8b: 61% yield, mp 165–166 °C; R_f 0.2 (ether/petroleum ether, bp 30–60 °C, 1:1); IR (Nujol) 3165, 1773, 1726, 1710, 1697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23 (br s, 1 H), 3.80 (s, 3 H), 3.65 and 3.41 (d, 1 H, J = 19 Hz), 2.87 and 2.60 (d, 1 H, J = 18 Hz), 2.0–1.0 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 205.3, 176.2, 169.1, 82.3, 63.2, 53.5, 48.2, 47.6, 38.6, 30.0, 25.2, 24.3, 24.0; LRMS (70 eV), m/e (relative intensity) 266 (obsd M^+, 0.1) 238 (2), 207 (100), 179 (10), 143 (80), 123 (40), 115 (15). Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.64; H, 6.81; N, 10.52. Found: C, 58.40; H, 6.74; N, 10.26.

9b: 14% yield, mp 205–206 °C; R_f 0.4 (ether/petroleum ether, bp 30–60 °C, 1:1); IR (Nujol) 1768, 1735, 1721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.67 (s, 3 H), 2.91 (s, 2 H), 2.48 (s, 2 H), 2.0–1.0 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 203.5, 168.9, 80.2, 61.2, 52.2, 46.8, 39.4, 38.3, 33.7, 25.5, 24.9, 24.0; LRMS (70 eV), m/e (relative intensity) 466 (obsd M^+, 25) 387 (100), 328 (15), 291 (6), 286 (3), 237 (8), 223 (30), 195 (10), 136 (20), 124 (30), 123 (15); HRMS calcd for $C_{24}H_{34}N_2O_6$ m/e 446.2417, found m/e 446.2418 ● 0.0044.

Reaction of 6c with Rhodium(II) Acetate. Formation of 8c. The α-diazo ketone **6c** was treated with rhodium(II) acetate as described above for the analogous reaction with **6a**, and the crude product was chromatographed on silica gel with ether/petroleum ether (bp 30–60 °C, 2:3) as solvent to give **8c**: 62% yield, mp 164–166 °C; R_f 0.3 (ether/petroleum ether, bp 30–60 °C, 1:1); IR (Nujol) 3348, 1760, 1740, 1728, 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47–7.03 (m, 10 H), 6.59 (br s, 1 H), 3.80 (s, 3 H), 3.48 (m, 2 H), 3.22 (q, 1 H, J = 8 Hz), 1.39 (d, 3 H, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 206.2, 177.6, 170.1, 146.1, 141.9, 128.8, 128.6, 128.4, 127.4, 126.9, 82.1, 71.4, 57.3, 53.4, 18.4; LRMS (70 eV), m/e (relative intensity) 364 (obsd M^+, 0.2) 305 (100), 227 (3), 265 (5), 207 (80), 180 (40), 179 (35), 178 (35), 165 (25). Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69. Found: C, 69.10; H, 5.70; N, 7.56.

Reaction of 6a with Rhodium(II) Acetate and Norbornene. Formation of the Adduct 12. The α-diazo ketone **6a** was treated with rhodium(II) acetate as described above but in the presence of 13 equiv of norbornene. The crude product was chromatographed on silica gel with ether/petroleum ether (bp 30–60 °C, 1:12) to ether/petroleum ether (bp 30–60 °C, 1:1) as solvent gradient to give a mixture of **8a** (48% yield) and the adduct **12** (15% yield): mp 136–139 °C, R_f 0.2 (ether/petroleum ether, bp 30–60 °C, 1:1); IR (Nujol) 1758, 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.53–7.16 (m, 10 H), 3.65 (s, 3 H), 3.32 and 3.05 (d, 2 H, J = 18 Hz), 3.02 (m, 2 H), 2.28 (m, 2 H), 1.84–0.70 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 209.2, 169.6, 147.0, 144.7, 128.2, 128.0, 127.3, 126.7, 84.6, 68.5, 58.1, 54.8, 52.2, 52.1, 48.9, 39.3, 33.2, 29.1, 27.6; LRMS (70 eV), m/e (relative intensity) 401 (obsd M^+, 3) 373 (5), 342 (100), 180 (60). Anal. Calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.52; H, 6.60; N, 3.24.

Acknowledgment. We are indebted to Eli Lilly & Co., Indianapolis, IN, for financial support of this work and to Mary W. Baum for carrying out the NOE experiment.

Registry No. **4** (R_1 = H; R_2 = R_3 = Ph), 20958-76-3; **4** (R_1 = H; R_2R_3 = c-C_5H_{10}), 80351-01-5; **4** (R_1 = CH_3; R_2 = R_3 = Ph), 79289-32-0; **5a**, 80351-20-8; **5b**, 87616-18-0; **5c**, 87616-19-1; **6a**, 87616-20-4; **6b**, 87616-21-5; **6c**, 87616-22-6; **8a**, 87616-23-7; **8b**, 87616-24-8; **8c**, 87616-25-9; **9a**, 87616-26-0; **9b**, 87616-27-1; **12**, 87616-28-2; methyl acetoacetate, 105-45-3; norbornene, 498-66-8.

Synthesis and Some Reactions of 5-Aryl-3,4-dihydro-2*H*-1,6-benzoxazocine and 5-Aryl-3,4-dihydro-2*H*-1,6-benzothiazocines[1]

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5-Aryl-3,4-dihydro-2*H*-1,6-benzothiazocines (**1**) were prepared in a two-step sequence from *o*-aminothiophenols (**2**) and γ-halobutyrophenones (**3**); 3a-aryl-1,2,3,3a-tetrahydropyrrolo[2,1-*b*]benzothiazoles (**4**) formed if the reaction was run in one step. Imine **1** could be reduced with lithium aluminum hydride to give amines **15** and reacted with alkyllithium reagents to give **19**. Imines **1c–e** reacted with lead tetraacetate to give benzothiazine derivatives **20**, **21**, and **22**; a possible mechanism is proposed. The oxygen analogues of **1** were more difficult to prepare, and only the 5-phenyl derivative **13** was prepared in order to investigate its spectral properties and to investigate the mechanism of the lead tetraacetate induced ring contraction of **1**.

Benzene-fused seven-member ring and eight-member ring heterocycles have provided a rich source of CNS and cardiovascular agents. Compounds such as diazepam (an anxiolytic 1,4-benzodiazepine),[2] nefopam (an analgesic 1*H*-2,5-benzoxazocine),[3] and diltiazam (a calcium channel blocking 1,5-benzothiazepinone)[4] are representative of such agents with clinically interesting biological activity. We became interested in the synthesis and chemistry of some derivatives of 5-aryl-3,4-dihydro-2*H*-1,6-benzothiazocines (**1**) and 5-phenyl-3,4-dihydro-2*H*-1,6-benzoxazocine (**13**) as part of our continuing program to develop novel CNS and cardiovascular agents.[5]

The synthesis of the desired benzothiazocine system **1b** from *o*-aminothiophenol (**2**, X = H) and γ-chlorobutyrophenone (**3**, Ar = Ph) is outlined in Scheme I. When the condensation is carried out using triethylamine as a hydrogen chloride scavenger, an easily separable mixture of **1b** and benzothiazole **4b** forms in a ratio of 2:7. Competitive formation of **1b** arises by deprotonation of **2** (X = H) with triethylamine and attack of the resultant mercaptide upon **3** (Ar = Ph) to give amino ketone **5b**. Ring closure of **5b** by imine formation gives the desired product. When the same reaction is performed using a weaker base (pyridine), **4b** forms exclusively in excellent yield.[6]

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(1) For a preliminary report concerning some of this work see: Press, J. B.; Eudy, N. H.; Lovell, F. M.; Perkinson, N. A. *Tetrahedron Lett.* **1980**, *21*, 1705.

(2) Sternbach, L. H.; Reeder, E. *J. Org. Chem.* **1961**, *26*, 4936.

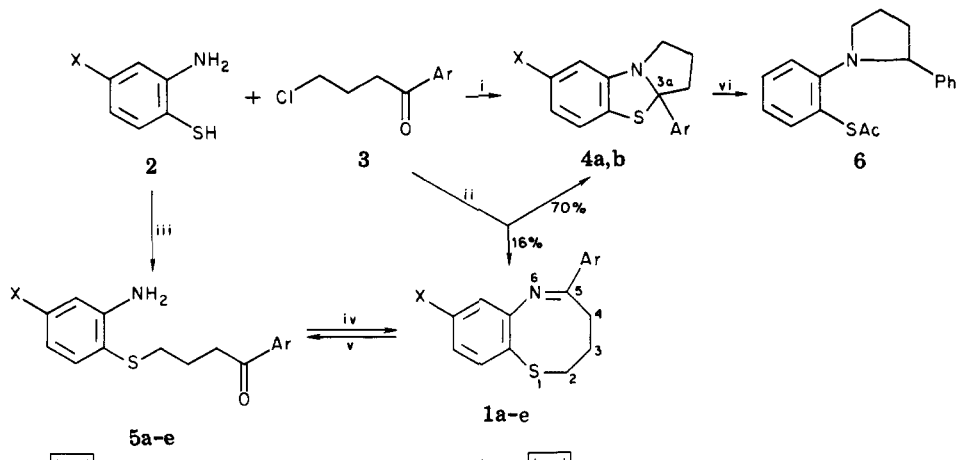
(3) Klohs, M. S.; Draper, M. D.; Petrocek, F. J.; Genzel, K. H.; Rê, O. N. *Arzneim.-Forsch.* **1972**, *22*, 132.

