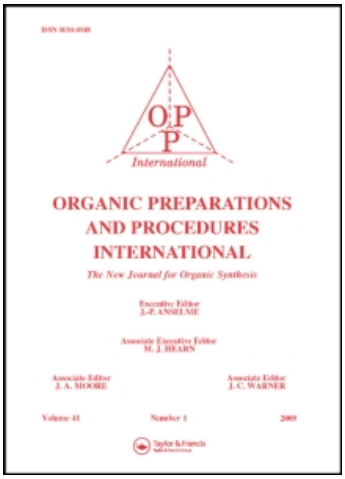

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N-SUBSTITUTED 3-OXA- AND 3-THIA-7-AZABICYCLO[3.3.1]NONANES AS POTENTIAL PRECURSORS OF ANTIARRHYTHMICS

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N-SUBSTITUTED 3-OXA- AND 3-THIA-7-AZABICYCLO[3.3.1]NONANES AS POTENTIAL PRECURSORS OF ANTIARRHYTHMICS

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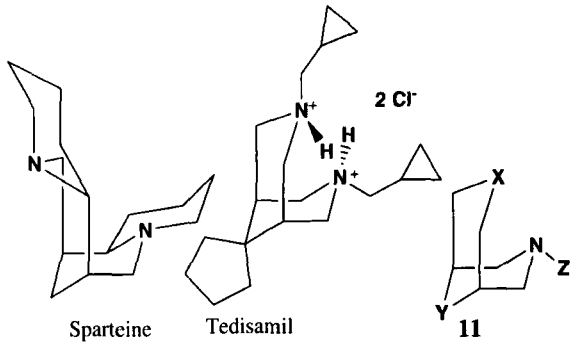
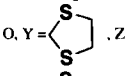
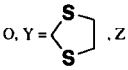
The need for useful antiarrhythmic agents to treat lethal ventricular tachycardia of the heart remains critical.[1] The skeleton of 3,7-diazabicyclo[3.3.1]nonane constitutes the B and C rings of a variety of lupane alkaloids, *e. g.* sparteine, which is a tetracyclic alkaloid possessing antiarrhythmic



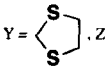
11a X = O, Y = CH_2, Z = CH_2Ph ($HClO_4$)

11b X = O, Y =  , Z = CH_2Ph

11c X = O, Y =  , Z = CH_2Ph ($HClO_4$)

11d X = O, Y = CH_2, Z = C(O)-C_6H_4-4-(1-imidazole) ($HClO_4$)

11e X = O, Y = CH_2, Z = SO_2-C_6H_4-4-NH_2

11f X = S, Y =  , Z = CH_2Ph ($HClO_4$)

11g X = S, Y = CH_2, Z = CH_2Ph (HCl)

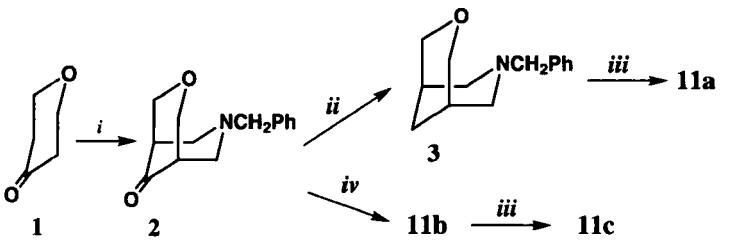
11h X = S, Y = CH_2, Z = C(O)-C_6H_4-4-(1-imidazole) ($HClO_4$)

properties.[2] A small number of examples[3] have appeared which demonstrate that the smaller combination of the B and C rings can lead to antiarrhythmic properties, but the area is still in its infancy.[4] We report herein the preparation and characterization of several unique 3-oxa- and 3-thia-7-azabicyclo[3.3.1]nonanes **11** which have potential as precursors for derivatization to important antiarrhythmics. The structures bear some resemblance to that of tedisamil,[5] a relatively new Class III antiarrhythmic agent which prevented electrically-induced ventricular fibrillation in rats.[6] In the general, structure **11**, X is O or S while Y = CH_2 or SCH_2CH_2S, the latter being a subunit similar to the five-membered spiro hydrocarbon ring in tedisamil. Antiarrhythmic properties of **11** await evaluation.

