Novel Polycyclic Heterocycles. XI.
Synthesis of 11,12-Dihydropyrido[2,1-*b*][1,3]benzodiazepines, 6*H*-Pyrido[1,2-*c*][1,3,5]benzoxadiazepines, and 6*H*-Pyrido[1,2-*c*][1,3,5]benzothiadiazepines (1)

R. B. Petigara (2) and Harry L. Yale (3)

Squibb Institute for Medical Research, Princeton, New Jersey 08540

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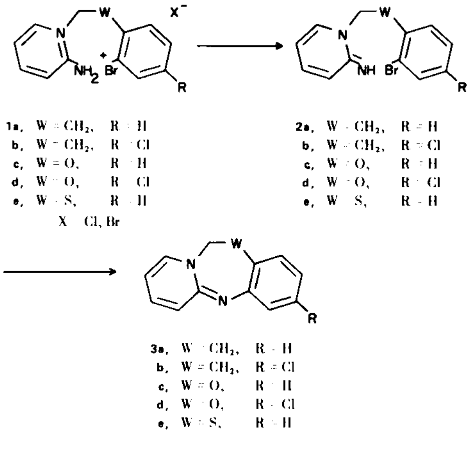
An unusually facile dehydrobromination, involving the *ortho*-bromine atom and the =NH proton of a 2-imino-1-(phenethyl)-, 2-imino-1-(phenoxymethyl)-, or 2-imino-1-(phenylthiomethyl)-pyridine (**2a-e**) has led to the synthesis of three novel bridgehead nitrogen tricyclic systems: 11,12-dihydropyrido[2,1-*b*][1,3]benzodiazepines (**3a,b**), 6*H*-pyrido[1,2-*c*][1,3,5]benzoxadiazepines (**3c,d**) and 6*H*-pyrido[1,2-*c*][1,3,5]benzothiadiazepines (**3e**). As anticipated, these cyclizations required a base, *e.g.*, potassium carbonate, and a catalyst, *e.g.*, copper bronze. What was unusual, was that these reactions occurred in methanol or *n*-propanol, under reflux, either under anhydrous conditions, *or in the presence of large amounts of water.* The pmr spectra of these compounds are discussed.

We are reporting the unusually facile displacement of an aromatic bromine atom by the nitrogen atom of an =NH group of the amidines, **2a-e**, derived from the quaternary derivatives, **1a-e** (4). The consequence of these dehydrobrominations was the formation of three classes of novel bridgehead nitrogen heterocycles represented by **3a-e**.



That these cyclizations would require a copper catalyst and a *base*, could have been anticipated. What was without precedent, was that these cyclizations were achieved under relatively mild conditions, *i.e.*, reflux temperature, in hydroxylated solvents like methanol or 1-propanol, first under anhydrous conditions, but, subsequently, in the presence of large amounts of water (4). While reaction rates have not been determined, the synthetic procedures employed would suggest that water appeated to have a promoting effect on these cyclizations (5).

To demonstrate that the cyclization occurred with the imino derivatives, **2a-e**, and required the presence of a copper catalyst, **1a** was heated under reflux with either two equivalents of sodium methoxide in methanol for 5 hours or with two molar equivalents of potassium carbonate in aqueous 1-propanol for 4 hours; only the imino derivative, **2a**, was isolated in 82 and 70% yields, respectively. When a catalytic quantity of copper bronze was added to each mixture followed by heating under reflux for 3 hours, the cyclized derivative, **3a**, was obtained in 74 and 80% yields, respectively.

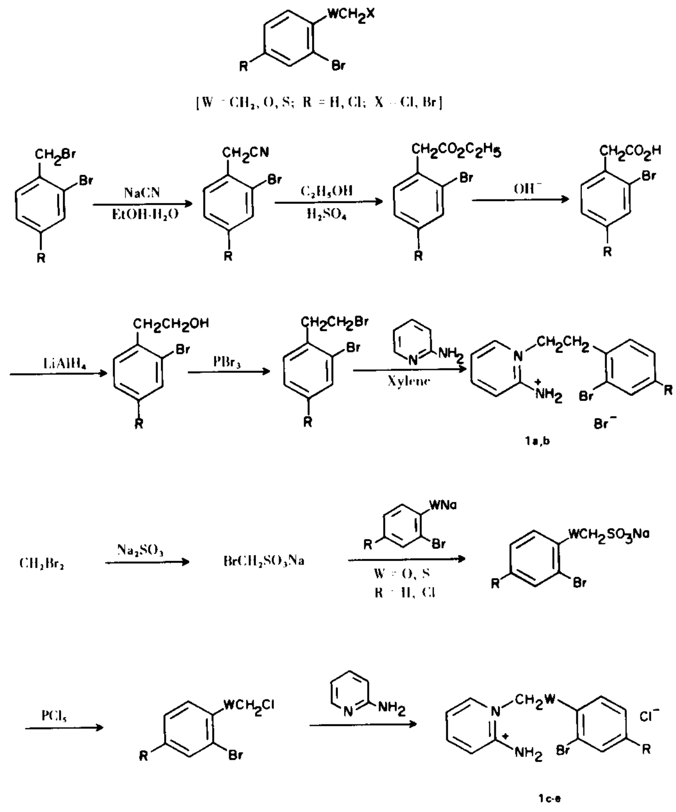
Compounds with structures **2a-d** were pale yellow crystalline solids; while **2e** was an oil; treatment with hydrogen chloride regenerated the colorless quaternary derivatives, **1a-e**. Compounds with structures **3a-e**, possessing an extended chromophore, were obtained as deep yellow crystalline solids; with hydrogen chloride, **3a-e** formed pale yellow crystalline hydrochlorides, **4a-e**.

The synthesis of compounds with the general structure, **1a-e**, was achieved by the routes summarized in Chart I. The quaternization reactions proceeded most readily with the chloromethyl ethers and chloromethyl sulfides.

An analysis of the proton magnetic resonance spectra of the several classes of neutral and ionized compounds

Chart I

Preparation of Derivatives of Structure

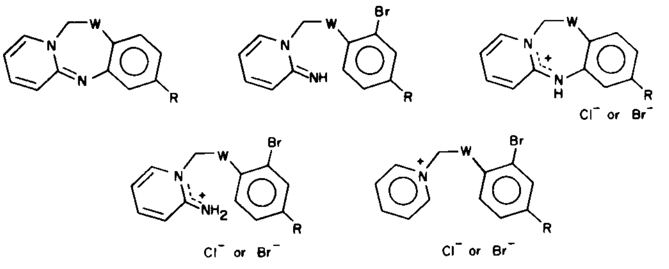


that are described in this paper has led to a rationalization as to whether the positive charge is localized or distributed between the two nitrogen atoms in **1a-e** and **4a-e**.

