Synthesis of 4-(2-Hydroxyethylsulfonyl)-1-naphthalenesulfonamide

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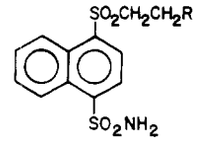
4-(2-Hydroxyethylsulfonyl)-1-naphthalenesulfonamide (**1**, HO-ENS) has been identified as one of the principal metabolites formed when the bladder carcinogen 4-ethylsulfonyl-1-naphthalenesulfonamide (**2**, ENS) is ingested by

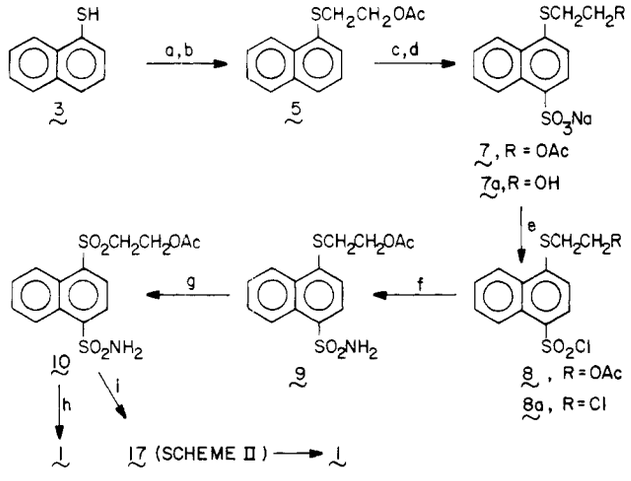


1, R = OH
2, R = H

mice.[1] This metabolite was identified on the basis of its chromatographic behavior; however, its synthesis has never been reported. We are reporting here the synthesis of **1** using an approach similar to the method reported for the synthesis of ENS[2] and ^{15}N-labeled ENS[3] in our laboratory.

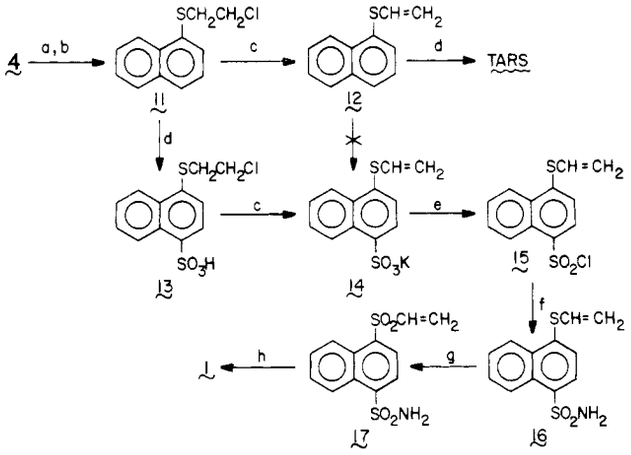
1-Naphthalenethiol (**3**)[4] (Scheme I) was converted to 2-(1-naphthylthio)ethyl acetate (**5**) via 2-(1-naphthylthio) ethanol (**4**)[5] in an overall yield of 75%. Sulfonation of the ester **5** was carried out using 1 equiv of chlorosulfonic acid in dry chloroform to give the 4-(2-acetoxyethylthio)-1-naphthalenesulfonic acid (**6**) which was isolated as the sodium salt **7** in 68% yield. The acetoxy acid chloride **8** was prepared from **7** in 68% yield by the method of Bosshard et al.,[6] the chloro acid chloride **8a** being isolated as a secondary product in 15% yield. The side product **8a** probably arose from the hydroxyethyl derivative **7a** present in the sodium salt **7**, **7a** being formed through partial ester exchange of the acetoxy group in the conversion of the sulfonic acid **6** to the sodium salt **7** in the presence of ethoxide.