(4) Kugita, H.; Inoue, H.; Ikezaki, M.; Konda, M.; Takeo, S. *Chem. Pharm. Bull.* **1971**, *19*, 595.

(5) For related work see: Press, J. B.; Eudy, N. H. *J. Heterocycl. Chem.*, in press.

0022-3263/84/1949-0116$01.50/0

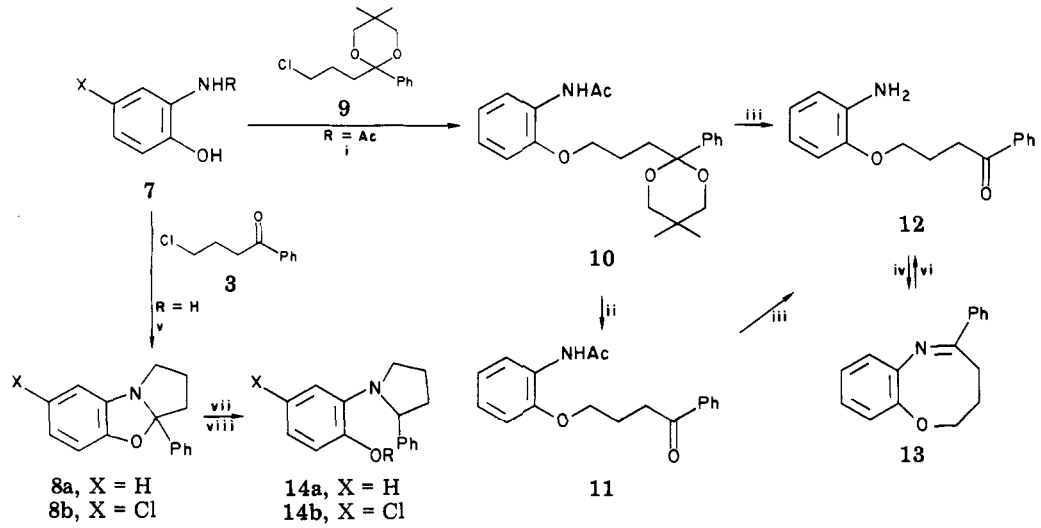
Scheme I[a]



a, X = H, Ar =  ; b, X = H, Ar = Ph—; c, X = Cl, Ar =  ; d, X = Cl, Ar = *p*-FPh—; e, X = Cl, Ar = Ph—

[a] (i) Pyr, PhMe, Δ; (ii) Et_3N, PhMe, Δ; (iii) NaOMe, MeOH; (iv) *p*-TsOH, PhMe, Δ; (v) H_3O^+; (vi) $NaBH_4$, Ac_2O.

Scheme II[a]



[a] (i) NaH, DMF; (ii) 75% AcOH; (iii) 2.5 N HCl, EtOH; (iv) *p*-TsOH, PhMe, Δ; (v) pyr, PhMe, Δ; (vi) H_3O^+; (vii) $NaBH_4$; (viii) Ac_2O/H^+.

Benzothiazocine **1b** is most expediently prepared using a two-step procedure wherein amino ketone **5b** is isolated; condensation of the mercaptide anion of **2** (preformed from **2** using sodium methoxide) with chloro ketone **3** gives **5b** in excellent yield. Subsequent ring closure is accomplished by acid catalysis and azeotropic removal of water. Additional derivatives **1a,c–e** are prepared similarly.

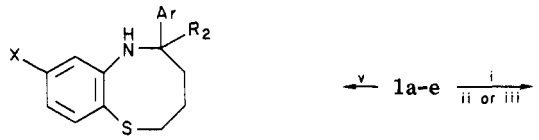
Structure assignment of **1** via â-vis **4** is ambiguous using routine IR, UV, and ^1H NMR but is supported by ^{13}C NMR analysis. The imine sp^2 C-5 of **1** absorbs at 167.1 ppm while the sp^3 C-3a of **4** exhibits a weak absorption at 87 ppm. Additional confirmation for the structure of **1** is derived by dilute acid hydrolysis to re-form amino ketone **5**. Chemical support of the structural assignment for **4b** is provided by reduction with sodium borohydride and subsequent acetylation of the unisolated mercaptan to give thioacetate **6**.

The analogous oxygen system **13** is prepared with much greater difficulty (Scheme II). As expected *o*-aminophenyl **7** (R = H) reacts with γ-chlorobutyrophenone (**3**, Ar = Ph) to give benzoxazole **8** directly.[7] In this case the reduced nucleophilicity of phenol as compared to thiophenol is evidenced by the lack of halide displacement by phenoxide regardless of the base strength of the hydrogen chloride scavenger used. If acetamide **7** (R = Ac, X = H) and chloro ketal **9** are allowed to react, formation of **8** is prevented and acetamido ketal is formed easily. Mild hydrolysis of **10** gives ketone **11** which is converted to amino ketone **12** by using ethanolic hydrogen chloride. Preferably **10** is converted directly to **12** in excellent yield. Ring closure of **12** to **13** occurs in a manner similar to the sulfur system, however, **13** forms in much lower yield. Benzoxazocine **13** is much more susceptible to hydrolytic ring opening as compared to **1** and must be stored in a cold inert atmosphere to prevent rapid reversion to **12**. ^{13}C NMR analysis again provides support for structural assignments of **8** and **13**: the imine sp^2 C-5 of **13** absorbs at 165 ppm while the sp^3 C-3 of **8** appears at 111.7 ppm. Analogous to the sulfur system, benzoxazole **8** is reduced with sodium borohydride to the corresponding phenol **14** (R = H) which acetylates to give **14** (R = Ac). While the approach outlined in

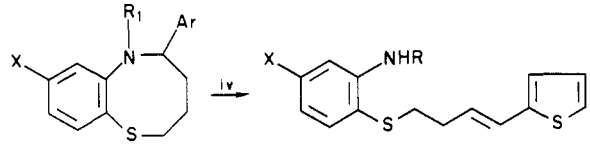
(6) For similar condensations using γ-halo aliphatic ketones see: Mushkalo, L. K.; Chuiguk, V. A.; Annamuradov, Ch. *Ukr. Khim. Zh.* **1971**, *37*, 568; *Chem. Abstr.* **1971**, *75*, 140752V.

(7) Mushkalo, L. K.; Chuiguk, V. A. Annamuradov, Ch. *Ukr. Khim. Zh.* **1971**, *37*, 682; *Chem. Abstr.* **1972**, *76*, 3737a.

Scheme III[a]



19a, X = H; Ar = Ph—; R_2 = C_4H_9—
19b, X = Cl; Ar = *p*-FPh—; R_2 = C_4H_9—
19c, X = Cl; Ar =  ; R_2 = CH_3
19d, X = Cl; Ar = *p*-FPh; R_2 = CH_3—



15a-e, R_1 = H
16a-d, R_1 = CH_3
17a-e, R_1 = Ac

18

a, X = H; Ar =  b, X = H; Ar = Ph— c, X = Cl; Ar =  d, X = Cl; Ar = *p*-FPh— e, X = Cl; Ar = Ph—

[a] (i) LAH, THF, Δ; (ii) NaH, R_1I, DMF; (iii) Ac_2O, Pyr, Δ; (iv) H_3O^+ or Δ; (v) R_2Li, THF.

Scheme II would allow synthesis of additional derivatives, we halted further work on the benzoxazocine system as a result of the instability of **13** and the relatively poor overall yield of its preparation.

The hindered nature of the imine moiety of **1** as well as the relative instability of the 8-ring system cause difficulties during attempts to derivatize **1**. Reduction of imine **1** with sodium borohydride, sodium cyanoborohydride, or borane under a variety of conditions leads to recovery of unchanged **1** or, in worst case examples, isolation of amino ketone **5**. Only when **1** is allowed to react with a 10-fold excess of lithium aluminum hydride in refluxing tetrohydrofuran does amine **15** form slowly in good yield (Scheme III). Amine **15** is quite unreactive and difficult to purify. Acetylation of **15** to give **17** is accomplished only in refluxing acetic anhydride/pyridine; other reaction conditions such as acetyl chloride/triethylamine or acetic anhydride/4-(dimethylamino)pyridine effected no reaction. Additionally, **15** does not react with alkyl or aryl isocyanates in ether at reflux temperatures. Alkylation of **15** may be accomplished by slow (6 h) reaction with sodium hydride followed by long (18 h) exposure to methyl iodide. Shorter reaction times lead to significantly lower yields of methylamine **16**.