The reference spectra for this analysis are those of the four quaternary derivatives, **5-8**, in Chart II, where the positive charge must be localized on the pyridine nitrogen atom. The chemical shifts for the methylene protons are δ 4.94, δ 6.54, δ 6.84 and δ 6.79, respectively. The corresponding signals of the methylene protons in the two ionized species, **4a** and **1a**, **4e** and **1e**, and **4c** and **1c**, are strikingly similar, δ 4.65 and 4.53, δ 5.85 and 5.87, and δ 6.25 and 6.35, respectively; yet, in each instance, the paired signals are upfield from those seen in **5-8**, where there exists a localization of the positive charge. Finally, as anticipated, the corresponding signals of the methylene protons in the two neutral species, **3a** and **2a**, **3e** and **2e**, and **3c** and **2c**, are seen at δ 4.00 and 4.08, δ 4.70 and 5.20, and δ 5.30 and 5.90, farthest upfield, in each instance, and thus representing points of reference for the effects of protonation. The inference, therefore, from these data is that in the protonated species, **4a-e** and **1a-e**, the charge is not localized on the pyridine nitrogen, but is, in all probability, distributed as shown in the structures at the head of columns 3 and 4 in Chart II.

CHART II

Chemical Shifts for Methylene Protons



W = CH_2, R = H	4.00	4.08	4.65	4.53	4.94
δ CH_2	**3a**	**2a**	**4a**	**1a**	**5**
W = CH_2, R = Cl	3.98	4.00	4.50	4.51	
δ CH_2	**3b**	**2b**	**4b**	**1b**	
W = S, R = H	4.70	5.20	5.85	5.87	6.54
δ CH_2	**3e**	**2e**	**4e**	**1e**	**8**
W = O, R = H	5.30	5.90	6.25	6.35	6.79
δ CH_2	**3c**	**2c**	**4c**	**1c**	**6**
W = O, R = Cl	5.30		6.23	6.29	6.84
δ CH_2	**3d**		**4d**	**1d**	**7**

EXPERIMENTAL

Melting points were determined in capillary tubes in an electrically heated oil bath and are uncorrected. The ir spectra were obtained on mineral oil mulls or on deuteriochloroform solutions, employing a Perkin-Elmer 621 spectrophotometer. The pmr spectra were obtained on deuteriochloroform, deuterium oxide, or DMSO-d_6 solutions with a Varian A60, a Perkin-Elmer R12B, or a Varian Associates XL-100-15 spectrophotometer. The mass spectra were obtained on an AEI-MS-902 spectrometer operating at 70 eV, using a direct insertion technique, with a probe temperature of 140-180°. The authors are indebted to Mrs. B. Toeplitz, Dr. M. A. Puar and Dr. P. T. Funke of this Institute for these spectra. The microanalyses were carried out by Mr. J. F. Alicino and his associates of this Institute. The authors acknowledge, in addition, the assistance of Dr. J. A. Bristol in some of the laboratory work and for helpful discussions concerning this manuscript.

2-Amino-1-(*o*-bromophenethyl)pyridinium Bromide (**1a**).

In a nitrogen atmosphere, a stirred solution of 211.6 g. (0.8 mole) of *o*-bromophenethyl bromide, 150.4 g. (1.6 moles) of 2-aminopyridine, and 1 liter of anhydrous xylene was heated under reflux for 2 hours and cooled. The supernatant liquid was decanted from the colorless solid, the solid was triturated with 300 ml. of 2-propanol at 0°, filtered, and dried to give 134.0 g. of **1a**, m.p. 195-198°. The 2-propanol filtrate was concentrated to dryness, the residue was dissolved in the above xylene supernatant, and the reflux continued for an additional 16 hours. The same workup described above gave 36.0 g. of additional **1a**. The combined yield was 170.0 g. (60%). An analytical sample was obtained by crystallizing 1.0 g. from 50 ml. of 2-propanol; the recovery was 0.80 g., m.p. 196-198°, ir (mull): 3320 (w), 3290 (w), 1650 (s), 1630 (m), 1570 (s), 1525 (m) cm^{-1}; pmr (DMSO-d_6): δ 3.25 (t, J = 10 Hz, 2H, $\overset{+}{N}CH_2C\mathit{H}_2$), 4.55 (t, J = 10 Hz, 2H, $\overset{+}{N}C\mathit{H}_2CH_2$), 6.55-8.1 (m, 8H, 4 Ar-*H* and 4 Py-*H*), 8.74 (s, 2H, $N\mathit{H}_2$).

Anal. Calcd. for $C_{13}H_{14}Br_2N_2$: C, 43.60; H, 3.94; N, 7.83; Br, 44.64. Found: C, 43.45; H, 3.84; N, 8.03; Br, 44.89.

1-(*o*-Bromophenethyl)-2-iminopyridine (**2a**).

(a) Sodium Methoxide in Methanol.

To a solution of 3.3 g. (0.06 mole) of sodium methoxide in 120 ml. of anhydrous methanol was added 10.8 g. (0.03 mole) of **1a** and the mixture heated, in a nitrogen atmosphere with stirring, under reflux for 5 hours. The yellow solution that formed was concentrated to dryness *in vacuo* and the residue distributed between 250 ml. of ether and 30 ml. of water. The ether layer was separated, washed, dried, and concentrated to give a solid residue, m.p. 59-66°. Recrystallization from hexane gave 6.8 g. (82% yield) of **2a**, m.p. 64-66°; ir (mull): 3300 (w), 1640 (s), 1570 (s), 1525 (s) cm^{-1}; pmr (deuteriochloroform): δ 3.2 (t, J = 10 Hz, 2H, $\mathrm{NCH_2C}H_2$), 4.08 (t, J = 10 Hz, 2H, $\mathrm{NC}H_2\mathrm{CH_2}$), 5.27 (broad s, 1H, =N*H*, equilibrates with deuterium oxide), 5.5-7.8 (m, 8H, 4 Ar-*H* and 4 Py-*H*).

Anal. Calcd. for $C_{13}H_{13}BrN_2$: C, 56.32; H, 4.73; N, 10.11; Br, 28.83; N.E., 277. Found: C, 56.28; H, 5.[illegible]2; N, 10.35; Br, 29.03; N.E., 282. Calcd: M^+ 277. Found: M^+ 277.

(b) Potassium Carbonate in Aqueous 1-Propanol.

A mixture of 18.0 g. (0.05 mole) of **1a**, 13.8 g. (0.1 mole) of potassium carbonate, 200 ml. of water, and 100 ml. of 1-propanol was heated under reflux for 4 hours. At that time a 75 ml. sample was withdrawn (for remaining reaction mixture, see below), cooled, and diluted with 120 ml. of ether. The ether layer was separated and worked up to give 2.1 g. (70% yield) of **2a**, m.p. 64-66°. The ir and pmr spectra were identical with those obtained with the product in (a).

Anal. Found: C, 56.55; H, 5.02; N, 10.02; Br, 28.57.

11,12-Dihydropyrido[2,1-*b*][1,3]benzodiazepine (**3a**).

(a) Potassium Carbonate in Aqueous 1-Propanol.

