Two New Bicyclic Ring Systems, 1,4,5-Benzodioxazocine and 1,4-Benzoxazepine

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Abstract □ Derivatives of two new bicyclic ring systems have been synthesized for pharmacological evaluation as central nervous system drugs. These derivatives were 7-chloro-5-phenyl-2,3,4,5H-1,4-benzoxazepine hydrochloride (I), 7-chloro-5-phenyl-2,3H-1,4-benzoxazepine-4-oxide (II), and 8-chloro-6-phenyl-2,3H-1,4,5-benzodioxazocine (III). The synthetic routes leading to these structures are presented.

Keyphrases □ Bicyclic ring systems, new—synthesis □ 1,4,5-Benzodioxazocine derivatives—synthesis □ 1,4-Benzoxazepine derivatives—synthesis □ IR spectrophotometry—identity

In a search for new compounds with central nervous system activity two new ring systems were investigated. The structures obtained were derivatives of the new bicyclic 1,3,4-benzodioxazocine and 1,4-benzoxazepine (Fig. 1) (1).

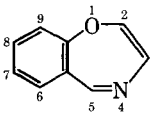
The compounds synthesized containing these ring systems were 7-chloro-5-phenyl-2,3,4,5H-1,4-benzoxazepine hydrochloride (I), 7-chloro-5-phenyl-2,3H-1,4-benzoxazepine-4-oxide (II), and 8-chloro-6-phenyl-2,3H-1,4,5-benzodioxazocine (III).

Scheme I shows the synthetic routes pursued during the course of this work.

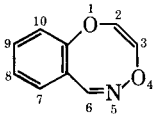
The 2-chloroethyl ether (V) of 5-chloro-2-hydroxybenzophenone (IV) (Dow Light Absorber HCB) was prepared by a modification of the method of Wheatley *et al.* (2). It was also obtainable in lower yield and purity by the reaction of IV with ethylene chlorobromide in the presence of dimethylformamide and dry potassium carbonate. At a higher temperature 1,2-bis-(4-chloro-2-benzoylphenoxy)-ethane was obtained. The 2-chloroethyl ether (V) readily formed a phthalimido derivative (VI) which was hydrolyzed by the Ing-Manske procedure (3, 4) to the amine, isolated as its hydrochloride salt (VII).

Compound I was obtained by a Leuckhart reaction on V followed by cyclization in refluxing hydrochloric acid without isolation of an intermediate. That VIII is the product of the Leuckhart reaction, which ultimately would undergo hydrolysis and cyclization in acid, is shown by the isolation in a separate run of a compound whose analysis and infrared spectrum supports structure VIII.

The isomeric compounds, *anti*-phenyl 5-chloro-2-(2-chloroethoxy)-phenyl ketoxime (IX) and *syn*-phenyl 5-chloro-2-(2-chloroethoxy)-phenyl ketoxime (X) were

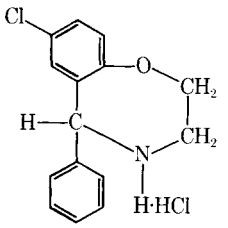


1,4-Benzoxazepine



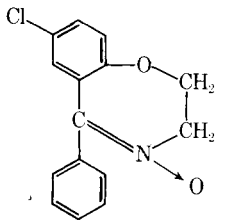
1,4,5-Benzodioxazocine

Figure 1—*Structures of new bicyclic ring systems.*



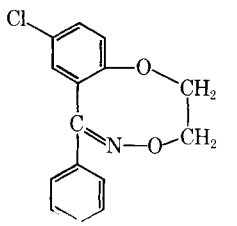
7-Chloro-5-phenyl-2,3,4,5H-1,4-benzoxazepine hydrochloride

