_6H_5CH_2CH_2$	$HCl \cdot 1/2H_2O$		213-215 (dec)	B	75	CH_3OH-$(C_2H_5)_2O$	$C_{32}H_{33}ClNO_{2.5}$	75.8	76.3	6.6	6.6	2.8	2.8
$C_6H_5CH_2$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2$	$HCl \cdot C_2H_5OH$		88-90	B	69	C_2H_5OH-$(C_2H_5)_2O$	$C_{36}H_{42}ClNO_5$	71.6	71.4	6.8	6.7	2.3	2.4
$C_6H_5CH_2$	Cyclopropyl		-	107-109	B	79	$(C_2H_5)_2O$-pentane	$C_{27}H_{27}NO_2$	81.6	81.6	6.9	7.0	3.5	3.5
$C_6H_5CH_2$	Cyclopropylmethyl	$HCl \cdot 1/2H_2O$		190-192 (dec)	B	70	CH_3OH-$(C_2H_5)_2O$	$C_{28}H_{31}ClNO_{2.5}$	73.6	73.7	6.8	6.7	3.1	3.1
H	H	$(CH_3)_2CHOH$		216-217 (dec)	C	84	$(CH_3)_2CHOH$	$C_{20}H_{25}NO_3$	73.4	73.8	7.7	8.0	4.3	4.4
H	CH_3		-	283-385 (dec)	C	55	$HCON(CH_3)_2$	$C_{18}H_{19}NO_2$	76.8	77.1	6.8	7.0	5.0	5.0
					D	39								
H	$HC\equiv CCH_2$		-	210-213 (dec)	F	57	CH_3CN	$C_{20}H_{19}NO_2$	78.7	78.3	6.3	6.4	4.6	4.7
H	$CH_3CH=CHCH_2$		-	162-164	G	65	CH_3OH	$C_{21}H_{23}NO_2$	78.5	78.2	7.2	7.2	4.4	4.6
H	$(CH_3)_2C=CHCH_2$		-	166-167	G	78	CH_3OH	$C_{22}H_{25}NO_2$	78.8	79.1	7.5	7.7	4.2	4.2
H	Cyclopropylmethyl	HCl		266-267 (dec)	C	86	C_2H_5OH	$C_{21}H_{24}ClNO_2$	70.5	70.6	6.8	6.8	3.9	3.9
H	Cyclobutylmethyl	HCl		280-285 (dec)	H	32	C_2H_5OH	$C_{22}H_{26}ClNO_2$	71.1	70.9	7.1	7.2	3.8	3.8
H	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2$		-	158-160	C	68	CH_3CN	$C_{27}H_{29}NO_4$	75.2	74.9	6.8	7.0	3.3	3.2
H	$4\text{-}FC_6H_4(CH_2)_4$		-	180-181	G	58	$(C_2H_5)_2O$	$C_{27}H_{28}FNO_2$	77.7	77.3	6.8	6.9	3.4	3.4
H	$C_6H_5CH=CHCH_2$		-	202-203	E	70	CH_3OH	$C_{26}H_{25}NO_2$	81.4	81.2	6.6	6.7	3.7	3.6
H	$C_6H_5COCH_2$		-	168-170	E	35	CH_3OH	$C_{25}H_{23}NO_3$	77.9	77.6	6.0	6.1	3.6	3.6
H	$4\text{-}FC_6H_4CO(CH_2)_3$		-	152-153	G	46	CH_3OH	$C_{27}H_{26}FNO_3$	75.1	75.1	6.1	6.2	3.3	3.2

chloroform): 1725 (ν C=O), only a trace of lactone C=O at 1800 cm^{-1}; pmr (deuteriochloroform): δ 2.5-4.0 [m, 5H, $BrCH_2$-$CH(O)CH_2$], δ 3.72 and 3.76 (2s, 3H, OCH_3 of *cis* and *trans* esters), δ 4.92 and 5.00 (2s, 2H, $ArCH_2O$ of *cis* and *trans* isomers), δ 6.8-7.6 (m, 13H, ArH). This material was used without purification in the next step.

4-Benzyl-8-benzyloxy-5-oxo-6-phenyl-3,4,5,6-tetrahydro-2,6-methano-2*H*-1,4-benzoxazocine (**5b**).

Procedure A.