The rationale for the synthesis of the 3,7-diheterabicyclo[3.3.1]nonanes is based on the following reasoning. 3,7-Diheterabicyclo[3.3.1]nonanes possess the B and C rings, as in sparteine,

and some have exhibited good antiarrhythmic activity in dog models.[7] Compounds **11a** and **11b** are related to the hydroperchlorate of the precursor amine to **11g** which possesses[7] Class Ib antiarrhythmic activity. Amines **11b**, **11c**, and **11f** have structural features reminiscent of those in Tedisamil while **11d** and **11h** are expected to exhibit Class III anatiarrhythmic activity as is known[8] with certain imidazole-substituted antiarrhythmics. Sulfonamide **11e** was included since some sulfonyl-aminobenzamides possess[9] Class III anti-arrhythmic activity. Classifications of antiarrhythmic action by agents are well established.[10]

The conversion of **1**→**2** (*Scheme 1*) was a simple double Mannich reaction, but, interestingly, the addition of HCl markedly facilitated the process. Wolff-Kishner reduction of the carbonyl

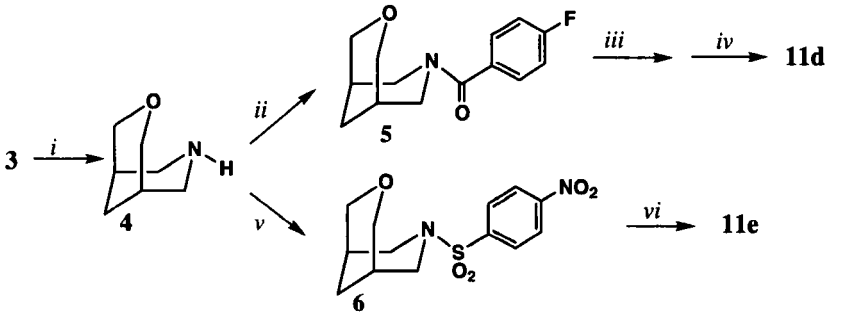


i) $(H_2CO)_n$, $PhCH_2NH_2$, HOAc, HCl *ii*) H_2NNH_2, KOH, TEG, 200° *iii*) $HClO_4$
iv) $F_3B{\bullet}OEt_2$, $HSCH_2CH_2SH$

Scheme 1

group in **2** led to **3** (95%) which was converted to stable salt **11a** in good yield (83%). Masking the carbonyl group in **2** occurred *via* the formation of the thioketal **11b** (82%),the latter being acidified to salt **11c**.

Debenzylation of **3** with *fresh* 10% Pd-C gave the important intermediate **4** which was acylated to give **5** (*Scheme 2*). Although **4** is a light oil and slightly air-sensitive, its potential as a



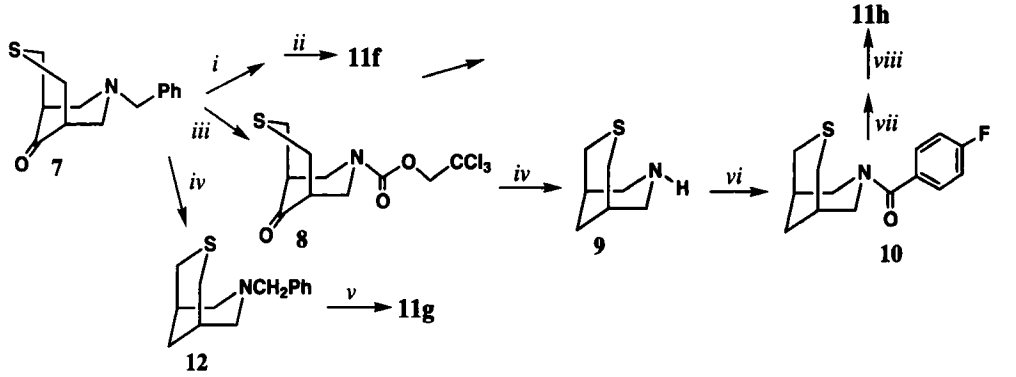
i) 10% Pd-C/H_3COH/HCO_2NH_4 *ii*)4-$FC_6H_4C(O)Cl$/NaOH/H_2CCl_2 *iii*) Imidazole/Δ/K_2CO_3/DMSO
iv) $HClO_4$ *v*) 4-$O_2NC_6H_4SO_2Cl$/NaOH/H_2CCl_2 *vi*) $TiCl_3$/HOAc

Scheme 2

useful synthon for a variety of *N*-substituted derivatives is significant. Nucleophilic addition/elimination in the reaction of **5** with imidazole required extremely dry conditions and finely powdered

K_2CO_3. The intermediate oil was isolated (38%) and was best converted immediately to stable salt **11d**. *N*-Sulfonation of intermediate **4**, followed by reduction of the nitro group with $TiCl_3$ in the product **6**, gave **11e**.

Masking the sulfur-containing ketone **7** with ethane-1,2-dithiol (*Scheme 3*) gave the expected intermediate (84%) which was acidified to give salt **11f** in a fashion similar to that of converting **2** to **11b** to **11c**. Surprisingly, ketone **7** (*Scheme 3*) was susceptible to debenzylation following *N*-acylation as shown. To the best of our knowledge, only the electrophilic proton has been successful in attacking a nitrogen atom in a chair-chair 3,7-di-heterabicyclo[3.3.1]nonane system. Indeed, a sparteine derivative, with a boat-chair conformation as a subunit, could only be successfully



i) $F_3B{\bullet}OEt_2$,$HSCH_2CH_2SH$ *ii*) $HClO_4$ iii) $ClCO_2CH_2CCl_3$,C_6H_6/cold; Δ/2 d *iv*) H_2NNH_2,KOH/TEG,200 *v*) HCl *vi*) 4-$FC_6H_4C(O)Cl$/NaOH,H_2CCl_2 *vii*) Imidazole, Δ/K_2CO_3,DMSO *viii*) $HClO_4$