I



7-Chloro-5-phenyl-2,3H-1,4-benzoxazepine-4-oxide

II



8-Chloro-6-phenyl-2,3H-1,4,5-benzodioxazocine

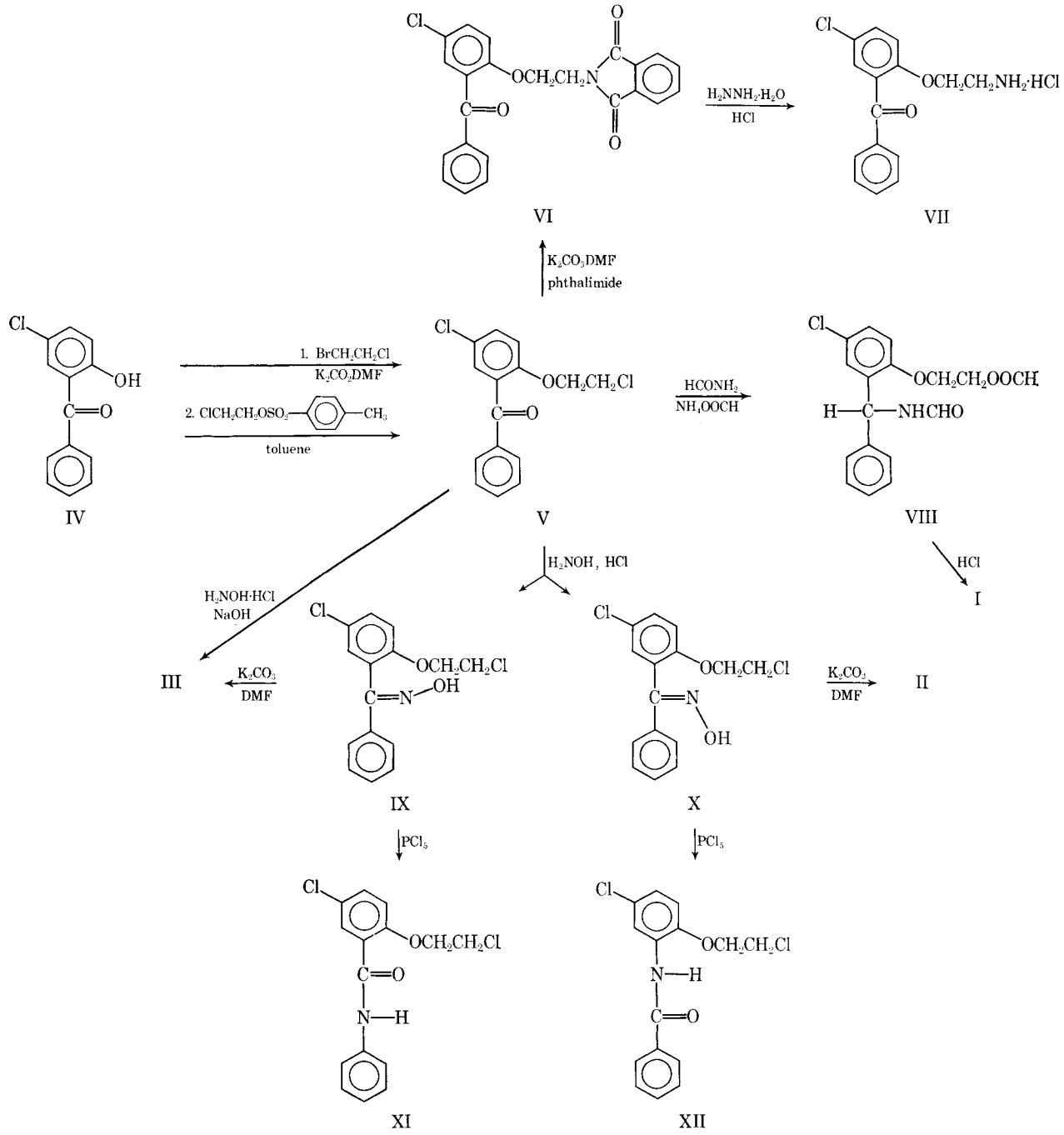
III

prepared under acidic conditions from V by the procedure of Blatt and Archer (5). They were readily separable because IX is soluble in benzene whereas X is not. A Beckmann rearrangement performed on these oximes produced isomeric amides XI and XII. The hydrolysis of XI gave aniline hydrochloride. The alkylation of oximes is known to produce mixtures of imine and *O*-ethers. In the *o*-hydroxybenzophenone oximes, one ether is obtained depending on the geometric configuration of the oxime (5). In this work intramolecular alkylation of IX and X was achieved in dimethylformamide using anhydrous potassium carbonate as condensing agent. Each oxime yielded a single product (II or III) which was isomeric to the other. The configuration of oxime IX would prohibit the rearward approach required for *N*-alkylation and favor *O*-alkylation, while oxime X should exhibit an opposite behavior. Compound II was assigned the *N*-ether structure on the basis of its slight solubility in dilute hydrochloric acid, for it is known that *N*-ethers of oximes are slightly basic whereas the *O*-ethers are neutral (6). It is interesting to note that Compound III was obtained directly from V by reaction in the presence of excess base.

EXPERIMENTAL[1]

5-Chloro-2-(2-chloroethoxy)benzophenone(V)—*Method A*—Twelve grams (0.52 mole) of clean sodium and 500 ml. of toluene were

[1] All melting points are uncorrected.



Scheme I

heated at reflux with vigorous stirring until a fine sand was obtained. The mixture was allowed to cool to about 80°, and a solution of 116.5 g. (0.50 mole) of 5-chloro-2-hydroxybenzophenone (Dow Light Absorber HCB) in 1350 ml. of toluene was added. The mixture was refluxed for 2 hr. with stirring, then 130 g. (0.55 mole) of 2-chloroethyl *p*-toluene-sulfonate was added and the refluxing action was continued for 16 hr. while removing water with the aid of a Barrett trap. The mixture was cooled to room temperature and filtered. The filtrate was evaporated *in vacuo* to an oil which was