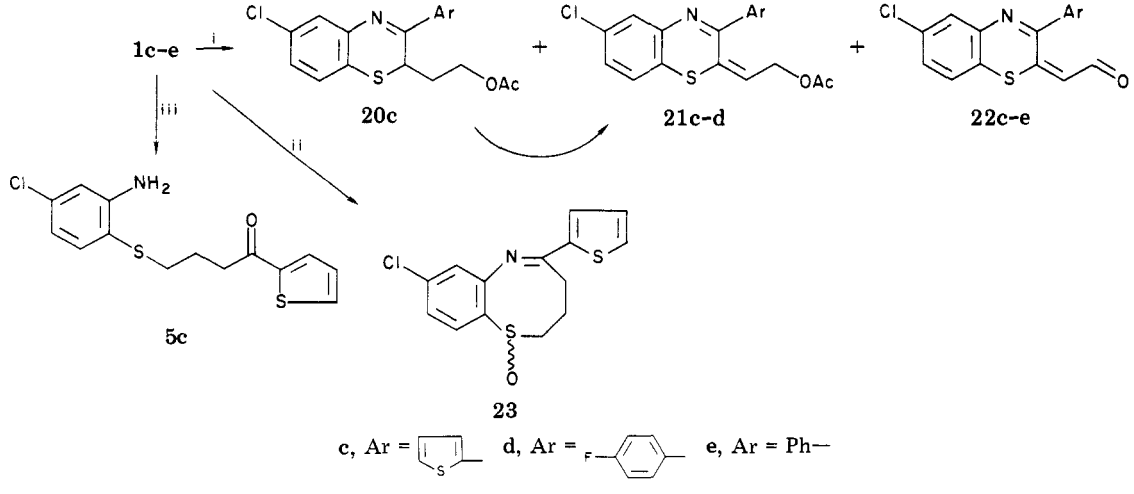
The inherent instability of **15a** is revealed upon attempts to prepare a crystalline hydrochloric salt for the purposes of purification, characterization, and storage. Olefinic amine **18** (R = H, X = H) is the sole isolable product from this reaction. *N*-Methylamine **16c** undergoes a much more facile ring opening to form **18** (R = CH_3, X = Cl). In this case, attempts to purify **16c** by silica gel chromatography or by distillation (if pot temperatures become excessive) cause the reaction. The formation of **18** probably arises as a result of internal elimination of **15** or **16** to relieve steric congestion. The trans configuration of the olefinic bond in **18** is determined by the typical ^1H NMR coupling constant (J = 16 Hz).

Although imine **1** does not react with Grignard reagents, organolithium compounds react to give the expected 1,2-addition products (Scheme III). Thus, **1b** reacts to form **19a** while **1d** forms **19b** with butyllithium. Similarly **1c** reacts with methyllithium to give **19c** while **1d** gives **19d**. These reactions occur in moderate yield with **19** difficult to isolate and purify. While not proven, these isolation problems presumably stem from internal elimination to give ring-open amines analogous to **18** since **19** is at least as sterically congested as amines **15** and **16**.

Another attempt to functionalize imine **1** leads to an unexpected ring contraction which we have previously reported (Scheme IV).[1] In our initial work, thienyl derivative **1c** is readily transformed to a mixture of **20c** and **21c** by the action of 1.1 equiv of lead tetraacetate. The structure of **21c** is known from spectral and X-ray analysis.[1] When **1c** is exposed to 2 equiv of lead tetraacetate for longer reaction times (18 vs. 5 h), aldehyde **22c** forms in addition to **21c** with less **20c** present in the reaction mixture. The structure of **22c** is assigned on the basis of spectral similarities to **21c**; the allylic aldehyde side chain is indicated by ^1H NMR wherein the aldehydic absorption appears at δ 9.90 as a doublet (J = 2.0 Hz) coupled to the olefinic proton at δ 6.60. The aldehyde carbonyl absorption of this conjugated system appears at the unusually low frequency of 1645 cm^{-1} in the infrared spectrum. When reactions are varied with more reagent or longer times, **22c** becomes the predominant product from the reaction while **20c** remains present in trace amounts.

Similar results are obtained for the 5-(*p*-fluorophenyl) imine or the 5-phenyl imine **1d** and **1e**, respectively. In the former case, only allyl acetate **21d** and aldehyde **22d**

Scheme IV[a]



20c 21c-d 22c-e

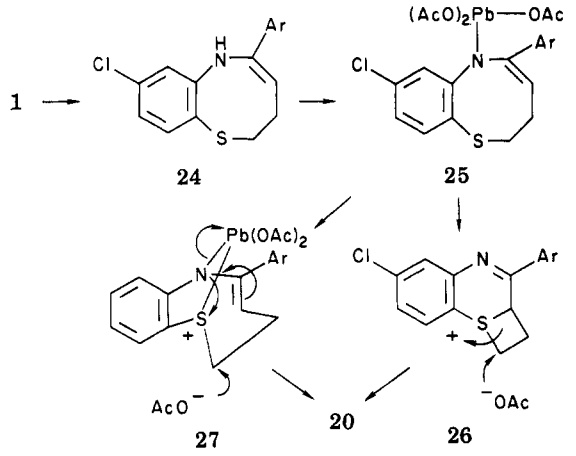
5c

23

c, Ar = d, Ar = e, Ar = Ph—

[a] (i) LTA, AcOH, Δ; (ii) $NaIO_4$, MeOH; (iii) $Hg(OAc)_2$, AcOH.

Scheme V



are obtained even when only 1.1 equiv of lead tetraacetate are used. In the case of **1e**, only small amounts of aldehyde **22e** are isolated. The reasons for this difficulty of product isolation from **1e** are obscure.

Several possible mechanisms for the transformation of imine **1** into benzothiazocine derivatives **20**, **21**, and **22** are possible. The intermediacy of a sulfoxide intermediate which might undergo Pummerer-like activation of the carbon α to sulfur with subsequent ring contraction to **20** is unlikely since sulfoxide **23** (Scheme IV) does not form **20c**, **21c**, or **22c** under the reaction or under Pummerer conditions.[8] The fact that the transannular ring contraction requires sulfur for the conversion of **1** to **20** is evidenced by the inability to convert the oxygen analogue **13** into the oxygen analogues of **20**, **21**, or **22**. Although mercuric acetate frequently reacts similarly to lead tetraacetate, in this case it transforms **1c** into amino ketone **5c** rather than benzothiazine derivatives (Scheme IV).

Consideration of these facts leads to the mechanism proposed in Scheme V. Lead tetraacetate coordination with imine tautomer **24** gives **25**. Transannular sulfur interaction leads to the 4-ring sulfonium intermediate **26** which collapses to **20** upon attack by acetate ion. Such charged 4-ring intermediates have been proposed to account for ring contractions that produce other 5-ring sulfur-containing heterocycles.[9] Another possible route involves sulfur–lead coordination of **25** to give **27**.[10] An intermediate such as **27** which brings sulfur into closer proximity with the carbon to which it migrates might more easily explain the observed facility of formation of **20**. Oxidation products **21** and **22** arise from additional reaction of **20** with the reagent or air.[11]

Thus 5-aryl-3,4-dihydro-2*H*-1,6-benzothiazocines (**1**) and 3,4,5,6-tetrahydro derivatives **15**, **16**, and **17** form with unexpected difficulty and frequently undergo reactions to give ring-altered products. Presumably steric congestion and strain relief are significant contributors to the observed reactivity of this series of compounds.

(8) For several examples of Pummerer conditions attempted see: (a) Numata, T.; Itoh, O.; Oae, S. *Tetrahedron Lett.* **1979**, 161. (b) Tanikaga, R.; Yabuki, Y.; Ono, N.; Kaji, A. *Tetrahedron Lett.* **1976**, 2257.

(9) (a) Chatterjee, A.; Sen, B.; Catterjee, S. K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1707. (b) Wilhelm, M.; Schmidt, P. *Helv. Chem. Acta* **1970**, *53*, 1697. (c) de Groot, A.; Boerma, J. A.; Wynberg, H. *Tetrahedron Lett.* **1968**, 2365.

(10) For other examples of proposed sulfur–lead tetraacetate co-ordination see: (a) Trost, B. M.; Hiroi, K., Jungheim, L. N. *J. Org. Chem.* **1980**, *45*, 1839 and references therein. (b) Trost, B. M., Tanigawa, Y. *J. Am. Chem. Soc.* **1979**, *101*, 4413.