Scheme 3

N-methylated with methyl iodide at 11kbars of pressure at 50° for 170 hours.[11] This successful *N*-debenzylation of **7** with $ClCO_2CH_2Cl_3$ is the first in this family of heterocycles as is the isolation of the intermediate **8**. Intermediate **8** was characterized and then converted to **9**. Acylation of the light oil **9** gave **10** which reacted with imidazole in the usual manner to give an intermediate that was converted to hydroperchlorate **11h**. Debenzylation of **7** gave known **12**[7] which was treated with hydrogen chloride gas to give **11g.** In summary, syntheses are reported for several 3,7-diheterabicyclo[3.3.1]nonanes with potential antiarrhythmic activity.

EXPERIMENTAL SECTION

Proton and carbon-13 NMR spectra were recorded on a Varian Gemini 300 MHz unit operating at 300.082 and 75.463 MHz, respectively, or on a Varian Inova 400 MHz spectrometer operating at 399.925 and 100.570 MHz, respectively. Chemical shifts are reported in δ values downfield from TMS. IR spectra were taken on a Perkin-Elmer 2000 FTIR unit either as KBr pellets or as films. Melting points were measured on a Thomas-Hoover apparatus and were uncorrected. All solvents were dried prior to use. Intermediate **12** was prepared as reported.[7] High resolution mass spectral data were collected on a VG analytical instrument, model ZAB-2SE, for all salts with a FAB ionization chamber. Some data on liquids were collected on this unit by the LSIMS/FAB mode using 3-

nitrobenzyl alcohol as the matrix. GC/MS data were gathered on Hewlett-Packard GC1800A (GCD-800 series) with an electron impact (EI) ionization chamber. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN 37921, or by Atlantic Microlab, Inc., Norcross, GA 30091. All reactions were performed under nitrogen unless otherwise specified. *Although no difficulties were encountered with the hydroperchlorates cited herein, due caution and the use of hoods should be exercised.*

Preparation of 2.- A mixture of benzylamine (3.21 g, 29.9 mmol), HCl (37%, 1.48 g, 14.9 mmol), glacial acetic acid (2.7 g, 44.9 mmol), and paraformaldehyde (7.2 g, 239.6 mmol) in deoxygenated H_3COH was stirred at reflux (0.25 h). A solution of **1** (3.0 g, 29.9 mmol) in glacial acetic acid (2.7 g, 44.9 mmol) and methanol (25 mL) was added dropwise (0.5 h), and the solution was then boiled (12 h). Cooling the reaction mixture to RT and evaporation of the solvents produced an orange oil which was redissolved in water (75 mL). Ether extracts of the aqueous mixture were discarded, and the remaining mixture was chilled (5°) and made basic (pH ~ 12, NaOH pellets). Extracts (ether, 3 x 50 mL) of the solution were dried (Na_2SO_4), filtered, and concentrated to a viscous, reddish oil. Vacuum distillation (130-140°/0.01 mm) of the oil gave **2** (3.55 g, 51%) as a clear oil which solidified with chilling (- 10°), mp. 37-38°. IR (KBr): 1735 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$): δ 2.53 (bs, 2 H), 2.93 (dd, 2 H), 3.12 (dd, 2 H), 3.56 (s, 2 H), 3.89 (dd, 2 H), 4.09 (d, 2 H), 7.33 (m, 5 H, Ar-H); ^{13}C NMR ($DCCl_3$) δ 49.4, 57.5, 61.1, 73.4, 127.0, 128.1, 128.4, 137.8 (Ar-C), 211.8 (C=O). GC-MS (EI): Calcd for $C_{14}H_{17}NO_2$: 231. Found: 231. Ketone **2** was converted directly to **3**.

Preparation of 3.- To a solution of **2** (3.55 g, 15.3 mmol) in triethylene glycol (20 mL) was added KOH pellets (85%, 10.0 g, 153.6 mmol) and hydrazine (95%, 2.58 g, 76.8 mmol). The stirred mixture was boiled (4 h) and then cooled (RT, 1 h). Chilled water (20 mL) was added, and resulting mixture was extracted (ether, 3 x 30 mL). The combined extracts were washed (10% NaOH and saturated brine) and dried (Na_2SO_4). Filtration and concentration of the solution gave a light yellow oil of **3** (3.16 g, 95%). IR (Film): 3030 (Ar-H), 2918, 2819 (alkyl-H) cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.54 (m, 1 H), 1.70 (bs, 2 H), 1.77 (m, 1 H), 2.31 (dd, 2 H), 2.94 (d, 2 H), 3.50 (s, 2 H), 3.77 (m, 2 H), 3.90 (d, 2 H), 7.36 (m 5 H, Ar-H); ^{13}C NMR ($DCCl_3$): δ 30.30, 30.35, 57.7, 61.7, 63.3, 126.5, 127.9, 128.7, 138.5 (Ar-C). GC-MS (EI): Calcd for $C_{14}H_{19}NO$: 217. Found: 217. Amine **3** appeared air sensitive and was converted to salt **11a**.