To the remaining reaction mixture from (b) above was added 0.3 g. of copper bronze and the mixture stirred and heated under reflux, in a nitrogen atmosphere, for 3 hours, cooled, and diluted with 350 ml. of ether. The ether layer was separated and worked up to give 8.9 g. of a dark yellow solid. The solid was redissolved in 250 ml. of ether, the solution was decolorized with Darco, filtered with the aid of Hyflo, and the filtrate concentrated to dryness to give 7.6 g. of a bright yellow crystalline product, m.p. 119-122°. This was recrystallized from 150 ml. of diisopropyl ether to give 5.9 g. (80% yield) of **3a**, m.p. 120-122°; ir (mull): 1635 (s), 1590 (m), 1580-1490 (broad), 1470 (s), 1465 (s) 1440 (s) cm^{-1}; pmr (deuteriochloroform): δ 3.15 (t, J = 10 Hz, 2H, $\mathrm{NCH_2C}H_2$), 4.00 (t, J = 10 Hz, 2H, $\mathrm{NC}H_2\mathrm{CH_2}$), 5.75-7.35 (m, 8H, 4 Ar*H* and 4 Py-*H*).

Anal. Calcd. for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.26. Found: C, 79.69; H, 6.09; N, 13.97.

(b) Potassium Carbonate in Anhydrous 1-Propanol.

A mixture of 6.0 g. (0.017 mole) of **1a**, 4.6 g. (0.033 mole) of anhydrous potassium carbonate, 0.2 g. of copper bronze, and 180 ml. of anhydrous 1-propanol was stirred and heated under reflux (nitrogen) for 2 hours. A 5 ml. probe at this point yielded a solid, m.p. 45-80°, whose ir spectrum showed both **2a** and **3a** to be present. The reflux was continued for a total of 9 hours; only at this point did a probe yield a solid, m.p. 117-119°, whose ir spectrum was that of crude **3a**. Workup as in (a) gave 2.7 g. (81% yield) of **3a**, m.p. 120-122°; the ir and pmr spectra of this material were identical with those obtained with (a) above.

(c) Sodium Methoxide in Anhydrous Methanol.

To a solution of 5.4 g. (0.1 mole) of sodium methoxide in 220 ml. of anhydrous methanol was added 18.0 g. (0.05 mole) of **1a** and the mixture heated and stirred under reflux (nitrogen) as in the preparation of **2a** (a) above. This phase of the overall reaction led to a methanol solution containing 0.05 mole of sodium methoxide and 0.05 mole of **2a**. A portion, 50 ml. of this solution was withdrawn (see below), and to the remaining reaction mixture was added 0.3 g. copper bronze and the heating under reflux, with stirring, continued for 24 hours. Workup, as above, gave 5.8 g. (74% yield) of **3a**, m.p. 120-122°; the ir and pmr spectrum of this material were identical with those of the product obtained in (a) above.

(d) Sodium Hydroxide in Aqueous Methanol.

The 50 ml. of solution from (c) above was diluted with 25 ml. of water, 0.070 g. of copper bronze was added, the mixture stirred and heated under reflux (nitrogen), for 3.5 hours and then worked up to give 1.6 g. (82% yield) of **3a**, m.p. 120-122°; its ir and pmr spectrum were identical with those obtained with the product from (a) above.

11,12-Dihydropyrido[2,1-*b*][1,3]benzodiazepine Hydrochloride (**4a**).

To a solution of 1.50 g. (0.0077 mole) of **3a** in 10 ml. of anhydrous methanol was added 5 ml. of 3.3 *N* (0.0175 mole) of ethereal hydrogen chloride. The solution that was formed was diluted with enough anhydrous ether to achieve a permanent turbidity at room temperature, and then cooled to 0° to give a crystalline solid. This was filtered, dried, and recrystallized from 20 ml. of 2-propanol to give 1.2 g. (67% yield) of **4a**, m.p. 205.0-206.5°; ir: 3480 (m), 3380 (m), 1660 (s), 1620 (m), 1585 (s), 1560 (s), 1510 (s) cm^{-1}; pmr (DMSO-d_6): δ 3.36 (t, J = 8 Hz, 2H, $\mathrm{NCH_2C}H_2$), 4.68 (t, J = 8 Hz, $\mathrm{NC}H_2\mathrm{CH_2}$), 6.95-8.44 (m, 8H, 4 Ar-*H* and 4-Py-*H*), 12.18 (s, 1H, *H*Cl).

Anal. Calcd. for $C_{13}H_{13}ClN_2$: C, 67.09; H, 5.63; N, 12.06; Cl^-, 15.22. Found: C, 66.96; H, 5.68; N, 12.22; Cl^-, 15.10.

2-Bromo-4-chlorophenethyl Bromide.

(a) 2-Bromo-4-chlorophenylacetonitrile.

2-Bromo-4-chlorobenzyl bromide [b.p. 98-104° (0.7 mm), n_D^{25} 1.6262] 218.0 g. (0.77 mole), dissolved in 220 ml. of 95% ethanol, was added in 0.33 hours to a stirred solution of 45.0 g. (0.92 mole) of sodium cyanide in 55 ml. of water and 80 ml. of 95% ethanol. The temperature rose spontaneously from 25° to 46°. The mixture was heated under reflux for 0.25 hour, filtered, the insoluble material was washed with 300 ml. of ether, and the combined filtrates concentrated to dryness. The residue was distributed between 500 ml. of ether and 150 ml. of water, the ether layer was separated, dried, and concentrated to give 171 g. (quantitative yield) of crude 2-bromo-4-chlorophenylacetonitrile; ir: 2270 cm^{-1} (CN), which was used in the following step without further purification.

(b) Ethyl 2-Bromo-4-chlorophenylacetate.

To the crude product from (a), 171.0 g. (~ 0.77 mole), dissolved in 760 ml. of absolute ethanol, was added, dropwise, and with stirring, 190.0 ml. of concentrated sulfuric acid, the whole stirred for 1 hour at room temperature, and then heated under reflux for 3 hours. The cooled mixture was poured on 2.5 kg. of crushed ice and the product isolated by extraction with ether. The yield of crude product was 204.0 g. (essentially quantitative). In the ir there was no absorption at 2270 cm^{-1} (CN), but strong absorption at 1750 cm^{-1}. Again, this material was used, without further purification, in step (c).

(c) 2-Bromo-4-chlorophenylacetic Acid.

The ester from (b), 204.0 g. (~ 0.73 mole), 3500 ml. of 95% ethanol, and 64 g. (1.0 mole) of 85% potassium hydroxide in 640 ml. of water were heated under reflux for 5 hours, concentrated to dryness *in vacuo*, and the residue treated with 1.5 liters of water. The aqueous solution was cooled, extracted with ether, and the aqueous solution adjusted to *p*H 2. The solid that separated was filtered, dried, and recrystallized from a mixture of 200 ml. of benzene and 300 ml. of hexane to give 90.3 g. (50% yield) of 2-bromo-4-chlorophenylacetic acid, m.p. 127-129°.

Anal. Calcd. for $C_8H_6BrClO_2$: C, 38.52; H, 2.43. Found: C, 38.68; H, 2.57.

(d) 2-Bromo-4-chlorophenethanol.

