New Synthesis of Some Arylthio-Substituted 2,3,4,5-Tetrahydro-1*H*-3-benzazepines[1]

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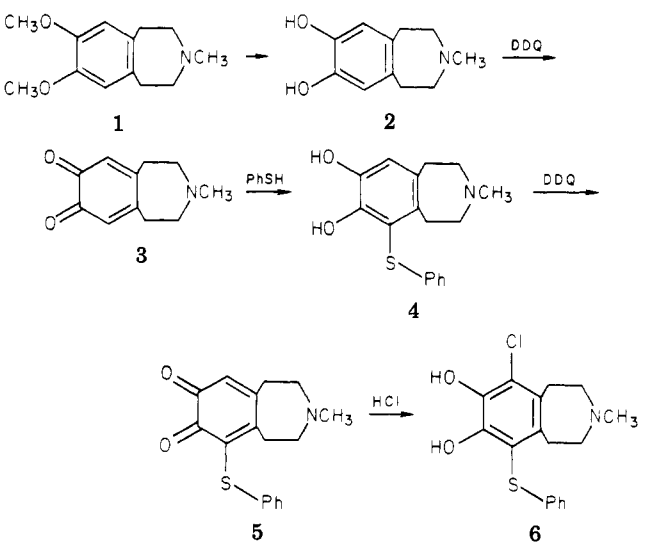
A new synthesis of 6-chloro-2,3,4,5-tetrahydro-7,8-dihydroxy-3-methyl-9-(phenylthio)-1*H*-3-benzazepine (**6**, SK&F 84636), a recently reported potent neuroleptic agent, was developed. This practical synthetic sequence involves Friedel–Crafts phenylsulfenylation of 2,3,4,5-tetrahydro-7,8-dimethoxy-3-methyl-1*H*-3-benzazepine (**1**), followed by oxidation to the corresponding sulfoxide **13**, reductive chlorination, and mild nucleophilic ether cleavage. The Friedel–Crafts reaction with benzenesulfenyl chloride, direct organometallic sulfenylation, thionyl chloride induced reductive chlorination, and the methionine–methanesulfonic acid demethylation reactions are the subjects of this study.

The synthesis and antidopaminergic and neuroleptic activities of 6-chloro-7,8-dihydroxy-3-methyl-9-(phenylthio)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**6**) have been described recently.[2] Interest in further biological evaluation required additional supplies of **6**. As a result of the low and erratic yield in the hydrogen chloride–quinone addition step (**5** to **6** in Scheme) and subsequent difficulties in purification, an alternative approach to **6** was investigated as part of an extensive study of the chemistry and biological properties of 3-benzazepines.[3-7] We now report (Schemes II and III) a new and improved synthesis of **6**. Our strategy was to introduce the phenylthio moiety by the Friedel–Crafts phenylsulfenylation of the ethyl carbamate **8** of the 3-benzazepine **7**[8] and then incorporate the chloro substituent by reductive chlorination of th sulfoxide **13**, followed by mild nucleophilic ether cleavage using methionine in methanesulfonic acid to give **6**.

As illustrated in Scheme II, two aromatic phenylsulfenylation procedures were developed to prepare the intermediate (phenylthio)-3-benzazepine **12**. In the first synthetic pathway, the benzazepine **7** was converted to the urethane **8** in 95% yield with ethyl chloroformate.

The Friedel–Crasts phenylsulfenylation[9] with benzenesulfenyl chloride utilizing anhydrous zinc chloride as the Lewis acid catalyst afforded the 6-(phenylthio)urethane **9** in 43% yield. Lithium aluminum hydride reduction gave the first key intermediate **12** in 50% yield (20% overall yield from **7**). Direct Lewis acid catalyzed phenylsulfenylation reaction of the basic 3-benzazepine **7** or its methyl congener **1**[8] failed to yield the expected products, apparently as a consequence of interaction between the basic nitrogen and the reactive phenylsulfenium cation. Protection of the nitrogen atom as a carbamate circumvented the unwanted reaction.