Preparation of 4.- Onto a fresh sample of Pd-C (10%, 0.436 g, ~ 30 mg of catalyst/mmol of **3**) in a system, which had been thoroughly flushed (0.5 h) with and was under nitrogen, was slowly poured deoxygenated H_3COH (30 mL). To this stirred suspension was quickly added amine **3** (3.16 g, 14.58 mmol) and anhydrous ammonium formate (3.67 g, 58.24 mmol). After boiling (1 h), the mixture was cooled to RT and then filtered (celite pad). Concentration of the filtrate gave a light oil which was dissolved in water (30 mL), and the new solution was made basic (pH ~12, 10% aqueous NaOH). Combined extracts ($HCCl_3$, 4 x 30 mL) of the aqueous solution were dried (Na_2SO_4), filtered, and concentrated to a very faint yellow oil of **4** (1.38 g, 75%). IR (Film): 3431 (N-H), 2933 (alkyl-H) cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.48 (bs, 2 H), 1.94 (m, 2 H), 2.88 (bs, 1 H), 3.05 (dd, 2 H), 3.16 (d, 2 H), 3.87

(dd, 2 H), 4.03 (d, 2 H); ^{13}C NMR ($DCCl_3$): δ 29.7, 31.6, 51.3, 72.8. MS (LSIMS): Calcd for $C_7H_{13}NO$: 127. Found: 128 ($M^+ + 1$). The sample of **4** was used immediately to prepare derivatives.

Preparation of 5.- To a mixture of **4** (0.30 g, 2.36 mmol) in H_2CCl_2 (7 mL) and aqueous NaOH (10%, 2.36 g, 5.90 mmol) was added dropwise a solution of 4-fluorobenzoyl chloride (0.56 g, 3.54 mmol) in H_2CCl_2 (8 mL) over a period of 5 min. After stirring (6 h), the mixture was extracted (H_2CCl_2, 3 x 10 mL), and the extracts were combined, dried (Na_2SO_4), filtered, and concentrated to a white solid. Recrystallization (EtOAc:hexane, 2:1) gave **5** (0.456 g, 77%), mp. 115-115.5°. IR (KBr): 3069 (Ar-H) 1618 (NC=O) cm^{-1}; ^{1}H NMR ($DCCl_3$): δ 1.52 (bs, 2 H), 1.90 (m, 4 H), 3.03 (d, 1 H), 3.26 (d, 1 H), 3.75 (m, 2 H), 4.07 (d, 1 H), 4.86 (d, 1 H), 7.25 (m, 2 H), 8.14 (d, 2 H); ^{13}C NMR ($DCCl_3$): δ 29.7, 29.9, 31.7, 46.8, 52.3, 71.9, 72.2, 115.6, 115.8, 116.4, 116.6, 129.0, 133.4 (Ar-C), 170.2 (NC=O). MS (LSIMS): Calcd for $C_{14}H_{16}FNO_2$: 249. Found: 250 ($M^+ + 1$).

Anal. Calcd for $C_{14}H_{16}FNO_2$: C, 67.46; H, 6.42; N, 5.62. Found: C, 67.31; H, 6.45; N, 5.67.

Preparation of 8.- To a solution of ketone **7**[7] (6.0 g, 24.2 mmol) in anhydrous benzene (80 mL) chilled to 5° was added dropwise (0.5 h) a solution of 2,2,2-trichloroethyl chloroformate (15.42 g, 72.78 mmol) in anhydrous benzene (15 mL). After stirring (2 h), the mixture was boiled (2 d), after which it was cooled (RT). Evaporation gave an oil which was mixed with 10% NaOH (~80 mL), and the resulting mixture was extracted (H_2CCl_2, 4 x 50 mL). Combined extracts were dried (Na_2SO_4) and concentrated to an oil which was chromatographed (neutral alumina). A mixture of EtOAc:hexane (1:20) removed contaminants, but a more polar mixture of EtOAc:hexane (3:7) allowed isolation of **8** (4.45 g, 53%), mp. 112-113°. IR (KBr): 1720 (C=O), 1707 [NC(O)O] cm^{-1}; ^{1}H NMR ($DCCl_3$): δ 2.73 (bd, 2 H), 3.99 (bd, 2 H), 3.40-3.56 (m, 4 H), 4.70-4.88 (m, 4 H); ^{13}C NMR ($DCCl_3$): δ 36.4, 36.5, 46.6, 47.0, 49.7, 49.9, 75.6, 153.5 (NC=O), 211.4. GC-MS (EI): Calcd for $C_{10}H_{12}Cl_3NO_3S$: 332. Found: 332.