To 11.5 g. (0.3 mole) of lithium aluminum hydride in 300 ml. of anhydrous ether, with stirring, under nitrogen, was added, in 1.5 hours, a solution of 52.0 g. (0.21 mole) of the product from (c) in 500 ml. of anhydrous ether. Subsequently, the mixture was heated under reflux for 40 minutes, cooled, treated with 20 ml. of ethyl acetate, and then poured on 1.5 kg. of crushed ice. Following the addition of 200 ml. of 20% aqueous hydrochloric acid, the product was isolated *via* ether extraction to give 44.3 g. (~ 90% yield) of pale yellow oil, n_D^{24} 1.5714, which in the ir showed OH absorption at 3400 cm^{-1} and no carbonyl absorption. It was used without further purification in step (e).

(e) 2-Bromo-4-chlorophenethyl Bromide.

To 44.2 g. (~ 0.18 mole) of the product from (d), cooled to 0°, was added 26.0 g. (0.096 mole) of phosphorus tribromide in 20 minutes. Following the addition, the mixture was heated for 1.25 hours at 100°, cooled, and poured on 1 kg. of crushed ice. The product was isolated *via* ether extraction; the yield was 55.8 g. (~ quantitative) of a viscous oil; b.p. 95-102° (0.4 mm), n_D^{22} 1.5838; ir: no OH absorption, 1580 (m), 1550 (w), 1485 (s), 1465 (s) cm^{-1}; pmr (deuteriochloroform): δ 3.0-3.8 (m, 4H, $C\mathit{H}_2C\mathit{H}_2$), 6.8-7.8 (m, 3H, 3 Ar-*H*).

o-Bromophenethyl Bromide.

By a similar series of reactions, *o*-bromobenzyl bromide, b.p. 130-132° (15 mm) was converted, in sequence, to *o*-bromophenylacetonitrile, b.p. 141-142° (12 mm); ethyl *o*-bromophenylacetate, b.p. 115-117° (4 mm), n_D^{26} 1.5434; *o*-bromophenethyl alcohol, b.p. 130-132° (8 mm), n_D^{20} 1.5760; and, *o*-bromophenethyl bromide, b.p. 86-88° (0.9 mm), n_D^{26} 1.5922 (6).

2-Amino-1-(2-bromo-4-chlorophenethyl)pyridinium Bromide (**1b**).

A solution containing 10.4 g. (0.11 mole) of 2-aminopyridine, 20.9 g. (0.07 mole) of 2-bromo-4-chlorophenethyl bromide, and 150 ml. of anhydrous xylene was heated under reflux for 10 hours, cooled, and the supernatant solution decanted from the solid product. The solid was filtered, dried, and recrystallized from 150 ml. of 2-propanol to give 17.6 g. (64% yield) of **1b** m.p. 189-191°; ir (mull): 3330 (w), 3300 (w), 1655 (s), 1630 (s), 1580 (s), 1550 (w) cm^{-1}; pmr (DMSO-d_6): δ 3.21 (t, J = 10 Hz, 2H, $\overset{+}{N}CH_2C\mathit{H}_2$), 4.51 (t, J = 10 Hz, 2H, $\overset{+}{N}C\mathit{H}_2CH_2$, 6.68-8.19 (m, 7H, 3 Ar-*H* and 4 Py-*H*), 8.69 [s, 2H, $N\mathit{H}_2$ (equilibrates with deuterium oxide)].

Anal. Calcd. for $C_{13}H_{13}Br_2ClN_2$: C, 39.78; H, 3.33; N, 7.17; Br^-, 20.36. Found: C, 39.52; H, 3.60; N, 6.90; Br^-, 20.30.

3-Chloro-11,12-dihydropyrido[2,1-*b*][1,3]benzodiazepine (**3b**).

A mixture of 6.0 g. (0.015 mole) of **1b**, 6.0 g. (0.044 mole) of anhydrous potassium carbonate, 0.2 g. of copper bronze, and 220 ml. of 1-propanol was stirred and heated under reflux for 12 hours. Workup as described for **3a** gave 2.3 g. (66% yield) of **3b**, as deep yellow crystals, m.p. 165-167°, after recrystallization from cyclohexane; ir (deuteriochloroform): 1637 (s), 1588 (w), 1535 (s) cm^{-1}; pmr (deuteriochloroform): δ 3.11 (t, J = 7.5 Hz, 2H, $NCH_2C\mathit{H}_2$), 3.98 (t, J = 7.5 Hz, 2H, $NC\mathit{H}_2CH_2$), 5.80-7.31 (m, 7H, 3 Ar-*H* and 4 Py-*H*).

Anal. Calcd. for $C_{13}H_{11}ClN_2$: C, 67.68; H, 4.81; N, 12.14. Found: C, 67.76; H, 4.88; N, 12.17.

3-Chloro-11,12-dihydropyrido[2,1-*b*][1,3]benzodiazepine Hydrochloride (**4b**).

To a solution of 1.0 g. (0.0044 mole) of **3b** in 10 ml. of warm, anhydrous methanol was added 5.0 ml. of 3.3 *N* (0.017 mole) of ethereal hydrogen chloride, dropwise. Subsequently, 200 ml. of anhydrous ether were added to give a crystalline precipitate. This was filtered and recrystallized from 40 ml. of 2-propanol to give 1.0 g. (86% yield) of **5b**, m.p. 232-234° dec.; ir (mull): 1608 (s), 1585 (m), 1584 (s), 1550 (m) cm^{-1}; pmr (DMSO-d_6): δ 3.02 (t, J = 12 Hz, 2H, $NCH_2C\mathit{H}_2$), 4.50 (t, J = 12 Hz, 2H, $NC\mathit{H}_2CH_2$), 6.64-8.02 (m, 7H, 3 Ar-*H* and 4 Py-*H*), 9.01 [s, 1H, *H*Cl (equilibrates with deuterium oxide).

Anal. Calcd. for $C_{13}H_{12}Cl_2N_2$: C, 58.44; H, 4.53; N, 10.49; Cl^-, 13.27. Found: C, 58.68; H, 4.76; N, 10.77; Cl^-, 13.12.

(*o*-Bromophenoxy)methanesulfonic Acid, Sodium Salt.

(a) Sodium Bromomethanesulfonate.

A mixture of 372.0 g. (2.07 moles) of dibromomethane, 261.0 g. (2.07 moles) of sodium sulfite, and 750 ml. of water was stirred and heated under reflux for 80 hours and then 600 ml. of water was distilled. The solid that separated was filtered and recrystallized from water to give 380.0 g. of sodium bromomethanesulfonate, m.p. 277-281°; the reported m.p. is 272-278° (7).

(b) (*o*-Bromophenoxy)methanesulfonic Acid, Sodium Salt.