Scheme I



Alternatively, the 6-(phenylthio)-3-benzazepine **12** can be prepared in 35% overall yield from **7** by bromination, Eschweiler–Clarke N-methylation, and organolithiation, followed by sulfenylation with diphenyl disulfide as illustrated in Scheme II.

Our original intent was to convert **12** to the 6-sulfinyl catecholamine **15** via the sulfoxide **13** from **12** (Scheme III) and use intermediate **15** to prepare the final product **6**. However, treatment of the sulfoxide **13**, obtained by sodium periodate oxidation of **12** in 85% yield, with boron tribromide failed to produce **15** but instead yielded a mixture of **4** and **16** according to GC/MS analysis. The catecholamine **4** is apparently the direct result of simple reduction of the sulfoxide, whereas the bromo(phenylthio) catecholamine **11** represents a net reductive bromination of **13** induced by boron tribromide.

The apparent reductive bromination of **13** prompted us to investigate the use of thionyl chloride as a reductive chlorinating agent in the synthesis of **6**. Treatment of sulfoxide **13** in methylene chloride at −78 to +25 °C with 10% excess of thionyl chloride gave a product mixture which TLC indicated to consist of only two compounds. The usual workup and silica gel column chromatography gave reductively chlorinated product **14** (55% yield) and the simple reduction product **12** (14% yield). Recovered **12** can be reoxidized and reductively chlorinated to **14**; however, optimization of conditions and yields was not

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(3) J. Weinstock, J. W. Wilson, D. L. Ladd, C. K. Brush, F. R. Pfeiffer, G. Y. Kuo, K. G. Holden, N. C. F. Yim, R. A. Hahn, J. R. Wardell, Jr., A. J. Tobia, P. E. Setler, H. M. Sarau, and P. T. Ridley, *J. Med. Chem.*, *23*, 973 (1980).
(4) P. E. Setler, H. M. Sarau, C. L. Zirkle, and H. L. Saunders, *Eur. J. Pharmacol.*, **50**, 419 (1978).
(5) R. G. Pendleton, L. Samler, C. Kaiser, and P. T. Ridley, *Eur. J. Pharmacol.*, **51**, 19 (1978).
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(7) R. A. Hahn and J. R. Wardell, Jr., *J. Cardiovasc. Pharmacol.*, **2**, 583 (1980).
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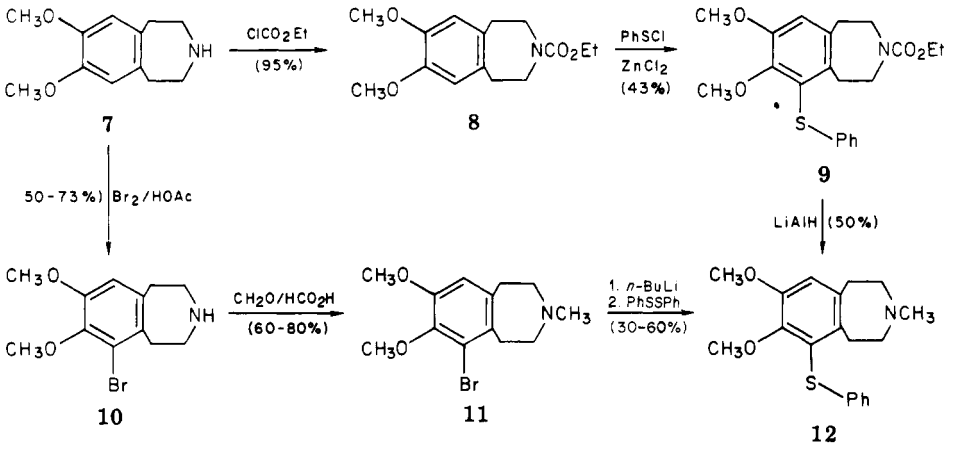
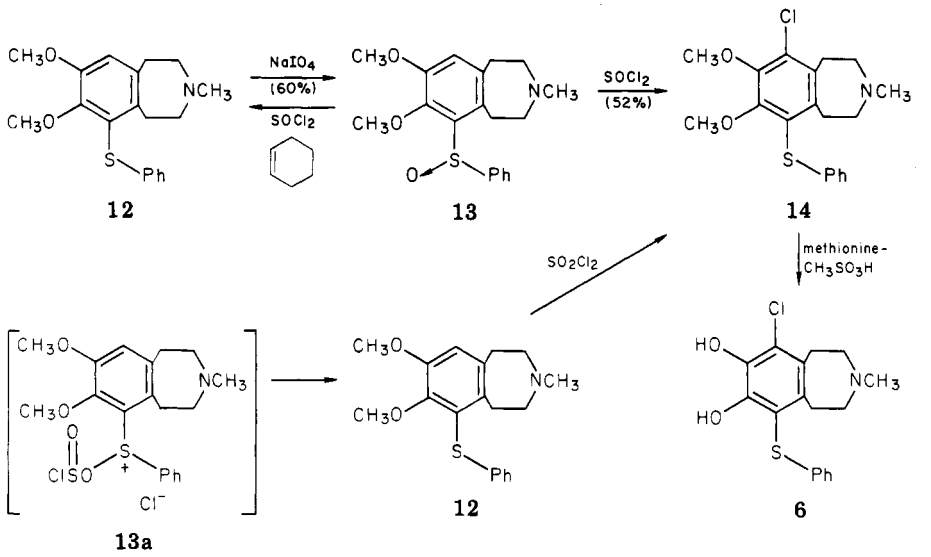
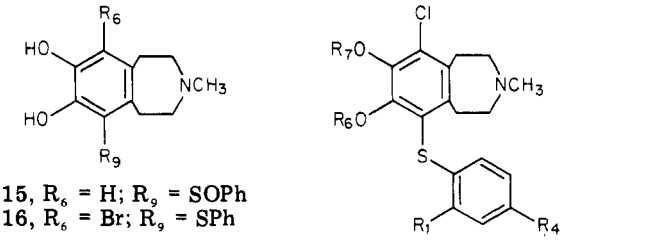
Scheme II