Scheme I



[a] NaOH (aq), $ClCH_2CH_2OH$, 90 °C. [b] Ac_2O, NaOAc, 70 °C. [c] $ClSO_3H$, $CHCl_3$. [d] NaOEt, EtOH. [e] $SOCl_2$, DMF. [f] Excess NH_3, CH_3CN. [g] MCPBA, CH_2Cl_2. [h] HCl, H_2O, EtOH, 60 °C. [i] NaOH, H_2O.

Scheme II



[a] NaOH (aq), $ClCH_2CH_2OH$, 90 °C. [b] $SOCl_2$, $CHCl_3$. [c] KOH, 95% EtOH, reflux. [d] $ClSO_3H$, $CHCl_3$. [e] $SOCl_2$, DMF. [f] Excess NH_3, CH_3CN. [g] H_2O_2, H_2O, HOAc, 90 °C. [h] NaOH, H_2O.

The reaction of the acid chloride **8** with excess ammonia in acetonitrile afforded an 89% yield of the desired sulfonamide **9**, which was smoothly oxidized with *m*-chloroperoxybenzoic acid (MCPBA) to the sulfone **10** in 84% yield.[7] Attempts to oxidize **9** to **10** with hydrogen peroxide in aqueous acetic acid[2] gave mixtures probably due to partial hydrolysis of the acetoxy group in **9**. Hydrolysis of **10** with dilute hydrochloric acid in aqueous ethanol at 60 °C readily afforded pure HO-ENS (**1**) in 95% yield.

Hydrolysis of the sulfonamide **10** over a short period with aqueous base at room temperature gave a mixture of several products, among which were the desired hydroxysulfonamide **1** and the vinylsulfone **17**, the ester **10** being consumed completely within 1 min (TLC). Indeed, such behavior of **10** was not unexpected and has precedence in the literature.[8] Furthermore, it was evident through TLC studies that the initial product formed in the reaction of **10** with aqueous base was the vinylsulfone **17** and that, over longer reaction periods, **17** was slowly being converted to HO-ENS (**1**) as would be expected.[9] These preliminary findings led to the investigation of an alternate approach to the synthesis of **1** utilizing the Michael type addition of hydroxide ion to the sulfone **17** as shown in Scheme II.

The reaction of 2-(1-naphthylthio)ethanol (**4**) with thionyl chloride according to the method of Kirner and Windaus[10] afforded the chloride **11** in excellent yield. Dehydrohalogenation of **11** with alcoholic potassium hydroxide[11] afforded 1-naphthyl vinyl sulfide (**12**) in 81% yield; however, the attempted sulfonation of **12** with chlorosulfonic acid in chloroform gave only dark tars. Consequently, **11** was sulfonated directly with chlorosulfonic acid in chloroform to give the sulfonic acid **13** which was dehydrohalogenated with alcoholic potassium hydroxide to the potassium salt **14** in 70% overall yield. Conversion of **14** to the acid chloride **15** using thionyl chloride in DMF gave a product that was contaminated with several minor side products (TLC). This crude material afforded the amide **16** with ammonia in acetonitrile in 76% overall crude yield from **14**. TLC showed the crude amide to contain several minor side products. Oxidation of recrystallized amide **16** with hydrogen peroxide in aqueous acetic acid[12] afforded the vinylsulfonylsulfonamide **17** in 87% yield. Treatment of **17** with excess 5% aqueous sodium hydroxide gave the desired HO-ENS (**1**); however, minor impurities were present that were difficult to remove.

^{13}C NMR and TLC studies showed conclusively that **1** could be prepared by the reaction of the vinylsulfone **17** with

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aqueous base, as well as by the reaction of aqueous base with the ester **10** via the vinylsulfone **17**; however, in each of these cases, the product is more difficult to purify than that obtained from the hydrolysis of **10** with aqueous alcoholic hydrochloric acid.