(11) For a recent review of lead tetraacetate reactions see Rubottom, G. M. "Oxidations in Organic Chemistry"; Trahanovsky, W. S., ed.; Academic Press: New York, 1982; Part D, pp 1–146.

Experimental Section

Melting points were determined on a Mel-Temp capillary block melting point apparatus and are uncorrected. All compounds are homogeneous by thin-layer chromatographic analysis using Whatman K5F or K6F (5 × 10 cm) silica gel analytical plates. ^1H and ^{13}C NMR measurements were obtained on a Varian Associates CFT20 spectrometer using tetramethylsilane as the internal standard.

1,2,3,3a-Tetrahydro-3a-phenylpyrrolo[2,1-*b*]benzothiazole (4b). *o*-Aminothiophenol (12.5 g, 0.1 mol), γ-chlorobutyrophenone (18.3 g, 16.5 mL, 0.1 mol), and pyridine (10 mL) were dissolved in toluene (75 mL) and the mixture was reluxed with a Dean–Stark water separator overnight. The solvent was removed in vacuo and the residue was distilled using a Kugelrohr apparatus: bp 150 °C (0.5 mmHg); 18.3 g (73%); UV (EtOH) 222, 310 nm; mass spectrum, m/z 253 (M^+); ^1H NMR ($CDCl_3$) δ 7.50 (m, 5 H), 6.85 (m, 4 H, all aromatic H), 3.40 (m, 2 H, NCH_2), 2.60 (m, $PhCCH_2$), 1.94 (m, 2 H, CH_2). Anal. Calcd for $C_{16}H_{15}NS$: C, 75.85; H, 5.97; N, 5.53; S, 12.66. Found: C, 75.83; H, 6.15; N, 5.51; s, 12.71.

Similarly **4a** was prepared from γ-chloro-2-butyrothienone: yield, 42%; mp 113–115 °C; IR (KBr) 1468 cm^{-1}; UV (EtOH) 225, 310 nm; mass spectrum, m/z 259 (M^+); ^1H NMR ($CDCl_3$) δ 6.95 (m, 7 H, aromatic H), 3.62 (m, 1 H, NCH_2), 3.25 (m, 1 H, NCH_2), 2.60 (t, 2 H, CCH_2), 1.96 (m, 2 H, CH_2). Anal. Calcd for $C_{14}H_{13}NS_2$: C, 64.48; H, 5.05; N, 5.40; S, 24.72. Found: C, 64.79; H, 5.11; N, 5.39; S, 24.68.

3,4-Dihydro-5-phenyl-2*H*-1,6-benzothiazocine (1b). Reaction of *o*-Aminothiophenol and γ-Chlorobutyrophenone with Triethylamine Catalysis. *o*-Aminothiophenol (12.5 g, 0.1 mol), γ-chlorobutyrophenone (18.3 g, 0.1 mol), and triethylamine (10 mL) were allowed to react in toluene (75 mL) overnight as above. After the solvent was removed, the residual red oil was diluted with ether (100 mL) and allowed to stand at 0 °C whereupon 1.92 g of **1b**, a white solid, precipitated. The filtrate was concentrated to dryness, rediluted with ether (50 mL), and cooled to 0 °C. An additional 2.20 g of product **1b** crystallized, total yield, 4.12 g (16%). The analytical sample was prepared by sublimation, (120 °C (0.05 mmHg) as a white solid: mp 124.5–126.5 °C; IR (KBr) 1626 cm^{-1}; UV (EtOH) 208, 245, 315 nm; mass spectrum, m/z 253 (M^+); ^1H NMR ($CDCl_3$) δ 8.00 (m, 2 H), 7.80 (dd, 1 H), 7.45 (m, 4 H), 7.10 (m, 2 H, all aromatic H), 3.00 (m, 2 H, SCH_2), 2.15 (br m, 4 H, CH_2). Anal. Calcd for $C_{16}H_{15}NS$: C, 75.85; H, 5.97; N, 5.53; 5, 12.66. Found: C, 75.80; H, 5.88; N, 5.53; S, 12.61.

The ether filtrate was concentrated and the residue distilled as described above to give **4b** (17.7 g (70%)) identical in all respects with our previously prepared material.

4-(2-Amino-4-chlorophenylthio)butyrophenone (5e). A solution of sodium methoxide (14.5 g, 0.27 mol) in methanol (125 mL) was treated portion wise with 2-amino-4-chlorobenzenethiol hydrochloride (25 g, 0.128 mol) and the solution was stirred for 0.5 h. γ-Chlorobutyrophenone (23.2 g, 0.128 mol) in methanol (25 mL) was added and the mixture was refluxed for 3 h. The reaction was quenched with water (500 mL) and extracted with ether (3 × 150 mL). The combined organic layers were dried over sodium sulfate, concentrated, and the resultant oil was distilled using a Kugelrohr apparatus, bp 190 °C (0.05 mmHg), to give the product **5e** as a yellow syrup: 25.5 g (73%); IR (neat) 1665 cm^{-1}; UV (EtOH) 210, 242, 310 nm; mass spectrum, m/z 305 (M^+); ^1H NMR ($CDCl_3$) δ 7.89 (m, 2 H), 7.35 (m, 4 H), 6.60 (m, 2 H, all aromatic H), 4.40 (br s, 2 H, NH_2), 3.06 (t, 2 H, SCH_2), 2.80 (t, 2 H, $COCH_2$), 1.97 (m, 2 H, CH_2). Anal. Calcd for $C_{16}H_{16}ClNOS$: C, 62.84; H, 5.27; N, 4.58; S, 10.48; Cl, 11.59. Found: C, 63.22; H, 5.42; N, 4.98; S, 10.68; Cl, 11.72.

8-Chloro-3,4-dihydro-5-phenyl-2*H*-1,6-benzothiazocine (1e). Amino ketone **5e** (7.65 g, 0.025 mol), *p*-toluenesulfonic acid (0.5 g), and toluene (75 mL) were refluxed using a Dean–Stark water separator for 18 h. The solvent was removed and the residue was eluted through magnesium silicate with methylene chloride. The eluate was crystallized from hexanes to give the product **1e** as yellow crystals: 3.76 g (54%); mp 124–126 °C; IR (KBr) 1634 cm^{-1}; UV (EtOH) 210, 250, 265 nm; mass spectrum, m/z 287 (M^+); ^1H NMR ($CDCl_3$) δ 7.95 (m, 2 H), 7.58 (m, 4 H), 7.06 (m, 2 H, all aromatic H), 3.05 (m, 2 H, SCH_2), 2.00 (m, 4 H, CH_2). Anal. Calcd for $C_{16}H_{14}ClNS$: C, 66.77; H, 4.90; N, 4.87; S, 11.14; Cl, 12.32.

Found: C, 66.71; H, 4.93; N, 4.87; S, 11.25; Cl, 12.54.

1c: 99.5%; mp 133–134 °C; IR (KBr) 1629 cm^{-1}; UV (EtOH) 213, 265 ,292 nm; mass spectrum, m/z 293 (M^+); ^1H NMR ($CDCl_3$) δ 7.56 (m, 3 H), 7.02 (m, 3 H, aromatic and thiophene H), 3.06 (m, 2 H, SCH_2), 2.20 (m, 2 H, N=CCH_2), 1.78 (m, 2 H, CH_2). Anal. Calcd for $C_{14}H_{12}ClNS_2$: C, 57.22; H, 4.12; N, 4.77; S, 21.83; Cl, 12.07. Found: C, 57.11; H, 4.17; N, 4.67; S, 22.03; Cl, 12.18.

1a: 71%; mp 125–127 °C; IR (KBr) 1618 cm^{-1}; UV (EtOH) 203, 265, 290 nm; mass spectrum, m/z 259 (M^+); ^1H NMR ($CDCl_3$) δ 7.68 (dd, 1 H), 7.35 (m, 3 H), 70.5 (m, 3 H, aromatic and thiophene H), 2.97 (m, 2 H, SCH_2), 2.0 (m, 4 H, CH_2).

1d: 84%; mp 100–101 °C; mass spectrum, m/z 305 (M^+). Anal. Calcd for $C_{16}H_{13}ClFNS$: C, 62.84; H, 4.28; N, 4.58; S, 10.49; F, 6.21; Cl, 11.60. Found: C, 62.64; H, 4.33; N, 4.44; S, 10.36; F, 6.30; Cl, 11.63.