Scheme III





15, R_6 = H; R_9 = SOPh
16, R_6 = Br; R_9 = SPh

14, R_1 = R_4 = H; R_6 = R_7 = CH_3
17, R_6 = R_7 = CH_3; R_1 = H; R_4 = Cl
18, R_6 = R_7 = CH_3; R_1 = R_4 = Cl
19, R_6 = R_7 = H; R_1 = H; R_4 = Cl
20, R_6 = R_7 = H; R_1 = R_4 = Cl

pursued. In a further study with excess thionyl chloride and longer reaction times, polychlorinated benzazepines **17** and **18** were obtained after HPLC separation of the reaction mixture.

Several reports[10] of deoxygenative chlorination of diaryl sulfoxide in refluxing thionyl chloride to give complicated mixtures of diaryl sulfide and chlorinated diaryl sulfides have appeared; however, no practical utilization of the procedure has yet been reported. Although the detailed mechanism of the thionyl chloride induced reductive chlorination of **13** is not known, there is some evidence suggesting that the reaction proceeds through the initial formation of an oxysulfonium chloride complex, **13a**, which then collapses to the deoxygenated product **12** and chlorine or sulfuryl chloride. Subsequent chlorination of **12** by the chlorinating species formed in situ may thus result in the formation of **14**, **17**, and **18** (Scheme III). Indeed, in separate experiments, treatment of sulfide **12** with gaseous chlorine or sulfuryl chloride at low temperatures gave a mixture of the chlorinated products. Furthermore, in the presence of cyclohexene and thionyl chloride, sulfoxide **13** as almost quantitatively converted to sulfide **12**. Apparently cyclohexene serves as an effective molecular chlorine scavenger; no chlorinated proucts were observed. Use of cyclohexene or reducing agents in conjunction with thionyl chloride has been reported previously by Olah[11] and other investigators[10] as a mild method of reducing simple diaryl

(10) (a) I. Granoth, *J. Chem. Soc., Perkin Trans.* 1, 2166 (1974); (b) C. W. Bird, *J. Chem. Soc. C* 1230 (1968).

(11) G. A. Olah, R. Malhotra, and S. C. Narong, *Synthesis*, 58 (1979).

sulfoxides to the corresponding sulfides.