To a solution of 15.5 g. (0.38 mole) of sodium hydroxide in 61 ml. of water was added in sequence, 61.3 g. (0.36 mole) of *o*-bromophenol and 68.0 g. (0.35 mole) of sodium bromomethane sulfonate. The mixture was stirred and heated by means of an oil bath maintained at 150°, collecting the water that distilled. During 3 hours, 61 ml. of water were collected. The oil bath temperature was then raised to 200° and kept at 200° for 2.5 hours. The solid product that formed was dissolved in 800 ml. of warm water, filtered, and the filtrate adjusted to *p*H 5. The solution was cooled, washed with two 200 ml. portions of ether, and then concentrated to 600 ml. *in vacuo*. The cooled solution deposited a crystalline solid; this was filtered and recrystallized from 600 ml. of 90% aqueous ethanol to give 57.5 g. (56% yield) of (*o*-bromophenoxy)methanesulfonic acid, sodium salt, m.p. 282-284°, pmr (deuterium oxide): δ 4.99 (s, 2H, $OC\mathit{H}_2SO_3$) 6.85-7.72 (m, 4 Ar-*H*).

Anal. Calcd. for $C_7H_6BrO_4SNa$: C, 29.09; H, 2.09; Br, 27.64. Found: C, 28.82; H, 2.12; Br, 27.35.

o-Bromo-α-chloroanisole.

A mixture of 29.0 g. (0.1 mole) of *o*-bromophenoxymethanesulfonic acid, sodium salt and 50.0 g. (0.24 mole) of phosphorus pentachloride was blended in a mortar until a vigorous reaction occurred; this coincided with liquifaction of the solid mixture. The liquid was stirred occasionally for 0.25 hour, diluted with

700 ml. of ether, and the solution poured on 750 g. of crushed ice. The ether layer was separated, dried, concentrated, and the residue distilled to give 19.5 g. (88% yield) of *o*-bromo-α-chloroanisole, b.p. 74-75° (0.2 mm); n_D^{25} 1.5799, pmr (deuteriochloroform): δ 5.88 (s, 2H, OCH_2Cl), 6.81-7.69 (m, 4H, 4 Ar-*H*).

Anal. Calcd. for C_7H_6BrClO: C, 37.96; H, 2.73. Found: C, 37.51; H, 2.69.

2-Amino-1-[(*o*-bromophenoxy)methyl]pyridinium Chloride (**1c**).

To a solution of 7.1 g. (0.075 mole) of 2-aminopyridine in 35 ml. of anhydrous xylene was added, dropwise, a solution of 11.1 g. (0.05 mole) of *o*-bromo-α-chloroanisole in 45 ml. of anhydrous xylene. Subsequently, the mixture was warmed to 50° for 5 minutes and then stirred at room temperature for 40 hours. The solid that separated was filtered and dried to give 16.0 g. of product, m.p. 166-168°. Recrystallization from 125 ml. of 2-propanol gave 14.8 g. (94% yield) of 2-amino-1-[(*o*-bromophenoxy)methyl]pyridinium chloride, m.p. 170-172°; pmr (DMSO-d_6): δ 6.35 (s, 2H, $\overset{+}{N}CH_2O$), 6.74-8.21 (m, 8H, 4 Ar-*H* and 4 Py-*H*), 9.34 (s, 2H, NH_2).

Anal. Calcd. for $C_{12}H_{12}BrClN_2O$: C, 45.67; H, 3.83; N, 8.88; Cl^-, 11.24. Found: C, 45.43; H, 4.01; N, 8.74; Cl^-, 11.18.

6*H*-Pyrido[1,2-*c*][1,3,5]benzoxadiazepine (**3c**).

A mixture of 9.5 g. (0.03 mole) of 2-amino-1-[(*o*-bromophenoxy)methyl]pyridinium chloride, 8.3 g. (0.06 mole) of anhydrous potassium carbonate, 0.4 g. of copper bronze, and 150 ml. of anhydrous 1-propanol was stirred and heated under reflux in a nitrogen atmosphere for 12 hours, and filtered hot. The deep yellow filtrate was concentrated to dryness, *in vacuo*, the residue was dissolved in 400 ml. of ether, the ether solution was washed, dried, and concentrated to give 6.4 g. of crude residue. Recrystallization from 200 ml. of cyclohexane gave 3.6 g. (70% yield) of the deep yellow 6*H*-pyrido[1,2-*c*][1,3,5]benzoxadiazepine, m.p. 125-127°; ir (mull): 1637 (s), 1589 (s), 1573 (s), 1536 (s) cm^{-1}; pmr (deuteriochloroform): δ 5.28 (s, 2H, NCH_2O), 5.88-7.28 (m, 8H, 4 Ar-*H* and 4 Py-*H*).

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.21; H, 5.09; N, 14.13; N.E., 198. Found: C, 72.42; H, 5.20; N, 14.20; N.E. (perchloric acid), 198.

6*H*-Pyrido[1,2-*c*][1,3,5]benzoxadiazepine Hydrochloride (**4c**).

To 1.0 g. (0.005 mole) of **3c** in 20 ml. of 2-propanol was added 5.0 ml. of 4.2 *N* (0.021 mole) of 2-propanolic hydrogen chloride. To the clear solution that formed at room temperature, was added anhydrous ether until a permanent turbidity persisted; cooling in ice caused a solid to separate. This was filtered and recrystallized from 50 ml. of acetonitrile to give 1.05 g. (86% yield) of **4c**, m.p. 232-234°; pmr (DMSO-d_6): δ 6.26 (s, 2H, NCH_2O), 7.05-8.51 (m, 8H, 4 Ar-*H* and 4 Py-*H*), 12.98 (s, 1H, *H*Cl).

Anal. Calcd. for $C_{12}H_{10}N_2O \cdot HCl$: C, 61.41; H, 4.72; N, 11.93; Cl^-, 15.11. Found: C, 61.42; H, 4.58; N, 11.83; Cl^-, 15.08.

1-*o*-Bromophenoxymethyl-2-iminopyridine (**2c**).

A suspension of 4.0 g. (0.013 mole) of the quaternary chloride, **1c**, 3.6 g. (0.026 mole) of anhydrous potassium carbonate, and 100 ml. of 1-propanol was heated under reflux, under nitrogen, for 9 hours, and filtered hot. The filtrate was concentrated to dryness *in vacuo*, and the residue dissolved in 200 ml. of ether. The ether solution was washed, dried, and concentrated to give 3.2 g. of a solid residue. This was recrystallized from 150 ml. of petroleum ether to give 2.7 g. (79% yield) of **2c**, m.p. 62.0-63.5°; ir (mull): 3310 (m), 1670 (m), 1647 (s), 1570 (s), 1530 (s), 1475 (s), 1455 (s) cm^{-1}; pmr (deuteriochloroform): δ 5.1 (broad s, 1H, N*H*) 5.88 (s, 2H, CH_2), 5.5-7.57 (m, 8H, 4 Ar-*H* and 4 Py-*H*).

Anal. Calcd. for $C_{12}H_{11}BrN_2O$: C, 51.63; H, 3.97; N, 10.04. Found: C, 51.44; H, 4.15; N, 10.26.