layered with 250 ml. of 10% sodium hydroxide and steam-distilled until about 30 ml. of distillate was obtained. The oily, nondistillable residue crystallized upon chilling and was collected and thoroughly washed with water. Recrystallization from 300 ml. of methanol gave 82.6 g. (56%) of crude 5-chloro-2-(2-chloroethoxy)benzophenone of sufficient purity for subsequent work, m.p. 69–71°. Further recrystallization from methanol gave an analytical sample, m.p. 73–74.5°.

Anal.—Calcd. for $C_{15}H_{12}Cl_2O_2$: C, 61.03; H, 4.10; Cl, 24.02. Found: C, 60.86; H, 4.12; Cl, 24.32.

Method B—A mixture of 11.7 g. (0.050 mole) of 5-chloro-2-hydroxybenzophenone, 6.9 g. (0.050 mole) of anhydrous powdered potassium carbonate, 14.4 g. (0.100 mole) of ethylene chlorobromide, and 100 ml. of dimethylformamide was heated at 60–75° for 16 hr. with stirring. The mixture was poured into 500 ml. of water and chilled in the refrigerator. The supernatant liquid was decanted, and the oily residue was triturated with 50 ml. of methanol at room temperature. The crude crystalline product was collected and its mother liquor was diluted with water until cloudiness to yield a second fraction. The two fractions were combined, heated with 25 ml. of methanol, and filtered hot. The filtrate upon chilling gave 5.1 g. of crude 5-chloro-2-(2-chloroethoxy)benzophenone (35%).

1,2-Bis-(4-chloro-2-benzoylphenoxy)ethane—A mixture of 23.3 g. (0.100 mole) of anhydrous powdered potassium carbonate, 14.4 g.

(0.100 mole) of ethylene chlorobromide, and 100 ml. of dimethylformamide was heated with stirring for 2.5 hr. at 95–105°. The mixture was poured into 500 ml. of water and extracted with 200- and 100-ml. portions of chloroform. The combined chloroform solutions were washed with three 100-ml. portions of water and evaporated *in vacuo* to dryness. The residue was triturated with 100 ml. of hot methanol and filtered hot to give 8.8 g. (36%) of crude product, m.p. 154–156°. Recrystallizations from chloroform–petroleum ether (50:30 ml.), benzene, (2 × 50 ml.), ethanol (300 ml.), and benzene–ethanol (50:250 ml.) gave pure 1,2-bis-(4-chlorobenzoylphenoxy)ethane, m.p. 156–157°.