Although a variety of reagents such as boron tribromide and refluxing 48% hydrobromic acid effectively demethylate aryl methyl ethers, we utilized a mild and efficient procedure using methionine in methanesulfonic acid[12] for converting the key dimethyl ether intermediate **14** into catecholamine **6**. Treatment of **14** with excess methionine in methanesulfonic acid at room temperature produced compound **6**. Catecholamines **19** and **20** were similarly prepared from their corresponding methyl ethers **17** and **18**. Conditions and yields of the methionine-induced O-demethylation were not optimized.

Experimental Section

Melting points were determined by using a Thomas-Hoover Unimelt capillary apparatus and are uncorrected. IR spectra were taken as Nujol mulls on a Perkin-Elmer Infracord spectrophotometer, and absorptions were reported in wavenumbers. NMR spectra were recorded on a Perkin-Elmer R24 spectrometer and are reported in parts per million downfield from internal Me_4Si. Mass spectra were determined by using a Hitachi Perkin-Elmer RMN-6E spectrometer. Combustion analysis were determined by the Analytical and Physical Chemistry Section of Smith Kline & French Laboratories.

3-(Ethoxycarbonyl)-2,3,4,5-tetrahydro-7,8-dimethoxy-1*H*-3-benzazepine (8). The dimethoxy compound **7**[8] (42.6 g, 0.206 mol) in 1.0 L of toluene was treated with triethylamine (35.7 mL, 0.256 mol) and ethyl chloroformate (24.5 mL, 0.256 mol) at room temperature. After the reaction mixture was refluxed overnight, the solid was filtered, and the filtrate was concentrated. The resulting brownish yellow solid (57 g, quantitative yield) was recrystallized from ethyl acetate: mp 91–93 °C; NMR ($CDCl_3$) δ 6.5 (2 H, s), 4.25–3.9 (2 H q), 3.75 (6 H, s), 3.55–3.4 (4 H, m), 2.8–2.6 (4 H, m), 1.35–1.1 (3 H, t); IR (Nujol) 2750 (s), 1650 (s), 1570 (m), 1500 (s), 1410 (s) cm^{-1}; mass spectrum, *m/e* 279 (M^+). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.57; H, 7.62; N, 4.69.

3-(Ethoxycarbonyl)-2,3,4,5-tetrahydro-7,8-dimethoxy-6-(phenylthio)-1*H*-3-benzazepine (9). To a stirred solution of the dimethoxyurethane **8** (57 g, 0.204 mol) in 1.0 L of carbon tetrachloride at −15 °C (ice/methanol) under argon was added dropwise benzenesulfenyl chloride (34.2 mL, 0.306 mol) over 20 min. Solid anhydrous zinc chloride (22.5 g, 0.165 mol) was added all at once, and stirring was continued at room temperature overnight. To complete the reaction, additional amounts of benzenesulfenyl chloride (10 mL) and zinc chloride (11 g) were added, and stirring was continued for another 24 h at room temperature. The suspension was filtered and the filtrate concentrated. The resulting oil was chromatographed on a column of silica, eluting with increasing concentrations of ethyl acetate in hexane (20–50%). The phenylthio product (33.3 g, 43%) was obtained as an oil: NMR ($CDCl_3$) δ 7.1 (5 H, s) 6.8 (1 H, s), 4.3–3.9 (2 H, q), 3.85 (3 H, s), 3.75 (3 H, s), 3.4–2.7 (8 H, m), 1.4–1.1 (3 H, t); IR (neat) 2800 (m), 1650 (s), 1570 (m), 1440 (s), 1405 (s), cm^{-1}; mass spectrum, *m/e* 387 (M^+).