Experimental Section

Melting points and boiling points are uncorrected. Anhydrous solvents were prepared by drying over 3A molecular sieve. Infrared spectra were recorded on a Perkin-Elmer Model 710 spectrophotometer. Proton magnetic resonance spectra were recorded on a Perkin-Elmer Hitachi Model R-24 spectrometer using Me_4Si as an internal standard, and ^{13}C magnetic resonance spectra were recorded on a Varian Model CFT-20 spectrometer. The ^{13}C chemical shifts, reported as ppm downfield from Me_4Si, were referenced to the solvent peaks, Me_2SO-d_6 (39.6 ppm) or $DCCl_3$ (76.9 ppm). In those spectra run in aqueous solution, a D_2O capillary containing 1% dioxane was used as a lock and external standard (dioxane: 67.4 ppm downfield from Me_4Si). Reactions were monitored and product purity checked by thin-layer chromatography on precoated silica gel 60 F-254 plates (EM Laboratories) using toluene–ethyl acetate (1:1, v/v), unless otherwise specified, as a developing solvent. The compounds and their approximate R_f values were **1** (0.13, fluorescent), **3** (0.93), **4** (0.63), **5** (0.85), **7** (0.68, EtOH–EtOAc, 1:1), **8** (0.82; 0.21, benzene), **8a** (0.93; 0.80, benzene), **9** (0.50), **10** (0.39, fluorescent), **11** (0.93; 0.85, benzene), **12** (0.84, benzene–cyclohexane, 1:1), **14** (0.73, 95% EtOH–EtOAc, 1:1),**15** (0.84, benzene), **16** (0.70), and **17** (0.53, fluorescent).

2-(1-Naphthylthio)ethyl Acetate (5). A 250-mL Erlenmeyer flask equipped with a magnetic stirrer and condenser was charged with 12 g (75 mmol) of 1-naphthalenethiol (**3**),[3] 40 mL of water, and 60 mL of 10% aqueous sodium hydroxide (~6 g NaOH). The mixture was cooled in an ice bath, and 6.8 mL (100 mmol) of 2-chloroethanol was added. After stirring for 5 min, the ice bath was removed, the mixture was heated to reflux (1 h), and a pale yellow oil separated. The cooled reaction mixture was extracted with ether (150 mL), and the organic layer was separated, washed with 10% aqueous NaOH followed by water, and dried over anhydrous $MgSO_4$. Evaporation of the ether afforded 14.9 g (97%) of crude 2-(1-naphthylthio)ethanol (**4**) as a pale yellow oil (TLC R_f: 0.63 major, 0.93 trace): ^1H NMR (CCl_4) δ 6.95–8.60 (7 H, m), 3.93 (1 H, s), 3.57 (2 H, t, J = 6.4 Hz), 2.89 (2 H, t, J = 6.4 Hz).

A mixture of crude **4**, 15 mL (159 mmol) of Ac_2O, and 0.2 g of anhydrous NaOAc was warmed at 70 °C for 2 h with stirring in an Erlenmeyer flask equipped with a magnetic stirrer, condenser, and drying tube. After the mixture was stirred for an additional 13 h at room temperature, 50 mL of water was added and stirring was continued for an additional 2 h at room temperature. The yellow oil which separated was extracted with ether (100 mL), and the ether layer was washed successively with 5% $NaHCO_3$ and with water and was dried over $MgSO_4$. The ether was removed and the product distilled to give 2-(1-naphthylthio)ethyl acetate (**5**) as a colorless liquid, bp 142–146 °C (0.1 mm) (13.8 g, 75% overall): TLC R_f 0.85; ^1H NMR (CCl_4) δ 7.10–8.63 (7 H, m), 4.14 (2 H, t, J = 6.8 Hz), 3.04 (2 H, t, J = 6.8 Hz), 1.83 (3 H, s); IR (neat) 1737 (C=O), 1243 cm^{-1} (AcO); ^{13}C NMR ($CDCl_3$) 170.0, 133.5, 132.7, 131.7, 129.0, 128.2, 127.5, 126.1, 125.8, 125.1, 124.6, 62.4, 32.4, 20.2.

Anal. Calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73. Found: C, 68.22; H, 5.80.