Anal. Calcd for $C_{10}H_{12}Cl_3NO_3S$: C, 36.11; H, 3.64; N, 4.21. Found: C, 36.10; H, 3.60; N, 4.18

Preparation of 9.- A mixture of carbamate **8** (4.45 g, 13.01 mmol) in triethylene glycol (60 mL), KOH pellets (85%, 8.04 g, 117.59 mmol), and hydrazine (95%, 4.39 g, 130.06 mmol) was heated (~200°) for 6 h. The reaction mixture was cooled to RT and diluted (chilled water, 80 mL). Combined extracts (ether, 4 x 80 mL) were washed (10% aqueous NaOH and brine), dried (Na_2SO_4), filtered, and concentrated to the oil **9** (1.57 g, 84%). IR (Film): 3200 (N-H) cm^{-1}; ^{1}H NMR ($DCCl_3$): δ 1.81-188 (m, 3 H), 1.99 (d, 1 H), 2.67 (d, 2 H), 3.18 (d, 2 H), 3.26 (d, 2 H), 3.35 (d, 2 H), 3.75 (s, 1 H); ^{13}C NMR ($DCCl_3$): δ 26.2, 31.6, 32.6, 51.1.

GC-MS (EI): Calcd for $C_7H_{13}NS$: 143. Found: 143. Amine **9** was used immediately.

Preparation of 10.- To a solution of **9** (1.14 g, 7.99 mmol) in a biphasic solution of H_2CCl_2 (35 mL) and aqueous NaOH (10%, 7.97 g, 19.87 mmol) was added dropwise a solution of 4-fluorobenzoyl chloride (1.39 g, 8.78 mmol) in H_2CCl_2 (15 mL) over 0.5 h. After stirring overnight (RT), the mixture was diluted with water (50 mL), the layers were separated, and the aqueous layer was extracted (H_2CCl_2, 4 x 30 mL). Combined extracts were dried (Na_2SO_4), filtered, and concentrated to an oil which was chromatographed (neutral alumina, ethyl acetate:hexane, 2:3). Evaporation of the solvent gave amide **10** (1.53 g, 72%, dried under vacuum), mp. 114-115°. IR (KBr): 3005 (Ar-H), 1640

(NC=O) cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.59 (bs, 2 H), 1.84 (d, 1 H), 1.90 (d, 1 H), 2.16 (s, 1 H), 2.39 (d, 1 H), 2.77 (d, 1 H), 3.17 (m, 2 H), 3.43 (d, 1 H), 3.88 (d, 1 H), 4.97 (d, 1 H), 7.08 (d, 2 H), 7.44 (d, 2 H); ^{13}C NMR ($DCCl_3$): δ 26.4, 26.7, 31.6, 31.7, 32.1, 46.2, 52.0, 114.9, 115.2, 128.7, 128.8, 133.60, 133.64, 161.0, 164.1 (d, *C*-F), 169.1 (NC=O). GC-MS (EI): Calcd for $C_{14}H_{16}FNOS$: 265. Found: 265. Although **10** appeared stable, it was usually converted to **11h** at once.

Preparation of 11a.- To a stirred and chilled solution of amine **3** (0.6 g, 2.76 mmol) in anhydrous ether (20 mL) was added $HClO_4$ (60%, 0.69 g, 4.14 mmol) dropwise over 10 min. Stirring for another 10 min produced a precipitate which was collected and washed (dry ether). Recrystallization (ether:H_3CCN, 2:1) afforded **11a** (0.72 g, 83%) as a white solid, mp. 188-189° (dec). IR (KBr): 3310 (N-H), 3035 (Ar-H) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.79 (d, 1 H), 1.85 (d, 1 H), 1.95 (bs, 2 H), 3.22 (d, 2 H), 3.40 (d, 2 H), 3.62 (d, 2 H), 3.95 (d, 2 H), 4.25 (s, 2 H), 7.45 (m, 5 H, Ar-H), 8.6 (bs, 1 H); ^{13}C NMR (DMSO-d_6): δ 28.2, 28.3, 56.0, 60.9, 71.0, 128.9, 129.66, 129.69, 131.2 (Ar-C); MS (HRMS): Calcd for $C_{14}H_{20}ClNO_5$: 218.1544. Found: 218.1539

Preparation of 11b.- To a solution of ketone **2** (1.40 g, 6.06 mmol) in methylene chloride (15 mL) was added 1,2-ethanedithiol (0.71 g, 7.57 mmol) followed by boron trifluoride etherate (2.22 mL) in one portion. After stirring overnight, the solution was treated with 5% sodium hydroxide (20 mL). The organic layer was washed (water and brine) and dried ($MgSO_4$). Concentration of the solution gave a solid which was recrystallized (hexane:EtOAc, 3:1) to give **11b** (1.52 g, 82%), mp. 79.5-80.5°. IR (KBr) 3039 (Ar-H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.89 (bs, 2 H), 2.87 (d, 2 H), 2.95 (d, 2 H), 3.22 (m, 4 H), 3.53 (s, 2 H), 3.98 (d, 2 H), 4.15 (d, 2 H), 7.30 (m, 5 H, Ar-H); ^{13}C NMR ($DCCl_3$) ppm 38.1, 44.0, 56.6, 62.0, 70.5, 71.7, 126.7, 128.1, 128.6, 138.5 (Ar-C). Amine **11b** was converted at once to **11c**.