6-Bromo-2,3,4,5-tetrahydro-7,8-dimethoxy-1*H*-3-benzazepine (10). The dimethoxy compound **7**[8] (140 g, 0.574 mol) was dissolved with heating (65 °C) in 750 mL of glacial acetic acid. This warm solution was then treated in a dropwise fashion with 31.5 mL (0.574 mol) of bromine in 100 mL of glacial acetic acid. After the addition was completed, the reaction was heated to 65 °C for 1 h and then allowed to attain room temperature. The precipitate which formed was collected and recrystallized from methanol/acetone/ether to give 130.4 g (71%) of product; mp (HCl salt) 217–218 °C; NMR (Me_2SO-d_6) δ 7.15 (1 H, s), 3.9 (3 H, s), 3.8 (3 H, s), 3.5 (8 H, br s); IR (Nujol) 2810 (s), 2400 (2), 1580 (m), 1445 (s), 1400–1300 (several bands, m) cm^{-1}; mass spectrum, *m/e* 285 (M^+).

6-Bromo-2,3,4,5-tetrahydro-7,8-dimethoxy-3-methyl-1*H*-3-benzazepine (11). A solution of 112.4 g (0.35 mol) of **10** in 450 mL of 90% formic acid was treated with 100 mL of a 37% solution of formaldehyde. The reaction mixture was refluxed for 20 h, diluted with ice–water, adjusted to pH 11 with sodium hydroxide, and extracted with methylene chloride. Drying with sodium sullfate and evaporation of the solvent gave 96 g (91%) of a brown oil: NMR ($CDCl_3$) δ 6.7 (1 H, s), 3.88 (3 H, s), 3.82 (3 H, s), 3.3–2.4 (8 H, m), 2.25 (3 H, s); IR (neat) 2850 (s), 2700 (s), 1580 (s), 1545 (w), 1440 (s), 1355 (m) cm^{-1}; mass spectrum, *m/e* 299 (M^+).

2,3,4,5-Tetrahydro-7,8-dimethoxy-3-methyl-6-(phenylthio)-1*H*-3-benzazepine (12). Method A. To a flask flushed with argon was added 700 mL of tetrahydrofuran and 12.9 g (0.34 mol) of lithium aluminum hydride. The sulfide **9** (32.9 g, 0.085 mol) dissolved in 400 mL of tetrahydrofuran was added dropwise over 40 min to this mechanically stirred suspension. After the addition was completed, the reaction mixture was refluxed for 3 h and then quenched by the gradual and sequential addition of 12.9 mL of water, 12.9 mL of 20% sodium hydroxide, and 38.7 mL of water. The resulting suspension was stirred overnight. The solid was collected and washed thoroughly with water, and the filtrate was concentrated. The resulting oil (25 g) was column chromatographed on silica, eluting with increasing concentrations of methanol in chloroform (2–10%). The product (13 g, 47%) was obtained as an oil: NMR ($CDCl_3$) δ 7.1 (5 H, s), 6.8 (1 H, s), 3.8 (3 H, s), 3.7 (3 H, s), 3.35–2.4 (8 H, m), 2.3 (3 H, s); IR (neat) 2900 (s), 2750 (s), 1580 (s), 1450 (s), 1360 (m) cm^{-1}; mass spectrum, *m/e* 329 (M^+).

Method B. A solution of 96 g (0.32 mol) of **11** in 450 mL of dry toluene was added dropwise to a flask at −78 °C (dry ice/2-propanol) under argon containing 474 mL (1.09 mol, 2.2 M in hexane) of *n*-BuLi diluted with 500 mL of anhydrous ether. After the addition was completed (45 min), a solution of 310.8 g (1.42 mol) of diphenyl disulfide in 2 L of anhydrous ether was added. The reaction mixture was kept at −78 °C for 5 h and then allowed to attain room temperature overnight. The reaction mixture was acidified with dilute HCl. The separated aqueous layer was washed twice with ether and then basified with aqueous sodium hydroxide. The product was extracted into methylene chloride. The organic extract was dried with sodium sulfate and evaporated to give 109.33 g of a brown oil. This crude product was chromatographed on a column of silica, eluting with increasing concentrations of methanol in chloroform (2–20%). The product was isolated as a yellow oil (83.22 g, 77%). All spectral and TLC data were consistent with the sample prepared in method A.