To the above product, 2.70 g. (0.01 mole), in 20 ml. of 2-propanol was added, dropwise, 5.0 ml. of 4.8 *N* 2-propanolic hydrogen chloride. Subsequently, 100 ml. of anhydrous ether was added to give a slight turbidity and the mixture was cooled to 0° to give a crystalline precipitate. This was filtered to afford a solid, m.p. 168.0-169.5°. Recrystallization from 180 ml. of acetonitrile gave 2.43 g. (81% yield) of colorless needles, m.p. 170-172°. A mixture m.p. with authentic **1c** was undepressed at 170-172°, and the ir and pmr spectra of the product were identical with those of authentic **1c**.

Anal. Calcd. for $C_{12}H_{12}BrClN_2O$: C, 45.67; H, 3.83; N, 8.88. Found: C, 45.56; H, 4.08; N, 9.03.

(2-Bromo-4-chlorophenoxy)methanesulfonic Acid, Sodium Salt.

Employing the procedure described above, 75.0 g. (0.36 mole) of 2-bromo-4-chlorophenol, 100.0 g. of sodium bromomethanesulfonate, and 16.0 g. (0.4 mole) of sodium hydroxide gave 74.5 g. (65% yield) of (2-bromo-4-chlorophenoxy)methanesulfonic acid, sodium salt, m.p. >315°, after recrystallization from 90% aqueous ethanol, pmr (deuterium oxide): δ 5.00 (s, 2H, OCH_2SO_3), 7.07-7.62 (m, 3H, 3 Ar-*H*).

Anal. Calcd. for $C_7H_5BrClO_4SNa$: S, 9.91. Found: S, 9.65.

2-Bromo-4-chlorophenyl Chloromethyl Ether.

By the procedure described above, 71.0 g. (0.22 mole) of (2-bromo-4-chlorophenoxy)methanesulfonic acid, sodium salt and 110.0 g. (0.53 mole) of phosphorus pentachloride gave 55.8 g. (quantitative yield) of crude product, m.p. 55-57°. From 1.5 g. of crude product, recrystallized from 10 ml. of pentane, the recovery was 1.3 (87% yield), m.p. 56.0-57.5°; pmr (deuteriochloroform): δ 5.91 (s, 2H, OCH_2Cl), 7.08-7.62 (m, 3H, 3 Ar-*H*).

Anal. Calcd. for $C_7H_5BrCl_2O$: C, 32.85; H, 1.97; Cl, 27.71. Found: C, 33.08; H, 2.17; Cl, 27.99.

2-Amino-1-[(2-bromo-4-chlorophenoxy)methyl]pyridinium Chloride (**1d**).

By the procedure described for **1c**, 14.1 g. (0.15 mole) of 2-aminopyridine, 25.6 g. (0.1 mole) of 2-bromo-4-chlorophenyl chloromethyl ether, and 250 ml. of anhydrous xylene, there was obtained 33.0 g. (94% yield) of **1d**, m.p. 237-239°. Recrystallization of 3.0 g. from 75 ml. of absolute ethanol gave 2.4 g. (80% recovery) of **1d**, m.p. unchanged at 237-239°; ir (mull): (3375 (w), 3350 (w), 1665 (s), 1645 (m), 1580 (s), 1565 (m) 1530 (m) cm^{-1}; pmr (DMSO-d_6): δ 6.29 [s, 2H, $\overset{+}{N}CH_2O$)], 6.75-7.02 (m, 1H, Py-*H*), 7.22-8.31 (m, 6H, 3 Ar-*H* and 3 Py-*H*), 9.40 [s, 2H, NH_2 (equilibrates with deuterium oxide)].

Anal. Calcd. for $C_{12}H_{11}BrCl_2N_2O$: C, 41.18; H, 3.17; N, 8.00; Cl^-, 10.13. Found: C, 40.90; H, 3.42; N, 8.30; Cl^-, 10.03.

2-Chloro-6*H*-pyrido[1,2-*c*][1,3,5]benzoxadiazepine (**3d**).

A mixture of 14.0 g. (0.04 mole) of **1d**, 11.1 g. (0.08 mole) of anhydrous potassium carbonate, 0.4 g. of copper bronze, and 350 ml. of 1-propanol was heated and stirred, under reflux, in a nitrogen atmosphere, for 8 hours, and then filtered hot. The filtrate was worked up as described for **3c** and the crude residue recrystallized from a mixture of 500 ml. of cyclohexane and 70 ml. of benzene to give 6.8 g. (73% yield) of **3d**, m.p. 175-177°; ir (deuteriochloroform): 1640 (s), 1562 (s), 1540 (s), 1534 (s) cm^{-1}; pmr (deuteriochloroform): δ 5.30 (s, 2H, NCH_2O, 5.85-6.18 (m, 1H, 1 Py-H), 6.57-7.40 (m, 6H, 3 Ar-H, 3 Py-H).

Anal. Calcd. for $C_{12}H_9ClN_2O$: C, 61.94; H, 3.90; N, 12.04; Cl, 15.24; N.E., 232. Found: C, 61.72; H, 3.90; N, 12.14; Cl, 15.19; N.E. (perchloric acid), 235.

2-Chloro-6*H*-pyrido[1,2-*c*][1,3,5]benzoxadiazepine Hydrochloride (**4d**).

To 2.0 g. (0.0086 mole) of **3d** in 50 ml. of warm 2-propanol was added 5.0 ml. of 4.8 *N* (0.024 mole) of 2-propanolic hydrogen chloride. A pale yellow crystalline solid separated. The mixture was diluted with 300 ml. of anhydrous ether, the solid filtered, and dried to give 2.2 g. of solid, m.p. 300-305° dec. Recrystallization from a mixture of 400 ml. of acetonitrile and 40 ml. of absolute ethanol gave 1.9 g. (82% yield) of **4d**, as yellow flakes, m.p. 303-305° dec.; ir (mull): 1700 (s), 1560 (s, broad), 1510 (s), 1470 (m) cm^{-1}; pmr (DMSO-d_6): δ 6.23 (s, 2H, NCH_2O), 7.06-7.45 (m, 3H, 3-Py-H and Ar-H), 7.80-8.55 (m, 4H, 4 Ar-H and Py-H), 13.10 (s, 1H, HCl).

Anal. Calcd. for $C_{12}H_9ClN_2O\cdot HCl$: C, 53.55; H, 3.75; N, 10.41; Cl$^-$, 13.18. Found: C, 53.59; H, 3.93; N, 10.64; Cl$^-$, 13.12.

[(*o*-Bromophenyl)thio]methanesulfonic Acid, Sodium Salt.

To a solution of 40.0 g. (0.22 mole) of *o*-bromobenzenethiol in 40 ml. of 25% aqueous sodium hydroxide solution (0.25 mole) was added 60.0 g. (0.28 mole) of bromomethanesulfonic acid, sodium salt. The mixture, reacted as described above, and then worked up gave 63.3 g. (95% yield) of crude product, m.p. > 310°. An analytical sample was prepared by recrystallizing 2.8 g. of this material from 50 ml. of 90% ethanol; the recovery of pure [(*o*-bromophenyl)thio]methanesulfonic acid, sodium salt, m.p. > 310°, was 2.3 g.; pmr (deuterium oxide): δ 4.30 (s, 2H, SCH_2SO$_3$), 7.01-7.79 (m, 4H, 4 Ar-H).