Anal. Calcd for $C_{16}H_{21}NOS_2$: C, 62.54; H, 6.84; N, 4.56. Found: C, 62.35; H, 6.91; N, 4.49

Preparation of 11c.- To a solution of amine **11b** (0.100 g, 0.325 mmol) in anhydrous ether (10 mL) was added $HClO_4$ (60%, 0.081 g, 0.488 mmol) dropwise over 5 min. The remainder of the procedure was identical to that to obtain **11a**. Recrystallization (H_3COH) of the product gave **11c** (0.120 g, 87%) as a white solid, mp. 196-196.5°. IR (KBr): 3015 (Ar-H), 1084 (Cl-O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.17 (s, 2 H), 3.32 (m, 6 H), 3.66 (d, 2 H), 3.97 (d, 2 H), 4.11 (d, 2 H), 4.30 (d, 2 H), 7.50 (m, 5 H, Ar-H), 8.85 (bs, 1 H); ^{13}C NMR (DMSO-d_6): δ 38.4, 41.4, 55.0, 60.1, 68.7, 70.2, 128.7, 128.8, 129.8, 131.6 (Ar-C).

Anal. Calcd $C_{16}H_{22}ClNO_5S_2$: C, 47.12; H, 5.39; N, 3.43. Found: C, 46.99; H, 5.38; N, 3.35

Preparation of 11d.- To amide **5** (0.450 g, 1.80 mmol) in DMSO (8 mL) was added imidazole (0.184 g, 2.70 mmol), K_2CO_3 (anhydrous powder, 0.561 g, 4.06 mmol) and 18-C-6 (0.100 g). The mixture was stirred and heated (~110°, 48 h), cooled to RT, and diluted with chilled (ice) water (10 mL). Combined extracts (H_2CCl_2, 4 x 8 mL) of the mixture were washed (water and brine) and dried ($MgSO_4$). Filtration and concentration of the solution gave a light yellow oil which was chromatographed (silica gel) with hexane:EtOAc:H_3COH (3:3:1) to give the expected intermediate (0.200 g, 38%) as a clear, viscous oil. IR (Film): 3108 (Ar-H), 1628 (NC=O) cm^{-1}; ^{1}HNMR ($DCCl_3$): δ 1.60 (bs, 1 H), 1.82 (bs, 1 H), 1.90 (dd, 1 H), 1.97 (dd, 1 H), 2.25 (bs, 2 H), 3.07 (d, 1 H), 3.42 (d, 1 H),

3.88 (m, 2 H), 4.13 (d, 1 H), 4.96 (d, 1 H), 7.18 (s, 1 H), 7.25 (d, 2 H), 7.39 (d, 1 H), 7.41 (d, 2 H), 7.85 (d, 1 H); ^{13}C NMR ($DCCl_3$): δ 28.7, 30.0, 30.7, 48.7, 52.8, 53.4, 55.0, 114.3, 120.0, 121.7, 130.9, 139.5, 166.2 (NC=O). GC-MS (EI): Calcd for $C_{17}H_{19}N_3O_2$: 297. Found: 297. To a chilled (0°) solution of the above amide (0.160 g, 0.53 mmol) in anhydrous ether:anhydrous THF (1:1, 10 mL) was added $HClO_4$ (60%, 0.135 g, 0.80 mmol) dropwise (5 min). The resulting solution was stirred vigorously to form a precipitate which was filtered, washed (ether), and recrystallized (H_3COH:H_3CCN, 3.5:1) to give **11d** (0.109 g, 51%), mp. 242-242.5°. IR (KBr): 3150 (N-H), 1625 (NC=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.61 (bs, 1 H), 1.80-1.89 (m, 3 H), 3.07 (d, 1 H), 3.44 (d, 1 H), 3.61-3.68 (m, 4 H), 3.91 (d, 1 H), 4.72 (d, 1 H), 7.56 (d, 2 H, imidazole C-*H*, Ar-H), 7.87-7.94 (m, 4 H, imdazole C-*H*, Ar-H), 8.32 (s, 1 H, C-H, imidazole), 9.70 (s, 1 H); ^{13}C NMR (DMSO-d_6): δ 28.78, 28.87, 30.6, 45.8, 51.4, 71.1, 71.4, 120.8, 121.1, 122.2, 127.9, 134.7, 134.8, 138.5 (Ar-C, imidazole *C*-H), 167.8 (NC=O). MS (LSIMS): Calcd for $C_{17}H_{20}ClN_3O_6$: 298 (- ClO_4^-). Found: 298.