2,3,4,5-Tetrahydro-7,8-dimethoxy-3-methyl-6-(phenylsulfinyl)-1*H*-3-benzazepine (13). The 6-thiophenyl compound **12** (13 g., 0.0395 mol) in 750 mL of methanol was treated with 0.5 M sodium periodate (0.158 mol, 315.5 mL) at room temperature. After being stirred for 1 h, the suspension was heated to 40 °C, and stirring was continued overnight. The inorganic solid was filtered and the filtrate concentrated. The residue was partitioned between chloroform and water. The aqueous layer was extracted with chloroform, and then the combined extracts were dried with anhydrous sodium sulfate and concentrated. The resulting oil (10.4 g, 76%) was triturated with ether, yielding an off-white solid: 8.3 g (61%); mp 128–132 °C; NMR ($CDCl_3$) δ 7.8–7.4 (5 H, m), 6.9 (1 H, s), 3.9 (6 H, s), 3.4–2.4 (8 H, m), 2.3 (3 H, s); IR (neat) 2800 (s), 2650 (s), 1560 (s), 1440 (s), 1350 (m), 1060 (s) cm^{-1}; mass spectrum, *m/e* 345 (M^+).

6-Chloro-7,8-dimethoxy-3-methyl-9-(phenylthio)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (14). Method A. To a solution of the sulfoxide **13** (8.3 g, 0.024 mol) in 200 mL of methylene chloride which had been cooled to −78 °C (dry ice/2-propanol) and flushed with argon was added dropwise 12.9 g (0.108 mol) of thionyl chloride in 75 mL of methylene chloride. The addition was carried out over 1 h, and the reaction mixture was stirred at 0–10 °C for 4 h and then allowed to gradually warm to room temperature. After stirring for 1 day, the reaction mixture was concentrated, and the resulting oil in methylene chloride was washed with dilute sodium hydroxide solution. The aqueous layer was extracted with methylene chloride, and the combined extracts were dried with anhydrous sodium sulfate and then concentrated. The resulting brown oil (9 g) was chromatographed on silica, eluting with increasing concentrations of methanol in chloroform (2–10%). The product was isolated as an oil (4.8 g, 55%); a pure fraction of the 6-phenylthio, dechloro compound **12** was also isolated (1.11 g, 14%). The product was converted into a crystalline HCl salt: mp 209–210 °C; NMR ($CDCl_3$, free base) δ 7.3–7.0

(12) F. Nobutaka, I. Hiroshi, and Y. Harauki, *J. Chem. Soc., Perkin Trans. 1*, 2288 (1977).

(5 H, m), 3.9 (3 H, s), 3.7 (3 H, s), 3.5–3.1 (4 H, m), 2.7–2.35 (4 H, m), 2.3 (3 H, s); IR (neat) 2900 (s), 2750 (s), 1580 (s), 1545 (m), 1475 (s), 1450 (s), 1400 (s), 1375 (s), 1330 (w), 1310 (m), 1280 (s) cm^{-1}; mass spectrum, m/e 363 (M^+). Anal. Calcd for $C_{19}H_{22}ClNO_2S \cdot 0.25H_2O$: C, 56.37; H, 5.85; N, 3.46,; Cl, 17.51. Found: C, 56.40: H, 5.89; N, 3.62; Cl, 17.55.

Method B. The reaction was carried out as described in method A by using 50 mg (0.000 15 mol) of **12** in 3 mL of methylene chloride and 0.05 mL (0.000 67 mol) of sulfuryl chloride in 2 mL of methylene chloride. The identity of the crude product was established as **14** by TLC and mass spectral analyses.