1,2,3,3a-Tetrahydro-3a-phenylpyrrolo[2,1-*b*]benzoxazole (8a). *o*-Aminophenol (10.9 g, 0.1 mol), γ-chlorobutyrophenone (18.3 g, 0.1 mol), and pyridine (10 mL) were dissolved in toluene (75 mL) and reacted as above to give the product as a white solid: 13.03 g (55%); mp 74–76 °C; IR (KBr) 1481 cm^{-1}; UV (EtOH) 200, 240, 292 nm; mass spectrum, m/z 237 (M^+); ^1H NMR ($CDCl_3$) δ 7.60 (m, 2 H), 7.32 (m, 3 H), 6.80 (m, 4 H, all aromatic H), 3.50 (m, 2 H, NCH_2), 2.40 (m, 2 H, $PhCCH_2$), 1.9 (m, 2 H, CH_2). Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.71; H, 6.24; N, 5.85.

Similarly **8b** was formed from 5-chloro-2-hydroxyaniline in 37%: bp 150 °C (0.05 mmHg); 10.32 g (37%); IR (KBr) 1480 cm^{-1}; UV (EtOH) 212, 245, 303 nm; mass spectrum, m/z 271 (M^+); ^1H NMR ($CDCl_3$) δ 7.55 (m, 2 H), 7.30 (m, 3 H), 6.70 (m, 3 H, all aromatic H), 3.60 (m, 1 H, NCH_2), 3.40 (m, 1 H, NCH_2), 2.50 (m, 2 H, CCH_2), 1.85 (t, 2 H, CH_2). Anal. Calcd for $C_{16}H_{14}ClNO$: C, 70.72; H, 5.19; N, 5.15; Cl, 13.05. Found: C, 70.72; H, 5.54; N, 4.72; Cl, 12.82.

2-[3-(5,5-Dimethyl-2-phenyl-1,3-dioxan-2-yl)propoxy]-acetanilide (10). *o*-Hydroxyacetanilide (11.20 g, 0.0744 mol) dissolved in dimethylformamide (100 mL) was treated with 50% sodium hydride suspended in mineral oil (3.45 g, 0.075 mol) and the resultant was stirred 0.5 h. A solution of (5,5-dimethyl-2-phenyl-1,3-dioxan-2-yl)propyl chloride (**9**, 19.97 g, 0.0744 mol) in dimethylformamide (50 mL) was then added and the mixture refluxed overnight. The reaction was quenched with water (900 mL) and the aqueous layer was extracted with petroleum ether and then with methylene chloride. The methylene chloride layer was concentrated and the residue distilled in a Kugelrohr apparatus (170 °C (0.05 mmHg)) to give the product as a clear oil which slowly crystallizes: mp 74–75 °C; IR (KBr) 1660 cm^{-1}; UV (EtOH) 208, 245, 280 nm; mass spectrum, m/z 383 (M^+); ^1H NMR ($CDCl_3$) δ 8.28 (m, 1 H), 7.38 (m, 4 H), 6.90 (m, 3 H, all aromatic H), 3.96 (t, 2 H, OCH_2), 3.40 (br s, 4 H, OCH_2), 2.14 (s, 3 H, $COCH_3$), 1.90 (m, 4 H, CH_2), 1.26 (s, 3 H, CH_3), 0.58 (s, 3 H, CH_3). Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 72.54; H, 7.82; N, 3.54.

4-(*o*-Acetamidophenoxy)butyrophenone (11). Acetamido ketal **10** (1.23 g, 0.0032 mol) was dissolved in 75% acetic acid (20 mL) and stirred for 1 day. The solvent was removed and the residue was distilled, bp 190 °C (0.15 mmHg), to give the product as a yellow liquid: 0.87 g (92%); ^1H NMR ($CDCl_3$) δ 8.31 (m, 1 H), 8.05 (m, 2 H), 7.5 (m, 3 H), 7.00 (m, 3 H, all aromatic H), 4.20 (t, 2 H, CH_2), 3.30 (t, 2 H, $COCH_1$), 2.40 (m, 2 H, CH_2), 2.20 (s, 3 H, $COCH_3$). This compound was not further purified but reacted in the next step.

4-(*o*-Aminophenoxy)butyrophenone (12). Acetamido ketal **10** (11.45 g, 0.03 mol) was dissolved in ethanol (40 mL), treated with water (5 mL) and 2.5 N ethanolic hydrogen chloride (20 mL), and refluxed for 4 h. The solution was cooled to 0 °C and the precipitate (5.75 g, 66%) was collected by filtration. Concentration of the filtrate and recooling provided an additional 1.68 g (19%) of the white solid hydrochloride salt of **12**: mp 173–174 °C. Anal. Calcd for $C_{16}H_{17}NO_2$·HCl: C, 65.86; H, 6.22; N, 4.80; Cl, 12.15. Found: C, 66.22; H, 6.41; H, 4.88; Cl, 11.72. The salt was basified with 28% ammonium hydroxide and extracted with methylene chloride (4 × 25 mL). The combined organic layers were concentrated and the residue distilled to give the product **12** as an orange liquid, bp 165 °C (0.1 mmHg), which crystallized upon standing: mp 48–50 °C; 5.61 g (73%); IR (KBr) 1689 cm^{-1}; UV (EtOH) 205, 240, 285 nm; mass spectrum, m/z 255 (M^+); ^1H NMR ($CDCl_3$) δ 8.00 (m, 2 H), 7.50 (m, 3 H), 6.76 (m, 4 H, all aromatic H), 4.10 (t, 2 H, OCH_2), 3.85 (br s, 2 H, NH_2), 3.20 (t, 2 H, $COCH_2$), 2.26 (q, 2 H, CH_2). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.20; H, 7.05; N, 5.28. Acetamido ketone **11** from above was converted to the same amino ketone **12** in 50% using the same conditions.

3,4-Dihydro-5 phenyl-2*H*-1,6-benzoxazocine (13). Amino ketone **12** (2.55 g, 0.01 mol) in toluene (25 mL) was treated with *p*-toluenesulfonic acid (0.2 g) and refluxed using a Dean–Stark water separator for 18 h. The solvent was removed and the residue was filtered through magnesium silicate with methylene chloride to give the product as a yellow crystalline solid, 1.59 g (67%). The analytical sample of **13** was prepared from petroleum ether as fine white crystals: mp 96–98 °C; IR (KBr) 1623 cm^{-1}; UV (EtOH) 205, 245, 320 nm; mass spectrum, m/z 237 (M^+); ^1H NMR ($CDCl_3$) δ 8.00 (m, 2 H), 7.42 (m, 3 H), 7.12 (s, 4 H, all aromatic H), 4.10 (t, 2 H, OCH_2), 2.62 (m, 2 H, N=CCH_2), 1.82 (m, 2 H, CH_2). Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.08; H, 6.64; N, 5.91.

***o*-(2-Phenyl-1-pyrrolidinyl)phenol (14a, R = H).** Pyrrolo[2,1-*b*]benzoxazole **8a** (2.37 g, 0.01 mol) was dissolved in methanol (50 mL) and treated portionwise with sodium borohydride (0.57 g, 0.015 mol). After the mixture was stirred for 0.5 h, acetic acid was added (to neutrality) and the mixture was diluted with water (10 mL). Extraction of the solution with methylene chloride (5 × 15 mL) and subsequent combination of organic layers, treated with charcoal and sodium sulfate, and concentration afforded 2.32 g (97%) of product. The analytical sample was prepared by sublimation: bath, 120 °C (0.05 mmHg); mp 115–117 °C; IR (KBr) 3330 cm^{-1}; UV (EtOH) 212, 252 nm; mass spectrum, m/z 239 (M^+); ^1H NMR ($CDCl_3$) δ 7.20 (m, 5 H), 6.80 (m, 4 H, all aromatic H), 4.30 (t, 1 H, NCHPh), 3.50 (m, H, NCH_2), 2.90 (m, 1 H, NCH_2), 2.0 (m, 4 H, CH_2). Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.05; H, 6.75; N, 5.57.

***o*-(2-Phenyl-1-pyrrolidinyl)phenol Acetate (14a, R = Ac).** Phenol **14a** (R = H) (2.63 g, 0.011 mol) was treated with acetic anhydride (10 mL) containing 1 drop of concetrated sulfuric acid overnight. The reaction was quenched with water (100 mL). The solid was collected by filtration (1.32 g, 43%) and recrystallized from petroleum ether: mp 103–104 °C; IR (KBr) 1754 cm^{-1}; UV (EtOH) 212, 255, 295 nm; mass spectrum, m/z 281 (M^+); ^1H NMR ($CDCl_3$) δ 7.19 (br s, 5 H), 6.80 (dd, 2 H), 6.63 (br t, 2 H, all aromatic H); 4.73 (m, 1 H, NCHPh), 3.78 (m, 1 H, NCH_2), 2.10 (s, 3 H, $COCH_3$), 1.88 (m, 4 H, CH_2). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.45; H, 6.82; N, 4.89.