Anal. Calcd for $C_{17}H_{20}ClN_3O_6{\cdot}H_2O$: C, 49.10; H, 5.29; N, 10.10. Found: C, 49.54; H, 4.96; N, 10.00

Preparation of 11e.- To a mixture of **4** (0.320 g, 2.51 mmol) in H_2CCl_2 (5 mL) and aqueous NaOH (10%, 2.01 g, 5.03 mmol) was added a solution of 4-nitrobenzenesulfonyl chloride (0.690 g, 3.14 mmol) in H_2CCl_2 (10 mL) dropwise (10 min). After stirring (15 h, RT), water (20 mL) was added, and the aqueous layer was separated and extracted (H_2CCl_2, 3 x 10 mL). Combining the organic layer/extracts gave a solution which was dried ($MgSO_4$) filtered, and concentrated. Recrystallization (EtOAc:-hexane, 3.5:1) of the solid gave **6** (0.455 g, 58%), mp. 177.5-178.5°. IR (KBr): 3113 (Ar-H) cm^{-1}; ^{1}H NMR ($DCCl_3$): δ 1.45 (d, 2 H), 1.73 (bs, 2 H), 2.70 (d, 2 H), 3.58 (d, 2 H), 3.72-3.79 (m, 4 H), 7.94-7.99 (d, 2 H), 8.38-8.43 (d, 2 H); ^{13}C NMR ($DCCl_3$): δ 28.1, 28.7, 49.4, 70.6, 124.6, 128.9, 141.8, 149.9 {Ar-C). MS (LSIMS): calcd for $C_{13}H_{16}N_2O_5S$: 312. Found: 313 (M^+ + 1).

Anal. Calcd for $C_{13}H_{16}N_2O_5S$: C, 50.00; H, 5.12; N, 8.97. Found: C, 50.04; H, 5.16; N, 8.96.

Sulfonamide **6** (0.140 g, 0.448 mmol) in acetic acid:water (1:1) was stirred vigorously until a homgeneous solution formed. To the solution was added $TiCl_3$ (12%, 4.84 g, 3.14 mmol) in one portion, and the resulting solution was stirred (1.5 h, RT). After cooling (0-5°), the solution was treated with aqueous 20% NaOH until a dark blue color persisted (pH~12). Combined extracts ($HCCl_3$, 4 x 15 mL) were washed (water and brine), dried ($MgSO_4$), and concentrated to an oil. Crystallization was induced (EtOAc), followed by chilling (-10°), and gave **11e** (0.100 g, 79%) as a solid, mp. 183-183.5°. IR (KBr): 3380 (N-H), 3040 (Ar-H), 1160 (S=O) cm^{-1}; ^{1}H NMR ($DCCl_3$): δ 1.87 (d, 1 H), 1.95 (d, 3 H), 2.18 (s, 1 H), 2.38 (d, 1 H), 2.79 (d, 2 H), 3.18 (m, 2 H), 3.48 (d, 1 H), 3.94 (bs, 2 H), 5.03 (d, 1 H), 7.64 (d, 2 H), 8.28 (d, 2 H)); ^{13}C NMR ($DCCl_3$): δ 26.3, 26.74, 31.6, 31.7, 32.1, 46.2, 52.0, 123.4, 123.8, 127.5, 143.4 (Ar-C). MS (LSIMS): Calcd for $C_{13}H_{18}N_2O_3S$: 282. Found: 283 (M^+ + 1).

Anal. Calcd for $C_{13}H_{18}N_2O_3S$: C, 55.31; H, 6.38; N, 9.92. Found: C, 55.26; H, 6.40; N, 10.00

Preparation of 11f.- A mixture of ketone **7**[7] (0.501 g, 2.03 mmol), ethanedithiol (0.286 g, 3.04 mmol), and boron trifluoride etherate (0.5 mL) was stirred at RT overnight and was then treated with 5% sodium hydroxide (20 mL). The aqueous mixture was extracted (H_2CCl_2, 3 x 40 mL), and the combined extracts were dried (Na_2SO_4), filtered, and concentrated to yield a light yellow solid (0.548

g, 83%), mp. 50-51°. IR (KBr): 3040 (Ar-H) cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.45-2.90 (m, 10 H), 3.10 (s, 4 H), 3.55 (s, 2 H), 7.1-7.5 (m, 5 H, Ar-H). GC-MS (EI): Calcd for $C_{16}H_{21}NS_2$: 323. Found: 323. The above aminoketone (0.30 g, 0.96 mmol) was immediately placed in a mixture of ether:H_3COH (1:1) at 0° and treated with $HClO_4$ (60%, 0.241 g, 1.44 mmol) with stirring over 10 min. After stirring for another 10 min, the mixture was allowed to warm to RT. Recrystallization (hot H_3COH using a ratio of approximately 25 mL/0.5 g of solid) of the filtered solid gave **11f** (0.25 g, 63%), mp. 139.5-141°. IR (KBr): 3040 (Ar-H) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.40-2.95 (m, 10 H), 3.11 (s, 4 H), 3.45 (bs, 2 H), 7.14-7.60 (m, 5 H, Ar-H), 8.95 (bs, 1 H); ^{13}C NMR (DMSO-d_6): δ 27.5, 31.5, 44.1, 53.1, 59.8, 61.2, 71.2, 127.2, 128.4, 128.9, 137.6 (Ar-C).