Anal.—Calcd. for $C_{28}H_{20}Cl_2O_4$: C, 68.44; H, 4.10; Cl, 14.43. Found: C, 68.10; H, 4.09; Cl, 13.85.

Anti-Phenyl 5-Chloro-2-(2-chloroethoxy)phenyl Ketoxime (IX)—A mixture of 53.1 g. (0.180 mole) of 5-chloro-2-(2-chloroethoxy)-benzophenone, 18.0 g. (0.26 mole) of hydroxylamine hydrochloride, 15 ml. of water, and 525 ml. of absolute ethanol was refluxed for 43 hr. and then evaporated *in vacuo* to dryness. The oily residue was shaken with a mixture of 220 ml. of benzene and 75 ml. of water. The benzene phase was separated and washed with 50 ml. of water. The benzene solution was evaporated *in vacuo* to dryness. The oily residue crystallized on standing and was triturated with ethanol–petroleum ether, b. 30–60° (100:100 ml.). The crude product was collected and washed with petroleum ether to give 27.8 g. (50%), m.p. 100–105°. Recrystallization from ethanol gave pure *anti*-phenyl 5-chloro-2-(2-chloroethoxy)phenyl ketoxime, m.p. 106–107°.

Anal.—Calcd. for $C_{15}H_{13}Cl_2NO_2$: C, 58.08; H, 4.22; N, 4.52. Found: C, 58.17; H, 4.22; N, 4.48.

Impure samples of this compound decomposed to a yellow, gummy material upon standing for several days. The pure substance is stable.

Beckmann Rearrangement of Anti-Phenyl 5-Chloro-2-(2-chloroethoxyphenyl Ketoxime (XI).—Ten grams (0.033 mole) of *anti*-phenyl 5-chloro-2-(2-chloroethoxy)benzophenone was readily dissolved in 120 ml. of anhydrous ether. To the above solution was added 7.3 g. (0.035 mole) of phosphorus pentachloride. A vigorous refluxing action occurred almost immediately with the development of a yellow color. After 1 hr. of stirring at room temperature, the solution was evaporated *in vacuo* to an oil with limited heating. While cooling in ice, 50 ml. of cold water was added and the residue triturated. After adding 20 ml. of methanol, further trituration gave a crude product which was collected and again triturated with ethanol-petroleum ether, b. 30-60° (50:50 ml.): 7.0 g. (70%), m.p. 113–115°. Recrystallization from methanol gave pure 5-chloro-2-(2-chloroethoxy)benzanilide, m.p. 112.5–114°.

Anal.—Calcd. for $C_{15}H_{13}Cl_2NO_2$: C, 58.08; H, 4.22; Cl, 22.86; N, 4.52. Found: C, 57.89; H, 4.23; Cl, 22.64; N, 4.47.

Supporting proof of this structure is given in the following section.

Hydrolysis of 5-Chloro-2-(2-chloroethoxy)benzanilide—To a solution of 2.1 g. of potassium hydroxide in 8.2 g. of glycerol was added 1.1 g. (0.0036 mole) of 5-chloro-2-(2-chloroethoxy)benzanilide. The solution obtained upon heating was stirred while heating in an oil bath for 1.5 hr. at 135–170° and 2.8 hr. at 170–175°. After cooling to room temperature, the mixture was shaken with a mixture of 50 ml. of water and 50 ml. of ether. The ethereal solution was separated, washed with two 10-ml. portions of water, and dried over anhydrous calcium sulfate.[2] Upon saturating with dry hydrogen chloride there was obtained 0.14 g. (30%) of an amine salt. Recrystallization from methanol–anhydrous ether (1:5 ml.) gave a product which melted at 191–194°. Admixture with an authentic sample of aniline hydrochloride showed no depression of the melting point. The IR spectra were also identical.