6-Chloro-2,3,4,5-tetrahydro-7,8-dihydroxy-3-methyl-9-(phenylthio)-1*H*-3-benzazepine (6). To a solution of the dimethoxy compound **14** (3 g., 8.3 mmol) in 120 mL of methanesulfonic acid was added 6.9 g (0.046 mol) of L-methionine. The reaction mixture was stirred for 48 h at room temperature, poured into ice–water, and adjusted to pH 7.6 by gradual addition of concentrated ammonium hydroxide. The resulting solid was collected. Methionine was selectively removed from the product by dissolving the bulk of the material in ethanol. The filtrate was concentrated and then partitioned between ethyl acetate and aqueous ammonium hydroxide (pH 9). The aqueous layer was exhaustively extracted with ethyl acetate, and the combined organic extracts were dried with anhydrous sodium sulfate and then concentrated. The resulting solid was treated with decolorizing carbon and recrystallized from Me_2SO to give 0.89 g (32%) of crystals: mp 174–176 °C; NMR (TFA) δ 7.3–6.9 (5 H, m), 4.0–3.1 (8 H, m), 2.8 (3 H, s); IR (Nujol) 3300 (w), 2800 (s), 1560 (m), 1440 (s), 1360 (m), cm^{-1}; mass spectrum, m/e 335 (M^+). Anal. Calcd for $C_{17}H_{18}ClNO_2S \cdot 0.75H_2O$: C, 58.45; H, 5.62; N, 4.01; Cl, 10.15. Found: C, 58.22; H, 5.51; N, 3.94; Cl, 9.95.

6-Chloro-9-[(4-chlorophenyl)thio]-2,3,4,5-tetrahydro-7,8-dimethoxy-3-methyl-1*H*-3-benzazepine (17) and 6-Chloro-9-[(2,4-dichlorophenyl)thio]-2,3,4,5-tetrahydro-7,8-dimethoxy-3-methyl-1*H*-3-benzazepine (18). The reaction was carried out as described prevously by using 90 g (0.261 mol) of **13** in 800 mL of methylene chloride and 86 mL (1.18 mol) of thionyl chloride in methylene chloride. The reaction mixture was worked up after 3 days at room temperature to give the di- and trichlorinated compounds **17** and **18** in yields of 50.8% and 26.3%, respectively, as determined by GC/MS. After a number of unsuccessful column chromatographies (open, wet column, medium-pressure JY column), **17** and **18** were separated by preparative HPLC (two Prepak silica columns, eluting with 3% methanol in methylene chloride) in yields of 2% and 4%, respectively. The dichlorinated compound **17** was converted to a crystalline HCl salt: mp 221–223 °C dec; NMR (Free base, $CDCl_3$) δ 7.2–6.8 (4 H, q), 3.85 (3 H, s), 3.75 (3 H, s)8 3.40–3.25 (4 H, m), 2.6–2.35 (4 H, m), 2.3 (3 H, s); IR (neat) 2800 (s), 2700 (s), 1520 (m), 1450 (s), 1430 (s), 1390 (s), 1350 (s), 1310 (m), 1200 (m), 1275 (s) cm^{-1}; mass spectrum, m/e 397 (M^+). Anal. Calcd for $C_{19}H_{21}Cl_2NO_2S \cdot HCl$: C, 52.48; H, 5.10; N, 3.22; Cl, 24.46. Found: C, 52.45; H, 5.14; N, 3.37; Cl, 24.31. The trichlorinated compound **18** was recrystallized from ethyl acetate: mp 126.5–129 °C; NMR ($CDCl_3$) δ 7.5–6.5 (3 H, m), 4.0 (3 H, s), 3.9 (3 H, s), 3.45–3.25 (4 H, m), 2.8–2.4 (4 H, m), 2.3 (3 H, s); IR (Nujol) 2900 (s), 1540 (w), 1450 (s), 1400 (m), 1360 (2), 1300 (w), 1280 (m) cm^{-1}; mass spectrum, m/e 431 (M^+). Anal. Calcd for $C_{19}H_{20}Cl_3NO_2S$: C, 52.78; H, 4.79; N, 3.14; Cl, 23.85. Found: C, 53.19; H, 4.67; N, 3.25; Cl, 23.86.