A mixture of 70 g. (0.15 mole) of **4** (*cis* + *trans*) and 150 ml. of benzylamine was heated at 215-220° (gentle reflux) in an oil bath for 4 hours. The excess benzylamine was removed by distillation under vacuum (1 mm; 150-160° bath temperature) using a rotary evaporator. The semi-solid residue was triturated with ether and allowed to stand overnight. The insoluble solid was collected at the filter, washed with ether and dried. This material (43.7 g.), consisting of a mixture of desired lactam **5b**, benzylamine hydrobromide and amino ester hydrobromide (from the *trans* bromoester), was stirred in water for 2 hours, collected at the filter, washed with more water and dried to give 18 g. (26% yield) of **5b**, m.p. 181-184°, of adequate purity for use in the next step. For analysis (see Table I) a sample was recrystallized from 2-butanone, m.p. 186-187°; ir (deuteriochloroform): 1650 (ν lactam C=O); pmr (deuteriochloroform): δ 2.32 [d, 2H, $OC(H)CH_2C$], δ 3.5-3.7 [m, 2H, $OC(H)CH_2N$], δ 4.62 (s, 2H, $ArCH_2N$), δ 4.6-4.8 [m, 1H, $C(H_2)CH(O)C(H_2)$], δ 4.91 (s, 2H, $ArCH_2O$), δ 6.8-7.7 (m, 18H, ArH).

Using the appropriate primary amine, the other lactams listed in Table I were prepared by the foregoing procedure, but with the following modifications in reaction conditions: **5a**, 24 hours at 125° (in toluene solution in a pressure reactor); **5c**, 4 hours at 220° followed by 24 hours at 110°; **5d**, 4 days at 100°; **5e** and **5f**, 6 days at reflux temperature.

4-Benzyl-8-benzyloxy-6-phenyl-3,4,5,6-tetrahydro-2,6-methano-2*H*-1,4-benzoxazocine (**6b**).

Procedure B.

To a stirred suspension of 1.9 g. (0.05 mole) of lithium aluminum hydride in 400 ml. of dry ether was added in portions 9.2 g. (0.02 mole) of the benzyl lactam **5b**. The stirred mixture was warmed under reflux overnight and then was cooled in ice and treated successively with water (2 ml.), 10% sodium hydroxide (3 ml.) and more water (5 ml.). After stirring again overnight, the mixture was filtered, the filter cake was washed well with ether and the combined filtrate and washings were dried over anhydrous magnesium sulfate. Filtration and treatment of the filtrate with a slight excess of ethereal hydrogen chloride precipitated an amorphous salt (10.13 g.) that could be recrystallized from ethanol to give 8.78 g. (90% yield) of the amine hydrochloride **6b**, m.p. 215-216° (with decomposition).

The other benzyloxy amines **6a-f**, listed in Table II were prepared by the foregoing procedure with the exception that the methyl and cyclopropyl derivatives (**6a** and **6e**, respectively) were isolated as solid bases rather than as hydrochlorides.

8-Hydroxy-6-phenyl-3,4,5,6-tetrahydro-2,6-methano-2*H*-1,4-benzoxazocine (**7**).

Procedure C.

A solution of 15.2 g. (0.034 mole) of the dibenzyl hydrochloride **6b** in 250 ml. of 95% ethanol was treated with 3 g. of 5% palladium-charcoal catalyst and hydrogenated at room temperature and 50 pounds pressure. Hydrogen uptake was complete in 3 hours. The reaction mixture was filtered and the mixture of catalyst and insoluble product hydrochloride was treated successively with two 500-ml. portions of boiling ethanol and filtered while hot. The combined filtrates (~1200 ml.) were concentrated to 500 ml. and cooled. Precipitated product (4.68 g., m.p. 330-335°, dec.) was collected at the filter and dried. A second crop (2.94 g., m.p. 330-335°, dec.) was obtained on further concentration to 200 ml. (yield, 84%). This material was used for the succeeding alkylation to **8**. For analyses, a sample was dissolved in excess 10% sodium hydroxide solution and the deep red solution was carefully neutralized with 10% hydrochloric acid. The pink solid that precipitated was recrystallized twice from isopropyl alcohol to give the base **7**, m.p. 216-217° dec., containing a molecule of solvent of crystallization (see Table II).

In a similar manner were prepared three *N*-substituted derivatives of **7**, namely, **8a**, **8e** and **8g**, by catalytic hydrogenolysis of the corresponding benzyloxy derivatives **6a**, **6f** and **6d**, respectively. However, attempts to reduce the *N*-phenethyl (**6c**) and *N*-cyclopropyl (**6e**) derivatives failed. Spectral evidence suggested that under these conditions, the cyclopropyl group of **6e** was destroyed and the phenethyl group of **6c** was removed.

8-Hydroxy-4-methyl-6-phenyl-3,4,5,6-tetrahydro-2,6-methano-2*H*-1,4-benzoxazocine (**8a**).

Procedure D.