Syn-Phenyl 5-Chloro-2-(2-chloroethoxy)phenyl Ketoxime (X)—A mixture of 106 g. (0.36 mole) of 5-chloro-2-(2-chloroethoxy)benzophenone, 36 g. (0.52 mole) of hydroxylamine hydrochloride, 324 ml. of water and 1350 ml. of absolute ethanol was refluxed for 2 hr. The solution was diluted with 600 ml. of water and chilled overnight. The solid material was collected and stirred thoroughly with a mixture of 100 ml. of benzene and 50 ml. of water. The insoluble material was collected to give 24.3 g. (22%) of crude product, m.p. 136–140°. Recrystallization from ethanol gave pure *syn*-phenyl 5-chloro-2-(2-chloroethoxy)phenyl ketoxime, m.p. 144–146°.

Anal.—Calcd. for $C_{15}H_{13}Cl_2NO_2$: C, 58.08; H, 4.22; Cl, 22.86; N, 4.52. Found: C, 57.89; H, 4.24; Cl, 22.31; N, 4.77.

[2] Drierite, W. A. Hammond Drierite Co.

Crude samples of this oxime decomposed to a yellow, gummy material upon standing for a few days. The pure compound is stable.

Beckmann Rearrangement of Syn-Phenyl 5-Chloro-2-(2-chloroethoxy)phenyl Ketoxime (XI)—Five grams (0.016 mole) of *syn*-phenyl 5-chloro-2-(2-chloroethoxy)benzophenone was suspended in 60 ml. of anhydrous ether. To this mixture was added 3.7 g. (0.018 mole) of phosphorus pentachloride. A vigorous reaction occurred immediately, and a yellow solution was obtained. After 1 hr. of stirring at room temperature, the solution was evaporated *in vacuo* to an oil with limited heating. While cooling on ice, 50 ml. of cold water was added, and then 40 ml. of methanol. After chilling overnight the product crystallized and was collected. Trituration with ethanol–petroleum ether, b. 30–60° (25:25 ml.) gave 2.8 g. (56%) of a product, m.p. 126.5–128°. Recrystallization from methanol (80 ml.) gave pure *N*-5-chloro-2-(2-chloro-ethoxy)-phenyl-benzamide, m.p. 127–129°.

Anal.—Calcd. for $C_{15}H_{13}Cl_2NO_2$: C, 58.08; H, 4.22; Cl, 22.86; N, 4.52. Found: C, 57.77; H, 4.23; Cl, 22.59; N, 4.46.

8-Chloro-6-phenyl-2,3H-1,4,5-benzodioxazocine (III)—A mixture of 34.0 g. (0.0110 mole) of *anti*-phenyl 5-chloro-2-(2-chloroethoxy)-phenyl ketoxime, 1.51 g. (0.0109 mole) of anhydrous powdered potassium carbonate, and 85 ml. of dimethylformamide was heated with stirring at 77–82° for 6 hr. The insoluble material was removed, and the solution was evaporated at 0.5 mm. to a thick residue while heating to 100°. The residue was heated for 1 min. with a mixture of 30 ml. of petroleum ether, b. 30–60° and 15 ml. of benzene and then filtered while hot. The filtrate was diluted with 60 ml. of petroleum ether. The first crude precipitate was removed, and the solution was chilled to 0° to give 1.26 g. of crude product. Recrystallization from 30 ml. of methanol gave 0.80 g. (27%) of 5-chloro-6-phenyl-2,3H-1,4,5-benzodioxazocine, m.p. 145–146°.

Anal.—Calcd. for $C_{15}H_{12}ClNO_2$: C, 65.82; H, 4.42; Cl, 12.95; N, 5.12. Found: C, 65.78; H, 4.44; Cl, 12.88; N, 5.24.

The compound was insoluble in dilute hydrochloric acid.

Preparation of 8-Chloro-6-phenyl-2,3H-1,4,5-benzodioxazocine from 5-Chloro-2-(2-chloroethoxy)benzophenone (III)—A mixture of 14.8 g. (0.050 mole) of 5-chloro-2-(2-chloroethoxy)benzophenone, 7.0 g. (0.101 mole) of hydroxylamine hydrochloride, 70 ml. of absolute ethanol, and a solution of 10 g. (0.25 mole) of sodium hydroxide in 40 ml. of water was refluxed for 1 hr. and 15 min. The mixture was cooled to room temperature and poured slowly into a solution of 30 ml. of concentrated hydrochloric acid in 200 ml. of water. After chilling at 0° for 3 days, the supernatant liquid was decanted from the crude precipitate which was then dissolved in 100 ml. of benzene. The benzene solution was washed with two 50-ml. portions of water and evaporated *in vacuo* to dryness. The residue was crystallized from 25 ml. of methanol to yield 2.75 g. (20%) of 8-chloro-6-phenyl-2,3H-1,4,5-benzodioxazocine. Identity was established by a mixture melting point with the product obtained in the previous section.