4-Chloro-2-(2-phenyl-1-pyrrolidinyl)phenol (14b, R = H). Benzoxazole **8b** (5.43 g, 0.02 mol) was treated with sodium borohydride (1.9 g, 0.05 mol) and isolated as above to give the product as a yellow liquid: 2.68 g (49%); IR (KBr) 3333 cm^{-1}; UV (EtOH) 215, 260, 303 m: mass spectrum, m/z 273 (M^+); ^1H NMR ($CDCl_3$) δ 7.17 (m, 5 H), 6.70 (m, 3 H, all aromatic H), 4.27 (br t, 1 H, NCHPh), 3.50 (m, 1 H, NCH_2), 2.93 (m, 1 H, NCH), 2.00 (m, 4 H, CH_2). Anal. Calcd for $C_{16}H_{16}ClNO$: C, 70.20; H, 5.89; N, 5.12; Cl, 12.59. Found: C, 70.55; H, 5.98; N, 5.13; Cl, 12.97.

4-Chloro-2-(2-phenyl-1-pyrrolidinyl)phenol Acetate (14b, R = Ac). Phenol **14b** (R = H) (2.44 g, 0.0089 mol) was treated with acetic anhydride as before to give the product, 1.45 g (52%), which was recrystallized from petroleum ether to prepare the analytical sample, mp 77–78 °C. Anal. Calcd for $C_{18}H_{18}ClNO_2$: C, 68.46; H, 5.75; N, 4.44; Cl, 11.23. Found: C, 68.89; H, 5.78; N, 4.45, Cl, 11.19.

***o*-(2-Phenyl-1-pyrrolidinyl)benzenethiol Acetate (6).** Benzothiazole **4b** (5.06 g, 0.02 mol) in methanol (100 mL) was treated with sodium borohydride (1.9 g, 0.05 mol) and stirred for 2 h. Workup as above and distillation of the crude isolate (Kugelrohr apparatus, 150 °C, 0.1 mmHg) gave the product as a pale yellow liquid, 4.48 g (75%). This material began to revert to the ring-closed starting material almost immediately and no further characterization was attempted. This thiol (4.15 g, 0.016 mol) was dissolved in toluene (25 mL), treated with acetyl chloride (1.2 mL) and triethylamine (2.1 mL), and stirred overnight. The reaction was washed with water (25 mL), dried with sodium sulfate, concentrated, and distilled in a Kugelrohr apparatus (155 °C, 0.1 mmHg) to give the product as a yellow oil (3.83 g, 79%) which was crystallized from petroleum ether: mp 103–105 °C;

IR (KBr) 1703 cm^{-1}; UV (EtOH) 210, 262, 315 nm; mass spectrum, m/z 297 (M^+); ^1H NMR ($CDCl_3$) δ 7.23 (m, 7 H), 6.8 (m, 2 H, all aromatic H), 4.80 (m, 1 H, NCHPh), 4.14 (m, 1 H, NCH_2), 3.26 (m, 1 H, NCH_2), 2.32 (s, 3 H, $COCH_3$), 1.92 (m, 4 H, CH_2).

8-Chloro-3,4,5,6-tetrahydro-5-phenyl-2*H*-1,6-benzothiazocine (15e). Imine **1e** (9.77 g, 0.034 mol) was added in portions to a slurry of lithium aluminum hydride (10.2 g, 0.255 mol) in tetrahydrofuran (300 mL) and the mixture was refluxed for 7 days. The excess hydride was quenched by addition of water (11 mL), 15% sodium hydroxide (11 mL), and water (33 mL) and the mixture was filtered to remove the granular precipitate. The organic layer was diluted with ether (200 mL), washed with water (100 mL) and brine (100 mL), dried over sodium sulfate, and concentrated to give the crude product as an oil, 9.43 g (96%). The product was purified by distillation in a Kugelrohr apparatus, bp 164 °C (0.025 mmHg), with subsequent crystallization from ether to give **15e** as pale cream crystals, 2.94 g (30%): mp 91–92 °C; UV (EtOH) 215, 248, 280, 320 nm; mass spectrum, m/z 289 (M^+); ^1H NMR ($CDCl_3$) δ 7.40 (m, 6 H), 6.88 (m, 2 H, all aromatic H), 4.96 (t, 1 H, CH), 4.54 (br s, 1 H, NH), 2.78 (m, 2 H, SCH_2), 1.90 (m, 4 H, CH_2). Anal. Calcd for $C_{16}H_{16}ClNS$: C, 66.30; H, 5.56; N, 4.83; S, 11.06; Cl, 12.23. Found: C, 66.13, H, 5.66; N, 4.76; S, 11.21; Cl, 12.10.

15a: 74%; mp 69–70 °C; mass spectrum, m/z calcd for $C_{14}H_{15}NS_2$, 261.0646; found, 261.0637. Anal. Calcd: C, 64.32; H, 5.78; N, 5.36. Found: C, 64.46; H, 5.86; N, 5.43.

15c: 80%; bp 162 °C (0.15 mmHg); mp 119–120 °C. Anal. Calcd for $C_{14}H_{14}ClNS_2$: C, 56.83; H, 4.77; N, 4.74; S, 21.68; Cl, 11.99. Found: C, 56.55; H, 4.88; N, 4.70; S, 21.99; Cl, 12.08.

15d: 65%; mp 62–65 °C. Anal. Calcd for $C_{16}H_{15}ClFNS$: C, 62.44; H, 4.91; N, 4.55; S, 10.41; Cl, 11.52; F, 6.17. Found: C, 62.53; H, 5.07; N, 4.54; S, 10.68; Cl, 11.65; F, 6.32.

15b: 68%; bp 142 °C (0.15 mmHz). Anal. Calcd for $C_{16}H_{17}NS$: C, 75.25; H, 6.71; N, 5.49; S, 12.56. Found: C, 75.44; H, 7.07; N, 5.37; S, 12.12.

6-Acetyl-8-chloro-3,4,5,6-tetrahydro-5-phenyl-2*H*-1,6-benzothiazocine (17e). Amine **15e** (0.50 g, 0.0017 mol) in pyridine (6 mL) and acetic anhydride (3 mL) was refluxed for 2 days and the solvents were removed. The residual oil was dissolved in methylene chloride (50 mL) and washed with saturated sodium bicarbonate (2 × 15 mL), 3 N hydrochloric acid (15 mL), and water (15 mL). The dried (sodium sulfate) organic phase was eluted through magnesium silicate and concentrated to give a white solid, 0.54 g (94%). The analytical sample was prepared from ether: mp 104–105 °C; IR (KBr) 1661 cm^{-1}; UV (EtOH) 205, 265 nm; mass spectrum, m/z 331 (M^+); ^1H NMR ($CDCl_3$) δ 7.28 (m, 7 H, aromatic H), 6.30 (t, 1 H, NCH), 6.04 (d, 1 H, aromatic H), 3.4 (m, 1 H, SCH_2), 2.7 (m, 1 H SCH_2), 2.1 (m, 4 H, CH_2), 1.84 (S, 3 H, CH_3). Anal. Calcd for $C_{18}H_{18}ClNOS$: C, 65.14; H, 5.47; N, 4.22; S, 9.66; Cl, 10.68. Found: C, 65.07; H, 5.77; N, 4.25; S, 9.43; Cl, 10.65.

17c: 53%; mp 141–142 °C. Anal. Calcd for $C_{16}H_{16}ClNOS_2$: C, 56.87; H, 4.77; N, 4.15; S, 18.98; Cl, 10.49. Found: C, 56.98; H, 4.85; N, 4.06;, S, 18.68; Cl, 10.21.

17a: 40%; mp 111.5–112 °C. Anal. Calcd for $C_{16}H_{17}NOS_2$: C, 63.33; H, 5.65; N, 4.62; S, 21.13. Found: C, 63.09; H, 5.72; N, 4.70; S, 21.18.

17d: 50%; mp 130–131 °C. Anal. Calcd for $C_{18}H_{17}ClFNOS$: C, 61.79; H, 4.90; N, 4.00; S, 9.17; Cl, 10.13; F, 5.43. Found: C, 62.20; H, 4.91; N, 4.10; S, 9.27; Cl, 10.09; F, 5.38.

17b: 72%; mp 82–83 °C. Anal. Calcd for $C_{18}H_{19}NOS$: C, 72.69; H, 6.44; N, 4.71; S, 10.78. Found: C, 72.48; H, 6.51; N, 4.72; S, 10.71.