Anal. Calcd for $C_{16}H_{22}ClNO_4S_2$: C, 49.33; H, 4.87; N, 10.15. Found: C, 49.34; H, 4.82; N, 10.06

Preparation of 11g.- Into a chilled (5°) solution of **12**[7] (5.00 g, 20.2 mmol) in ether (150 mL) was bubbled (~4 small bubbles/sec) anhydrous HCl gas over 0.25 h. The mixture was stirred for another 0.25 h and a precipitate formed. Filtration, washing with cold, dry ether, and recrystallization (H_3COH:ether, 1:1) gave a solid **11g** which was dried (80°/0.2 mm, 3.31 g, 61%,), mp. 246-247°. IR (KBr): 3040 (Ar-H) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.84 (m, 2 H), 2.38 (m 2 H), 2.71 (d, 2 H), 3.13 (d, 2 H), 3.36 (bs, 2 H), 3.60 (d, 2 H), 4.29 (d, 2 H), 7.61-7.79 (m, Ar-H), 9.25 (bs, 1 H); ^{13}C NMR (DMSO-d_6): δ 25.9, 28.6, 30.9, 56.4, 60.8, 129.2, 129.8, 130.1, 130.4 (Ar-C); MS (HRMS): Calcd for $C_{14}H_{20}ClNS$: 233.1238. Found: 233.1239.

Anal. Calcd for $C_{14}H_{20}ClNS$: C, 62.32; H, 7.47; N, 5.19. Found: C, 62.20; H, 7.38; N, 5.16

Preparation of 11h.- To amide **10** (1.14 g, 4.31 mmol) in dry DMSO (10 mL) was added imidazole (0.44 g, 6.46 mmol) and oil-free KH (0.26 g, 6.46 mmol) along with 18-C-6 (0.100 g). This mixture was stirred at ~105° (24 h) and was then allowed to cool to RT before adding ice water (30 mL). Combined extracts (H_2CCl_2, 4 x 30 mL) of the aqueous layer were washed (chilled water and brine) and dried (Na_2SO_4). Filtration and concentration of the solution gave a light yellow oil which was chromatographed (neutral alumina) with EtOAc:-hexane (2:3) to yield a light oil which was further chromatographed (silica gel, EtOAc:-methanol, 25:1) to give the intermediate as a light, colorless oil. IR (Film): 3110 (Ar-H), 1620 (NC=O) cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.64 (bs, 2 H), 1.87 (d, 1 H), 1.91 (d, 1 H), 2.19 (s, 1 H), 2.40 (d, 1 H), 2.78 (d, 1 H), 3.15 (m, 2 H), 3.47 (d, 1 H), 3.90 (d, 1 H), 5.05 (d, 1 H), 7.24 (s, 1 H), 7.41-7.54 (dd, 4 H), 7.67 (s, 1 H), 7.89 (s, 1 H); ^{13}C NMR ($DCCl_3$): δ 27.3, 27.9, 29.8, 41.6, 42.5, 48.3, 55.6, 115.8, 116.2, 118.0, 127.6, 128.9, 131.2, 135.7, 136.9, 137.5 (Ar-C, *C*-H imidazole), 168.8 (NC=O). GC-MS (EI): Calcd for $C_{17}H_{19}N_3OS$: 313. Found: 313. To this intermediate (0.27 g, 0.86 mmol) in chilled (5°) ether:methanol (1:1, 30 mL) was slowly added $HClO_4$ (60%, 0.22 g, 1.29 mmol) which gave a white solid. The mixture was stirred (10 min) and allowed to warm to RT. Filtration and recrystallization (hot H_3COH, ~10 mL/0.5 g of solid) gave **11h** (0.22 g, 61%), mp. 168-170°. IR (KBr): 3200 (N-H), 3005 (Ar-H), 1645 (NC=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.76 (d, 1 H), 1.86 (d, 1 H), 2.03 (d, 2 H), 2.34 (d, 1 H), 2.50 (s, 2 H), 2.62 (d, 2 H), 3.09 (m, 3 H), 3.50 (d, 1 H), 3.67 (d, 1 H), 7.62 (d, 2 H), 7.80 (d, 2 H), 7.95 (s, 1 H), 8.32 (s, 1 H), 9.71 (bs, 1 H); ^{13}C NMR (DMSO-d_6): δ 27.8, 29.7, 41.6, 55.4,

120.6, 121.3, 122.0, 1128.7, 135.3, 137.5 (Ar-C, C-H imidazole), 171.5 (NC=O).

Anal. Calcd for $C_{17}H_{20}ClN_3O_5S$: C, 49.33; H, 4.87; N, 10.15. Found: 49.34; H, 4.82; N, 10.06

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