7-Chloro-5-phenyl-2,3H-1,4-benzoxazepine-4-oxide (II)—A mixture of 1.80 g. (0.0059 mole) of *syn*-phenyl 5-chloro-2-(2-chloroethoxy)phenyl ketoxime, 0.80 g. (0.0058 mole) of anhydrous powdered potassium carbonate and 45 ml. of dimethylformamide was heated with stirring at 50–56° for 6 hr. The insoluble material was removed and the solution was evaporated at 0.5 mm. to a thick residue while heating to 100°. The residue was triturated with benzene–petroleum ether, b. 30–60° (5:15 ml.) and there was collected 1.04 g. (64%) of product, m.p. 150–153°. Recrystallization from ethanol–water gave pure 7-chloro-5-phenyl-2,3H-1,4-benzoxazepine-4-oxide, m.p. 151–153°.

Anal.—Calcd. for $C_{15}H_{12}ClNO_2$: C, 65.82; H, 4.42; Cl, 12.95; N, 5.12. Found: C, 65.58; H, 4.45; Cl, 12.72; N, 5.26.

This product, in contrast to 8-chloro-6-phenyl-2,3H-1,4,5-benzodioxazocine, was soluble in dilute hydrochloric acid and decomposed upon exposure to light.

2-[4-Chloro-2-(α-formamidobenzyl)phenoxy]ethyl formate (VIII)—A mixture of 2.95 g. (0.0100 mole) of 5-chloro-(2-chloroethoxy)-benzophenone and 8.1 g. (0.18 mole) of formamide was heated for 3 hr. with stirring at 175–183°. After cooling to room temperature, 30 ml. of 10% hydrochloric acid was added. The mixture was extracted with 50 ml. of ether. The ethereal solution was washed with 20 ml. of water, treated with charcoal, and evaporated to dryness. The product was crystallized from benzene–petroleum ether, b. 30–60° and recrystallized from methanol to give 0.17 g. (5%)

of 2-[4-chloro-2-(α-formamidobenzyl)-phenoxy]ethyl formate, m.p. 144–146°.

Anal.—Calcd. for $C_{17}H_{16}ClNO_4$: C, 61.17; H, 4.83; Cl, 10.62; N, 4.20. Found: C, 60.93; H, 4.92; Cl, 10.51; N, 4.28.

The IR spectrum of the compound exhibited two carbonyl peaks at 5.8 and 5.9 (in chloroform). A peak at 2.84 was attributed to the amide N-H stretch vibration.

7-Chloro-5-phenyl-2,3,4,5H-1,4-benzoxazepine Hydrochloride (I)—A mixture of 29.5 g. (0.100 mole) of 5-chloro-2-(2-chloroethoxy)benzophenone, 20 ml. (0.51 mole) of formamide and 6.3 g. (0.100 mole) of ammonium formate was heated with stirring for 15 hr. and 30 min. at 157–169°. The mixture was cooled to room temperature and shaken with a mixture of 100 ml. of water and 175 ml. of benzene. The benzene phase was separated, washed with three 50-ml. portions of water, dried over anhydrous calcium sulfate, and evaporated *in vacuo* to dryness. The residue was refluxed with 50 ml. of concentrated hydrochloric acid for 1 hr. The cooled solution was shaken with a mixture of 150 ml. of water and 200 ml. of benzene and chilled overnight at 0°. The precipitate was collected and heated to 75° with 1 l. of water. The insoluble material was removed, and the solution was cooled and made basic with two 250-ml. portions of chloroform. The combined chloroform extracts were washed with two 125-ml. portions of water, dried over anhydrous calcium sulfate, evaporated *in vacuo* to 150 ml., and saturated with dry hydrogen chloride. The solution was evaporated *in vacuo* to dryness and dissolved in 100 ml. of benzene. The insoluble material was removed and the filtrate was diluted with 250 ml. of petroleum ether, b. 30–60°. The precipitate was collected and dissolved in 250 ml. of ethanol. The solution was diluted with 400 ml. of petroleum ether, a small amount of precipitate was removed, and the solution was evaporated *in vacuo* to dryness. The residue was triturated successively with a mixture of 80 ml. of benzene and 80 ml. of petroleum ether, b. 30–60°- and two 50-ml. portions of benzene. The crude product was recrystallized from 100 ml. of ethanol to give 0.70 g. (2.4%) of 7-chloro-5-phenyl-2,3,4,5H-1,4-benzoxazepine hydrochloride, m.p. 278–280° (dec.).