6-Methyl-3,4,5,6-tetrahydro-5-(2-thienyl)-2*H*-1,6-benzothiazocine (16a). Amine **15a** (1.77 g, 0.0068 mol) was added to a suspension of sodium hydride (1.01 g, 0.021 mol) in dimethylformamide (30 mL) and stirred for 6 h. Methyl iodide (2.1 mL, 0.035 mol) in dimethylformamide (5 mL) was added and the mixture stirred an additional 20 h. The reaction was quenched with water (50 mL) and extracted with methylene chloride (4 × 25 mL). The combined organic layers were dried over sodium sulfate and concentrated; the residual oil was distilled using a Kugelrohr apparatus (152 °C, 0.075 mmHg) to give the product as a clear viscous oil: 1.40 g (75%); UV 210, 242, 275 nm; mass spectrum, m/z 275 (M^+); ^1H NMR ($CDCl_3$) δ 6.92 (br m, 7 H, aromatic H), 5.12 (m, H, NCH), 3.62 (m, 1 H, SCH_2). Anal. Calcd for $C_{15}H_{17}NS_2$: C, 65.42; H, 6.22; N, 5.09; S, 23.27. Found: C, 65.66; H, 6.28; N, 5.33; S, 23.62.

16c: 54%; bp 148–150 °C (0.1 mmHg). Anal. Calcd for $C_{15}H_{16}ClNS_2$: C, 58.14; H, 5.20; N, 4.52; S, 20.69; Cl, 11.44. Found: C, 58.41; H, 5.37; N, 4.48; S, 20.63; Cl, 11.46.

16b: 61%; bp 138 °C (0.075 mmHg). Anal. Calcd for $C_{17}H_{19}NS$: C, 75.79; H, 7.11; N, 5.20; S, 11.90. Found: C, 76.17; H, 7.12; N, 4.90; S, 12.24.

16d: 86%; bp 162 °C (0.06 mmHg). Anal. Calcd for $C_{17}H_{17}ClFNS$: C, 63.44; H, 5.33; N, 4.35; S, 9.96; Cl, 11.02; F, 5.90. Found: C, 63.64; H, 5.32; N, 4.32; S, 9.85; Cl, 11.04; F, 5.63.

5-Chloro-*N*-methyl-2-[4-(2-thienyl)-3-butenylthio]aniline (18c, R = CH_3). Amine **16c** (0.31 g, 0.001 mol) dissolved in ether (6 mL) was shaken with 5 N hydrochloric acid (6 mL) overnight. The aqueous layer was made alkaline with 5 N sodium hydroxide and extracted with ether (2 × 15 mL). The combined organic layers were dried over sodium sulfate and concentrated to give the product as a yellow oil, 0.30 g (97%). The analytical sample was prepared by thick-layer chromatography: 0.119 g (36%); mass spectrum, m/z calcd for $C_{15}H_{16}ClNS_2$, 309.0345; found, 309.0342; ^1H NMR ($CDCl_3$) δ 7.28 (d, 1 H), 6.85 (m, 2 H), 6.52 (m, 3 H, aromatic and thiophene H), 7.00 (d, J = 16 Hz, 1 H, thi—CH=), 5.98 (dt, J = 8, 16 Hz, 1 H, CH_2CH=), 5.14 (br s, 1 H, NH), 2.80 (m, 5 H, SCH_2, CH_3), 2.35 (q, 2 H, CH_2).

2-[4-(2-Thienyl)-3-butenylthio]aniline (18, R = X = H). Amine **15a** (0.266 g, 0.001 mol) was treated as above and worked up to give 0.268 g (ca. 100%) of product which was purified by thick-layer chromatography to give the product as a yellow oil: 0.027 g (10%); mass spectrum, m/z calcd for $C_{14}H_{15}NS_2$, 261.0645; found, 261.0646; ^1H NMR ($CDCl_3$) δ 7.0 (m, 7 H, aromatic and thiophene H), 6.00 (dt, J = 15, 8 Hz, CH_2CH=), 4.34 (br s, 2 H, NH_2), 2.86 (t, 2 H, SCH_2), 2.45 (m, 2 H, CH_2).

5-Butyl-3,4,5,6-tetrahydro-5-phenyl-2*H*-1,6-benzothiazocine (19a). A solution of imine **1b** (2.5 g, 0.01 mol) in dry tetrahydrofuran (50 mL) under nitrogen atmosphere was treated with 2 M *n*-butyllithium in hexanes (6.25 mL, 0.0125 mol) and the mixture was stirred for 18 h at room temperature. An additional aliquot of butyllithium (1.2 mL, 0.0025 mol) was added and stirring continued for an additional 5 h. The reaction was quenched with water, concentrated to dryness, and triturated with methylene chloride (50 mL). The solution was washed with water (3 × 10 mL), filtered through magnesium silicate, and concentrated, and the residue was purified on a silica gel column (150 g) using hexanes as the eluant to give the product as a clear oil, 1.61 g (52%). The analytical sample was prepared by molecular distillation: 160 °C (0.06 mmHg); UV (EtOH) 208, 246, 273, 283 nm; mass spectrum, m/z 311 (M^+); ^1H NMR ($CDCl_3$) δ 7.20 (m, 9 H, aromatic H), 4.58 (br s, 1 H, NH), 2.68 (m, 2 H, SCH_2), 1.66 (m, 10 H, CH_2), 0.82 (br t, 3 H, CH_3). Anal. Calcd for $C_{20}H_{25}SN$: C, 77.12; H, 8.09; N, 4.50; S, 10.30. Found: C, 77.21; H, 8.23; N, 4.49; S, 10.38.

8-Chloro-3,4,5,6-tetrahydro-5-(*p*-fluorophenyl)-5-methyl-2*H*-1,6-benzothiazocine (19d). A solution of imine **1d** (3.05 g, 0.01 mol) in dry tetrahydrofuran (50 mL) was treated with 1.8 M methyllithium in ether (7 mL, 0.0126 mol) as described above. Additional methyllithium (3.5 mL, 0.0063 mol) was added after 18 h. The reaction was quenched after stirring an additional 3 days and worked up as above to give the product as a yellow oil which slowly crystallized, 1.20 g (40%). The analytical sample was prepared from methylene chloride/hexanes: mp 72–73 °C; UV (EtOH) 213, 239, 262, 305 nm; mass spectrum, m/z 321 (M^+); ^1H NMR ($CDCl_3$) δ 7.54 (m, 3 H), 6.96 (m, 4 H, all aromatic H), 4.54 (br s, 1 H, NH), 2.70 (m, 2 H, SCH_2), 2.12 (m, 2 H, CH_2), 1.64 (m, 2 H, CH_2), 1.50 (s, 3 H, CH_3). Anal. Calcd for $C_{17}H_{17}ClFNS$: C, 63.44; H, 5.33; N, 4.35; S, 9.96; Cl, 11.02; F, 5.90. Found: C, 63.40; H, 5.53; N, 4.30; S, 9.82; Cl, 10.79; F, 6.28.

5-Butyl-8-chloro-3,4,5,6-tetrahydro-5-(*p*-fluorophenyl)-2*H*-1,6-benzothiazocine (19b). Imine **1d** (0.305 g, 0.001 mol) was treated as above with *n*-butyllithium (0.00025 mol) to give 0.0768 g (23%) of the product as a yellow oil: mass spectrum, m/z 363 (M^+); ^1H NMR ($CDCl_3$) δ 7.52 (m, 3 H), 7.00 (m, 3 H, all aromatic H), 4.54 (br s, 1 H, NH), 2.70 (m, 2 H, SCH_2), 0.82 (t, 3 H, CH_3).

8-Chloro-5-methyl-3,4,5,6-tetrahydro-5-(2-thienyl)-2*H*-1,6-benzothiazocine (19c). Imine **1c** (2.94 g, 0.01 mol) was treated with 1.8 M methyllithium (0.02 mol) as above and worked

up to give 1.86 g (60%) of the crude product. The analytical sample was prepared by thick-layer chromatography (5% ethyl acetate in hexanes) to give the product as fine white crystals: 0.78 g (25%); mp 113–114 °C; mass spectrum, m/z calcd for $C_{15}H_{16}ClNS_2$, 309.0413; found, 309.0370. Anal. Calcd for C, 58.14; H, 5.20; N, 4.52. Found: C, 58.09; H, 5.31; N, 4.45.

6-Chloro-3-(2-thienyl)-2*H*-1,4-benzothiazine-$\Delta^{2,\beta}$-ethanol Acetate (21c) and 6-Chloro-3-(2-thienyl)-2*H*-1,4-benzothiazine-2-ethanol Acetate (20c). Imine **1c** (0.294 g, 0.001 mol) was dissolved in glacial acetic acid (10 mL) and treated with lead tetraacetate (0.55 g, 0.0011 mol) at 75 °C for 5 h. The mixture was cooled, diluted with water (10 mL), and extracted with methylene chloride (4 × 15 mL). The combined organic layers were washed with 5% aqueous sodium bicarbonate and water and dried over sodium sulfate; concentration gave a yellow oil (0.33 g) which was a mixture of **21c** (42%) and **20c** (58%) by ^1H NMR analysis. The compounds were separated by thick-layer chromatography with 15% ethyl acetate in hexanes as the eluant. Compound **20c**, 0.127 g (36%), had the properties previously reported[1] and converted slowly to **21c** upon standing. Compound **21c**, mp 102–104 °C, 0.074 g (21%), was reported previously,[1] as was its X-ray crystallographically determined structure.[1]

6-Chloro-3-(2-thienyl)-2*H*-1,6-benzothiazine-$\Delta^{2,\alpha}$-acetaldehyde (22c). When imine **1c** (0.294 g, 0.001 mol) was treated as above with lead tetraacetate (0.985 g, 0.002 mol) overnight at 70 °C, the product mixture consisted of **20c** (14%), **21c** (43%), and the previously unreported aldehyde **22c** (43%) as evidenced by ^1H NMR analysis.