6-Chloro-9-[(4-chlorophenyl)thio]-2,3,4,5-tetrahydro-7,8-dihydroxy-3-methyl-1*H*-3-benzazepine (19). The starting dimethoxy compound **17** (1.4 g, 0.0035 mol) was dissolved in 60 mL of methansulfonic acid; L-methionine (2.63 g, 0.0176 mol) was then added all at once. The reaction was stirred at room temperature for 24 h, poured into ice–water and then adjusted to pH 8 with concentrated ammonium hydroxide. The product was extracted into ethyl acetate, and the organic extract was then dried with anhydrous sodium sulfate and concentrated. The crude solid was recrystallized from ethyl acetate to give 440 mg (34%) of product: mp 204 °C dec; NMR (Me_2SO-d_6) δ 7.4–6.9 (4 H, q) 3.4–2.9 (4 H, m), 2.7–2.4 (4 H, m), 2.3 (3 H, s); IR (Nujol) 3200 (w), 2800 (s), 1430 (s), 1345 (s), 1320 (m), 1250 (s), cm^{-1}; mass spectrum, m/e 369 (M^+). Anal. Calcd for $C_{17}H_{17}Cl_2NO_2S$: C, 55.14; H, 4.63; N, 3.78. Found: C, 54.74; H, 4.85; N, 3.58.

6-Chloro-9-[(2,4-dichlorophenyl)thio]-2,3,4,5-tetrahydro-7,8-dihydroxy-3-methyl-1*H*-3-benzazepine (20). The reaction was carried out as described previously by using 1.63 g (3.78 mmol) of **18**, 2.82 g (0.0189 mol) of L-methionine, and 80 mL of methanesulfonic acid. After the usual workup, the crude solid was recrystallized from ethyl acetate to give 710 mg (46%) of product: mp 202–203 °C dec; NMR (Me_2SO-d_6) δ 7.5–6.4 (3 H, m), 3.3–2.9 (4 H, m), 2.7–2.4 (4 H, m), 2.3 (3 H, s); IR (Nujol) 3200 (w), 2850 (s), 1440 (s), 1350 (m), 1330 (w), 1250 (m), cm^{-1}; mass spectrum, m/e 403 (M^+). Anal. Calcd for $C_{17}H_{16}Cl_3NO_2S$: C, 50.45; H, 3.98; N, 3.46. Found: C, 50.55; H, 4.27; N, 3.32.

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Registry No. 6, 73943-05-2; **7**, 37462-47-8; **8**, 73943-26-7; **9**, 73943-27-8; **10**, 73954-41-3; **11**, 73943-23-4; **12**, 73942-96-8; **13**, 73943-28-9; **14**, 82614-92-4; **17**, 82614-93-5; **18**, 82614-94-6; **19**, 82614-95-7; **20**, 82614-96-8.

Synthesis and Ring-Opening Reactions of Functionalized Spiro-Δ^3-1,2,3-thiadiazoline 1-Oxides and 1,1-Dioxides. A New Approach to Unsymmetrically Disubstituted α-Chloro Azines

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A general procedure for the synthesis of functionalized spiro-Δ^3-1,2,3-thiadiazoline 1-oxides from previously unreported (perfluoroalkylidene)hydrazides derived from cycloalkanecarboxylic acids (**3**) is described. Reaction of **3** with thionyl chloride in the presence of dimethylformamide gives diastereoisomeric pairs of 4-chloro-2-(1-chloroperfluoroalkyl)-spiro-Δ^3-1,2,3-thiadiazoline 1-oxides **6**, **7**, and **8**. Cleavage of **7** lead to 4-chloro-1-thia-2,3-diazaspiro[4.5]dec-3-ene 1-oxide (**14**). Peracid oxidation of **7** gave the corresponding 1,1-dioxide **10**. Both nucleophilic and thermal reactivity of **10** have been investigated. Reaction of **10** with nucleophilic reagents afforded products resulting from initial dehydrochlorination and ring opening to *N*-[(1-cyanocyclohexyl)sulfonyl]trifluoroacetimidoyl chloride (**15**). Thermolysis of **10**, at 110 °C, resulted in dissociation (–SO_2, –HCl) to give *N'*-[(2,2,2–trifluoroethylidene)amino]-1-cyclohexenecarboximidoyl chloride (**20**). Some reactions of **20** are also described.

Perfluorinated aliphatic aldehyde aroylhydrazones react with thionyl chloride in the presence of dimethylformamide at reflux to give 1-aryl-1-chloro-4-(perfluoroalkyl) azines.[1] Surprisingly, we find that the acylated hydrazine,

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