Anal. Calcd. for $C_7H_6BrO_3S_2Na$: Br, 26.20; S, 21.02. Found: C, 25.95; S, 20.75.

o-Bromophenyl Chloromethyl Sulfide.

A mixture of 60.4 g. (~0.2 mole) of crude [(*o*-bromophenyl)-thio]methanesulfonic acid, sodium slat and 98.0 g. (0.47 mole) of phosphorus pentachloride was reacted as above and then worked up to give 43.7 g. (93% yield) of *o*-bromophenyl chloromethyl sulfide, b.p. 86° (0.6 mm), m.p. 28-30°; pmr (deuteriochloroform): δ 5.00 (s, 2H, SCH_2Cl), 6.95-7.82 (m, 4H, 4 Ar-H).

Anal. Calcd. for C_7H_6BrClS: S, 13.42. Found: S, 13.10.

2-Amino-1-[[(*o*-bromophenyl)thio]methyl]pyridinium Chloride (**1e**).

A solution of 14.1 g. (0.15 mole) of 2-aminopyridine, 24.0 g. (0.1 mole) of *o*-bromophenyl chloromethyl sulfide, and 220 ml. of anhydrous xylene was stirred for 10 minutes at 50-55° and then for 15 hours at 90-95°. The mixture was cooled, the solid filtered, and recrystallized from 90 ml. of absolute ethanol to give 9.1 g. (27% yield) of **1e**, m.p. 199-201°; ir (mull): 1660 (s), 1630 (s), 1573 (m), 1550 (s), 1509 (s) cm^{-1}; pmr (DMSO-d_6): δ 5.78 (s, 2H, $\overset{+}{N}$CH_2S), 6.45-6.75 (m, 1H, Py-H), 7.16-8.00 (m, 7H, 4 Ar-H and 3 Py-H), 9.26 (s, 2H, NH_2, equilibrates with deuterium oxide).

Anal. Calcd. for $C_{12}H_{12}BrClN_2S$: C, 43.46; H, 3.65; N, 8.45; S, 9.67; Cl$^-$, 10.69. Found: C, 43.34; H, 3.73; N, 8.65; S, 9.38; Cl$^-$, 10.47.

6*H*-Pyrido[1,2-*c*][1,3,5]benzothiadiazepine Hydrochloride (**4e**).

The quaternary chloride, **1e**, 2.90 g. (0.009 mole), 4.2 g. (0.03 mole) of anhydrous potassium carbonate, 0.26 g. of copper bronze, and 250 ml. of anhydrous 1-propanol were heated and stirred under reflux, in a nitrogen atmosphere. The course of the reaction was monitored by tlc; **1e** with $R_f \sim 0.1$, could be distinguished readily from **3e**, with $R_f \sim 0.4$ in chloroform: methanol 4:1, on alumina. Seven days were required for the complete disappearance of the **1e** from the reaction mixture. Workup of the reaction mixture gave 1.45 g. of crude **3e**, as a yellow oil that could not be induced to crystallize.

To the oil, 1.45 g., in 20 ml. of methanol, was added, dropwise, 5.0 ml. of 3.4 *N* methanolic hydrogen chloride. The pale yellow crystals that separated on cooling were filtered and dried to give 1.65 g. of crude **4e**, m.p. sinters at 223-225°, melts 256-258°. Recrystallization from 2-propanol gave 1.42 g. (60% yield) of pure **4e**, m.p. sinters at 223-225°, melts at 258-260°; ir (potassium bromide): 3470 (s), 1645 (s), 1585 (s), 1570 (s), 1545 (s) cm^{-1}; pmr (DMSO-d_6): δ 5.85 (broad s, 2H, NCH_2S), 7.02-8.38 (m, 8H, 4 Ar-H and 4 Py-H), 12.5 (broad s, 1H, HCl, equilibrates with deuterium oxide).

Anal. Calcd. for $C_{12}H_{10}N_2S\cdot HCl\cdot H_2O$: C, 53.63; H, 4.87; N, 10.42; S, 11.93; Cl, 13.20. Found: C, 53.30; H, 4.88; N, 10.64; S, 11.93; Cl, 13.42; Calcd. M$^+$ ($C_{12}H_{10}N_2S$), 214. Found: M$^+$ 214 (base peak), and other ions of m/e 198, 186, 136, 135, 79, 78.

6*H*-Pyrido[1,2-*c*][1,3,5]benzothiazepine (**3e**).

To a solution of 0.50 g. of sodium bicarbonate in 5.0 ml. of water and 10.0 ml. of ether was added with stirring, 100 mg. of **4e**, in portions. The two layers were allowed to stratify, the the ether layer was separated, and the water layer extracted repeatedly with ether. The combined ether extracts were washed, dried, and concentrated. The residual yellow oil solidified when dried at 56°/1 mm, and was recrystallized from hexane at -70° to give yellow, crystalline **3e**, m.p. 97-98°; ir (mull): 1640 (m), 1585 (w), 1550 (m), 1535 (m), 1455 (s) cm^{-1}; pmr (deuteriochloroform): δ 4.74 (s, 2H, CH_2), 5.65-7.40 (m, 4 Ar-H and 4 Py-H).

Anal. Calcd. for $C_{12}H_{10}N_2S$: C, 67.35; H, 4.71; N, 13.09; S, 14.98. Found: C, 67.12; H, 4.91; N, 12.96; S, 14.81.

Isolation of Thianthrene.

The methanol filtrate from the crude **4e** was concentrated to dryness and the residue extracted with 200 ml. of boiling hexane. The hexane extract was filtered at the boiling point, the filtrate was decolorized with Darco, refiltered, concentrated to 10 ml., and the solution cooled. The colorless solid that crystallized was filtered and dried to give 50 mg. of thianthrene, m.p. 158-159° (8); ir (mull): 1450 (s), 1375 (m), 750 (m) cm^{-1}; pmr (deuteriochloroform): δ 7.10-7.55 (AA'BB' symmetrical multiplet).

Anal. Calcd. for $C_{12}H_8S_2$: C, 66.72; H, 3.73; S, 29.69. Found: C, 66.71; H, 3.80; S, 29.45.

1-[[(*o*-Bromophenyl)thio]methyl]-2-iminopyridine (**2e**).

To a solution of 0.55 g. (0.01 mole) of sodium methoxide in 40 ml. of anhydrous methanol was added 3.32 g. (0.01 mole) of **1e** and the mixture heated, in a nitrogen atmosphere with stirring, under reflux for 4 hours. The yellow solution was concentrated to dryness *in vacuo* and the residue distributed between 45 ml. of ether and 10 ml. of water. The ether layer was separated, the water layer was reextracted with ether, the ether solutions combined, washed, dried and concentrated to give 1.2 g. of **2e** as a viscous gum that could not be induced to crystallize; pmr (deuteriochloroform): δ 5.20 (s, 2H, CH_2), 5.54 [m, 2H, 1 Py-*H* and N*H*] (equilibrates with deuterium oxide), δ 6.20-7.70 (m, 7H, 4 Ar-*H* and 3 Py-*H*).