Anal.—Calcd. for $C_{15}H_{15}Cl_2NO$: C, 60.82; H, 5.10; Cl, 23.94; N, 4.73. Found: C, 60.87; H, 5.13; Cl, 23.89; N, 4.68.

N-[2-(4-Chloro-2-benzoylphenoxy)ethyl]phthalimide (VI)—A mixture of 27.8 g. (0.094 mole) of 5-chloro-2-(2-chloroethoxy)benzophenone, 13.8 g. (0.04 mole) of phthalimide, 13.0 g. (0.094 mole) of anhydrous powdered potassium carbonate, and 100 ml. of dimethylformamide was heated with stirring for 4 hr. at 95°. The mixture was poured into 500 ml. of water, and the product was extracted with one 250-ml. and two 125-ml. portions of chloroform. The combined chloroform solutions were washed with 100 ml. of 0.2 *N* sodium hydroxide and two 100-ml. portions of water. After drying over anhydrous calcium sulfate, the solution was evaporated *in vacuo* to dryness. The residue crystallized upon cooling and was collected with the aid of a 1:1 mixture of chloroform–petroleum ether b. 30–60°. The yield was 15.0 g. (39%), m.p. 122–144°. Recrystallization from ethanol gave pure *N*-[2-(4-chloro-2-benzoylphenoxy)-ethyl]phthalimide, m.p. 114–115°.

Anal.—Calcd. for CHClNO: C, 68.07; H, 3.97; Cl, 8.74; N, 3.45. Found: C, 68.28; H, 4.09; Cl, 9.00; N, 3.46.

5-Chloro-2-(2-aminoethoxy)benzophenone Hydrochloride (VII)—A mixture of 20.8 g. (0.051 mole) of *N*-[2-(4-chloro-2-benzoylphenoxy)ethyl]phthalimide, 4.9 ml. of 99% hydrazine hydrate, and 200 ml. of methanol was refluxed for 3.5 hr. After removing the solvent, the residue was refluxed for 3 hr. with a mixture of 60 ml. of concentrated hydrochloric acid and 60 ml. of water. The mixture was cooled and filtered. The filtrate was evaporated *in vacuo* to an oil which was dissolved in 150 ml. of water. The solution was made basic with 50 ml. of 10% sodium hydroxide and diluted with 150 ml. of water. The mixture was extracted with 750 ml. of benzene. The benzene solution was washed with three 100-ml. portions of water and evaporated *in vacuo* to dryness. The oily residue was dissolved in 100 ml. of ether. The ethereal solution was dried over anhydrous calcium sulfate and saturated with dry hydrogen chloride. After adding 6 ml. of absolute ethanol, the solution was chilled at 0° for 3 days to yield 11.5 g. of crude material. Three recrystallizations from ethanol-ether gave 2.1 g. (13%) of pure 5-chloro-2-(2-aminoethoxy)benzophenone hydrochloride, m.p. 135–136°.

Anal.—Calcd. for $C_{15}H_{15}Cl_2NO_2$: C, 57.71; H, 4.84; Cl, 22.71; N, 4.49. Found: C, 57.66; H, 4.94; Cl, 23.05; N, 4.58.

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