A solution of 2 g. (0.0066 mole) of **7** hydrochloride and 1.33 g. (0.0132 mole) of triethylamine in 10 ml. of dimethylformamide was treated with 1.25 g. (0.009 mole) of methyl iodide. After standing overnight at room temperature, the reaction mixture was poured into water. The light brown precipitate was collected at the filter, washed with water, and dried. The crude product (1.56 g., m.p. 260-263°) was recrystallized from dimethylformamide to give 1.02 g. (39%) of pure **8a**, m.p. 283-285° dec., identical (pmr and mixture m.p.) with the compound prepared by Procedure C.

4-Cinnamyl-8-hydroxy-6-phenyl-3,4,5,6-tetrahydro-2,6-methano-2*H*-1,4-benzoxazocine (**8i**).

Procedure E.

A stirred mixture of 2.0 g. (0.0066 mole) of **7** hydrochloride, 1.01 g. (0.0066 mole) of cinnamyl chloride, 1.33 g. (0.0132 mole) of triethylamine, and 100 ml. of dry benzene was heated at reflux under an atmosphere of dry nitrogen for 65 hours. The hot reaction mixture was filtered from triethylamine hydrochloride (1.84 g.) and the filtrate was taken to dryness by distillation. The glassy residue crystallized on trituration with methanol and was collected at the filter, washed with methanol, and dried. There was obtained 1.78 g. (70%) of **8i**, m.p. 200-203°. Recrystallization from methanol gave pure **8i**, m.p. 202-203°.

Also prepared by Procedure E, using α-bromoacetophenone, was the analogous 4-phenacyl derivative **8j** (see Table II).

8-Hydroxy-6-phenyl-4-propargyl-3,4,5,6-tetrahydro-2,6-methano-2*H*-1,4-benzoxazocine (**8b**).

Procedure F.

A stirred mixture of 2 g. (0.0066 mole) of **7** hydrochloride, 0.79 g. (0.007 mole) of propargyl bromide, 1.58 g. (0.015 mole) of anhydrous sodium carbonate, and 50 ml. of absolute ethanol was heated at reflux for 4 hours under an atmosphere of dry nitrogen. After being stirred overnight at room temperature the reaction mixture was filtered from insoluble material and concen-

trated to dryness. The solid residue was slurried in water, collected at the filter and dried. This crude product (2.18 g., m.p. 190-195°) was recrystallized from acetonitrile (decolorizing with charcoal) to give 1.16 g. (57%) of pure **8b** (see Table II).

4-[3-(*p*-Fluorobenzoyl) propyl]-8-hydroxy-6-phenyl-3,4,5,6-tetrahydro-2,6-methano-2*H*-1,4-benzoxazocine (**8k**).

Procedure G.

A stirred mixture of 2 g. (0.0066 mole) of **7** hydrochloride, 1.77 g. (0.0072 mole) of 2-(3-chloropropyl)-2-(*p*-fluorophenyl)-1,3-dioxolane (6), 2.29 g. (0.0138 mole) of powdered potassium iodide, 1.86 g. (0.0135 mole) of powdered anhydrous potassium carbonate, and 50 ml. of dry dimethylformamide was heated at 110° for 20 hours under an atmosphere of dry nitrogen. The hot reaction mixture was filtered from insoluble material and concentrated to dryness *in vacuo* in a rotary evaporator. The residue was treated with excess boiling 10% hydrochloric acid for 30 minutes, cooled, and the insoluble semi-solid material was washed with water several times by trituration and decantation. Then it was treated with a mixture of ether and saturated sodium bicarbonate solution, the ether layer was washed with water and dried over anhydrous magnesium sulfate. Filtration, decolorizing with charcoal and removal of the ether by distillation gave an amorphous solid (1.91 g.) that was recrystallized from methanol to give 1.32 g. (46%) of pure **8k** (see Table II); ir (deuteriochloroform): 1685 (ν C=O).

In a similar manner, but omitting the treatment with hot hydrochloric acid, were prepared **8c**, **8d**, and **8h**, using crotyl chloride, 3-methylcrotyl chloride, and 4-(*p*-flurophenyl)butyl chloride (7), respectively, as alkylating agents.

4-Cyclobutylmethyl-8-hydroxy-6-phenyl-3,4,5,6-tetrahydro-2,6-methano-2*H*-1,4-benzoxazocine (**8f**).

Procedure H.

The nitrogen atom of **7** was acylated in a triethylamine-dimethylformamide mixture (Procedure D), using cyclobutane carboxylic acid chloride. The crude amide that resulted was reduced directly with lithium aluminum hydride in ether (Procedure B) to give **8f** in a 32% overall yield (see Table II).

Acknowledgements.

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