22c: mass spectrum, calcd for $C_{14}H_8ClNOS_2$, 304.9736; found, 304.9733; IR (neat) 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.90 (d, J = 2 Hz, 1 H, COH), 7.5 (m, 3 H), 7.1 (m, 3 H, thiophene and aromatic H), 6.60 (d, J = 2 Hz, =CH).

6-Chloro-3-(*p*-fluorophenyl)-2*H*-1,4-benzothiazine-$\Delta^{2,\beta}$-ethanol Acetate (21d) and 6-Chloro-3-(*p*-fluorophenyl)-2*H*-1,4-benzothiazine-$\Delta^{2,\alpha}$-acetaldehyde (22d). Imine **1d** (3.06 g, 0.01 mol) was treated with lead tetraacetate (5.50 g, 0.011 mol) in glacial acetic acid (50 mL) at 75 °C for 2 h. Workup as above gave the crude reaction product as a yellow oil, 2.09 g. Separation of the mixture was effected on a silica gel column with 5% ethyl acetate in hexanes to give **21d** (0.495 g, 16%) and **22d** (0.404 g, 11%).

21d: mp 61–63 °C; IR (KBr) 1748 cm^{-1}, UV (EtOH) 215 sh, 254, 270 sh, 320, 378 nm; ^1H NMR ($CDCl_3$) δ 7.85 (m, 2 H), 7.53 (m, 1 H), 7.14 (m, 4 H, aromatic H), 6.22 (t, J = 6.3 Hz, 1 H, =CH), 4.82 (d, J = 6.3 Hz, 2 H, CH_2), 2.08 (s, 3 H, CH_3). Anal. Calcd for $C_{18}H_{13}FClNO_2S$: C, 59.75; H, 3.62; N, 3.87; S, 8.86; Cl, 9.80; F, 5.25. Found: C, 59.86; H, 3.82; N, 3.87; S, 9.07; Cl, 10.01; F, 5.11.

22d: mp 189–190 °C; IR (KBr) 1645 cm^{-1}; UV (EtOH) 218 sh, 254, 275 sh, 320, 380 nm; mass spectrum, calcd for $C_{16}H_9ClFNO_5$, 317.0077; found, 317.0092; ^1H NMR ($CDCl_3$) δ 9.80 (d, J = 2.5 Hz, 1 H, COH), 7.66 (m, 3 H), 7.30 (m, 4 H, aromatic H), 6.66 (d, J = 2.5 Hz, =CH—). Anal. Calcd for $C_{16}H_9ClFNOS \cdot {}^1/_2H_2O$: C, 58.81; H, 3.08; N, 4.29; S, 9.81. Found: C, 58.42; H, 3.10; N, 3.99; S, 9.54.

6-Chloro-3-phenyl-2*H*-1,4-benzothiazine-$\Delta^{2,\alpha}$-acetaldehyde (22e). Imine **1e** (0.288 g, 0.001 mol) in glacial acetic acid (10 mL) and lead tetraacetate (0.985 g, 0.002 mol) were heated to 75 °C overnight. Workup as above gave the crude product as a yellow oil, 0.183 g (5%), which was purified using thick-layer chromatography: mp 170–171.5 °C; IR (KBr) 1645 cm^{-1}; UV (EtOH) 238, 252, 270 sh, 312, 395 nm; mass spectrum m/z calcd for $C_{16}H_{10}ClNOS$, 299.0171; found, 299.0171; ^1H NMR ($CDCl_3$) δ 9.78 (d, J = 2 Hz, 1 H, COH), 7.52 (m, 8 H, aromatic H), 6.64 (d, J = 2 Hz, 1 H, =CH—). Anal. Calcd for $C_{16}H_{10}ClNOS \cdot {}^1/_2H_2O$: C, 62.32; H, 3.58; N, 4.54; S, 10.40. Found: C, 62.37; H, 3.67; N, 4.29; S, 10.26.

8-Chloro-3,4-dihydro-5-(2-thienyl)-2*H*-1,6-benzothiazocine 1-Oxide (23). A solution of imine **1c** (2.5 g, 0.0085 mol) in ethanol (650 mL) was treated with sodium periodate (2.16 g, 0.101 mol) in water (25 mL) was the mixture was refluxed 48 h. The reaction mixture was poured into saturated brine (600 mL) and extracted with methylene chloride (3 × 250 mL). The organic layers were dried over sodium sulfate and concentrated to give the product as an off-white solid, 2.63 g (99%). The analytical sample was prepared from methylene chloride–hexane, mp 152–153 °C, with previously reported properties.[1]

Reaction of Imine 1c with Mercuric Acetate. Imine **1c** (0.59 g, 0.002 mol) in glacial acetic acid (20 mL) was treated with mercuric acetate (0.70 g, 0.0022 mol) for 24 h at 70 °C. The reaction was quenched with water (20 mL) and the mixture was extracted with methylene chloride to give 0.435 g of a 1:2 mixture of the starting imine **1c** and amino ketone **5c** as evdienced by ^1H NMR and thin-layer chromatographic analysis. The materials were separated by thick-layer chromatography to give imine **1c**, 0.105 g (18% recovery), mp 132–134 °C, and amino ketone **5c**: 0.156 g (15%); mp 78–80 °C; IR (KBr) 1659 cm^{-1}; mass spectrum, m/z 311 (M^+); ^1H NMR ($CDCl_3$) δ 7.60 (m, 2 H, thiophene H), 7.18 (d, 1 H, aromatic H), 7.06 (t, 1 H, thiophene H), 6.64 (m, 2 H, aromatic H), 4.44 (br s, 2 H, NH_2), 2.98 (t, 2 H, SCH_2), 2.78 (t, 2 H, $COCH_2$). Anal. Calcd for $C_{14}H_{14}ClNOS_2$: C, 53.93; H, 4.53; N, 4.49; S, 20.55; Cl, 11.37. Found: C, 53.92; H, 4.51; N, 4.48; S, 20.23; Cl, 11.45.

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Registry No. **1a**, 76293-59-9; **1b**, 76293-51-1; **1c**, 76293-50-0; **1d**, 87696-85-3; **1e**, 76293-52-2; **2** (X = H), 137-07-5; **2** (X = Cl), 1004-00-8; **3** (Ar = Ph), 939-52-6; **3** (Ar = 2-thienyl), 43076-59-1; **3** (Ar = 4-FC_6H_4), 3874-54-2; **4a**, 87696-86-4; **4b**, 87696-87-5; **5c**, 87696-88-6; **5e**, 87696-89-7; **6**, 87696-90-0; **7** (R = X = H), 95-55-6; **7** (R = H; X = Cl), 95-85-2; **7** (R = Ac; X = H), 614-80-2; **8a**, 87696-91-1; **8b**, 87696-92-2; **9**, 56327-34-5; **10**, 87696-93-3; **11**, 87696-94-4; **12**, 87696-95-5; **12**·HCl, 87696-96-6; **13**, 87696-97-7; **14a** (R = H), 87711-04-4; **14a** (R = Ac), 87696-98-8; **14b** (R = H), 87696-99-9; **14b** (R = Ac), 87697-00-5; **15a**, 87697-01-6; **15b**, 87697-02-7; **15c**, 87697-03-8; **15d**, 87697-04-9; **15e**, 87697-05-0; **16a**, 87697-06-1; **16b**, 87697-07-2; **16c**, 87697-08-3; **16d**, 87697-09-4; **17a**, 87697-10-7; **17b**, 87697-11-8; **17c**, 87697-12-9; **17d**, 87697-13-0; **17e**, 87697-14-1; **18a** (R = H), 87697-15-2; **18c** (R = Me), 87697-16-3; **19a**, 87697-17-4; **19b**, 87697-18-5; **19c**, 87697-19-6; **19d**, 87697-20-9; **20c**, 76293-53-3; **21c**, 76293-54-4; **21d**, 87697-21-0; **22c**, 87697-22-1; **22d**, 87697-23-2; **22e**, 87697-24-3; **23**, 76293-58-8.