1-(*o*-Bromophenethyl)pyridinium Bromide (**5**).

A mixture of 3.35 g. (0.013 mole) of *o*-bromophenethyl bromide and 1.00 g. (0.013 mole) of pyridine in 7 ml. of sulfolane was heated in an oil bath maintained at 90° for about 70 hours. The cooled mixture was diluted with 20 ml. of 2-propanol to give 1.33 g. of crude **5**, m.p. 190-192°. Recrystallization from 20 ml. of acetonitrile gave 0.88 g. (20% yield) of pure **5**, m.p. 192-194°; ir (mull): 1625 (m), 1485 (s), 1460 (s), 1170 (s) cm^{-1}; pmr (DMSO-d_6): δ 3.41 (t, J = 10 Hz, 2H, NCH_2CH_2), 4.94 (t, J = 10 Hz, 2H, NCH_2CH_2), 7.15-9.25 (m, 10H, 5 Ar-*H* and 5 Py-*H*).

Anal. Calcd. for $C_{13}H_{13}Br_2N$: C, 45.52; H, 3.82; N, 4.08; Br, 46.60. Found: C, 45.80; H, 4.05; N, 4.19; Br, 46.80.

1-[(*o*-Bromophenoxy)methyl]pyridinium Chloride (**6**).

The procedure described for **5** gave a 32% yield of **6**, m.p. 130-132°, after recrystallization from acetonitrile; ir (mull): 3470 (m), 3390 (w), 1630 (m), 1580 (m), 1570 (m), 1505 (m), 1490 (s), 1475 (s), 1440 (s), 1410 (m) cm^{-1}; pmr (DMSO-d_6): δ 6.79 (s, 2H, CH_2), 6.90-9.50 (m, 9H, 4 Ar-*H* and 5 Py-*H*).

Anal. Calcd. for $C_{12}H_{11}BrClNO$: C, 48.04; H, 3.70; N, 4.67; Cl^-, 11.82. Found: C, 47.81; H, 3.62; N, 4.81; Cl^-, 11.93.

1-[(2-Bromo-4-chlorophenoxy)methyl]pyridinium Chloride (**7**).

The procedure described for **5** gave a 66% yield of **7**, m.p. 127-131°, after recrystallization from acetonitrile; ir (mull): 3460 (s), 3390 (s), 1625 (s), 1465 (s), 1370 (m) cm^{-1}; pmr (DMSO-d_6): δ 6.84 (s, 2H, CH_2), 7.50-9.60 (m, 8H, 3 Ar-*H* and 5 Py-*H*).

Anal. Calcd. for $C_{12}H_{10}BrCl_2NO$: C, 43.02; H, 3.01; N, 4.18; Br, 23.86; Cl, 21.17. Found: C, 42.74; H, 3.08; N, 4.03; Br, 23.58; Cl, 20.92.

1-[(*o*-Bromophenylthio)methyl]pyridinium Chloride (**8**).

The procedure described for **5** gave a 15% yield of **8**, m.p. 137-139° after recrystallization from acetonitrile; ir (mull): 3440 (s), 1635 (w), 1625 (m), 1510 (w), 1480 (s), 1450 (m), 1420 (w) cm^{-1}; pmr (DMSO-d_6): δ 6.54 (s, 2H, CH_2), 7.35-9.50 (m, 9H, 4 Ar-*H* and 5 Py-*H*).

Anal. Calcd. for $C_{12}H_{11}BrClNS$: C, 45.61; H, 3.51; N, 4.43; Cl^-, 11.32. Found: C, 45.43; H, 3.67; N, 4.44; Cl^-, 11.32.

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(2) Present address: Rohm and Haas Co., Research Laboratories, Spring House, Pa., 19477.

(3) To whom all correspondence should be addressed.

(4) Cyclizations involving dehydrobromination have generally been carried out in anhydrous *N,N*-dimethylformamide at *ca.* 150-160°, using potassium carbonate as the base, and Cu bronze as catalyst [*cf.*, H. L. Yale, B. Beer, Jelka Pluscec, and E. R. Spitzmiller, *J. Med. Chem.*, 13, 713 (1970), and E. Schenker and H. Herbst, in "Progress in Drug Research, Birkhauser Verlag, Basel, Switzerland, Vol. 5, 1963, pp. 284-287]. While Yale, *et al.* *(loc. cit.)* have shown that other solvents, and in particular, diethylbenzene, are superior to *N,N*-dimethylformamide for the synthesis of dibenz[*b,e*][1,4]oxazepines and -thiazepines, the present authors have found no references in the literature that would serve as a precedent for the effective role of water, methanol or 1-propanol in the cyclizations now being reported.

(5) It is interesting to speculate as to the existence of benzyne intermediates in these reactions. The authors are aware of a single reference [M. M. Boudakian, R. J. Eber, W. E. Kuehlewind, Jr., and R. E. McArthur, *J. Org. Chem.*, 26, 4641 (1961)] to the possible formation of a benzyne intermediate in an aqueous system. Thus *p*-bromofluorobenzene and aqueous sodium hydroxide, *in the absence of a copper catalyst*, gave *p*-fluorophenol, phenol, and *m*-fluorophenol in 20, 20, and 2% yields, respectively. These products were, however, not isolated, but were estimated by means of infrared scanning; thus, the absorption bands at 8.9 and 10.5 μ were used as the only means of both identifying and estimating the *m*-fluorophenol in the crude reaction mixture. Invariably, benzynes have been generated in liquid ammonia and in aprotic solvents. In the single example found in the literature, where a protic solvent was used, benzenediazonium-2-carboxylate was the benzyne precursor employed. Under anhydrous conditions, that compound decomposed slowly in benzene or toluene, yielding nitrogen (100% yield), carbon dioxide (59% yield) and benzyne (trapping experiments with furan gave a 55% yield of 1,4-dihydronaphthalene-1,4-endoxide). In aqueous solution, the same compound decomposed slowly at 45° during 36 hours to give salicyclic acid in 88% yield, *cf.* M. Stiles and R. G. Miller, *J. Am. Chem. Soc.*, 82, 3802 (1960) and L. Friedman and F. M. Logullo, *ibid.*, 85, 1549 (1963). T. Jen, P. Bender, H. Van Hoeven, B. Dienel, and B. Loev, *J. Med. Chem.*, 16, 407 (1973), have suggested that a benzyne intermediate may have been formed during the treatment of 2-[(*o*-chlorobenzyl)amino]-4,5-dihydroimidazole with sodium amide in liquid ammonia to give 1,2,4,5-tetrahydroimidazo[1,2-*a*]quinazoline in 24% yield, but again, rigorous proof for this suggested mechanism was not presented.

(6) The preparation of *o*-bromophenethyl bromide by this procedure has been described by F. Bickelhaupt, K. Stach, and M. Thiel, *Chem. Ber.*, 98, 685 (1965).

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(8) F. Krafft and R. E. Lyons, *Ber.*, 29, 435 (1896) report a m.p. of 157.5-158.5° for thianthrene.