Sodium 4-(2-Acetoxyethylthio)-1-naphthalenesulfonate (7). A solution of 12.3 g (50 mmol) of 2-(1-naphthylthio)ethyl acetate (**5**), bp 142–146 °C (0.1 mm), in 50 mL of dry $CHCl_3$ was placed in a 125-mL Erlenmeyer flask equipped with a magnetic stirrer, addition funnel, condenser, and drying tube. The reaction mixture was cooled in an ice bath, and a solution of 5.8 g (50 mmol) of chlorosulfonic acid in 85 mL of anhydrous chloroform was added dropwise over a period of 1.5 h. The mixture was stirred in the cold for an additional 2 h, after which time the chloroform was removed on a rotary evaporator, and the viscous oily product was dissolved in 100 mL of 95% ethanol. This solution was neutralized to pH 7 (indicator paper) by the addition of a solution of sodium ethoxide in ethanol, during which time the salt separated as colorless plates. After cooling in an ice bath, the salt was collected, washed with 95% ethanol, and dried for 15 h at 120 °C in an evacuated desiccator to give 11.14 g of sodium 4-(2-acetoxyethylthio)-1-naphthalenesulfonate (**7**). An additional 0.8 g was obtained from the mother liquor for a total yield of 68%: TLC R_f 0.68 (EtOH–EtOAc, 1:1); IR (KBr) 3400 (OH), 1740 (C=O), 1200 (br, AcO, $ArSO_3Na$), 1060 ($ArSO_3Na$) cm^{-1}.

4-(2-Acetoxyethylthio)-1-naphthalenesulfonyl Chloride (8) and 4-(2-Chloroethylthio)-1-naphthalenesulfonyl Chloride (8a). A mixture of crude **7** (5.14 g, 14.8 mmol) and anhydrous DMF (30 mL) was placed in a 125-mL flask equipped with a magnetic stirrer and drying tube and was cooled in an ice bath. To this mixture was added 2.14 mL (29.6 mmol) of thionyl chloride and, after 5 min, the ice bath was removed and the mixture stirred at room temperature for 2.5 h. Evaporation of the DMF at reduced pressure (rotary evaporator) afforded 4.9 g of a tan oil which slowly turned to an oily solid upon scratching. Trituration of this residue with 5 mL of CCl_4 gave 1.74 g of **8**: mp 80–82 °C; TLC R_f 0.21 (benzene); ^1H NMR ($CDCl_3$) δ 7.24–8.90 (6 H, m), 4.37 (2 H, t, J = 7.2 Hz), 3.36 (2 H, t, J = 7.2 Hz), 2.02 (3 H, s); IR (KBr) 1730 (C=O), 1363 ($ArSO_2Cl$), 1245 (AcO), 1163 ($ArSO_2Cl$), 1065 ($AcOCH_2$) cm^{-1}.

Anal. Calcd for $C_{14}H_{13}S_2O_4Cl$: C, 48.77; H, 3.77. Found: C, 48.77; H, 3.65.

The mother liquor from the isolation of **8** contained two major components as indicated by TLC [**8** (0.21) and **8a** (0.80), benzene]. The CCl_4 was replaced with benzene, and the mixture was chromatographed on a silica gel (30 mm × 15 cm) using benzene as the eluent. The first fraction (110 mL) contained only material with R_f 0.80 (0.73 g, **8a**) and, after an intermediate fraction of 40 mL, a third fraction (420 mL) contained only material with R_f 0.20 (1.72 g, **8**). The total yield of **8** suitable for the next step thus amounted to 3.46 g (68%).

The material of R_f 0.80 was identified as 4-(2-chloroethylthio)-1-naphthalenesulfonyl chloride (**8a**) which, after crystallization from CCl_4, gave pale yellow crystals: mp 108–109 °C; IR (KBr) 1364 ($ArSO_2Cl$), 1161 ($ArSO_2Cl$) cm^{-1}; ^{13}C NMR ($CDCl_3$) 145.4, 136.8, 132.0, 129.8, 128.7, 127.8, 127.2, 125.0, 124.7, 120.2, 41.1, 34.1.

Anal. Calcd for $C_{12}H_{10}S_2O_2Cl_2$: C, 44.86; H, 3.11. Found: C, 44.99; H, 3.08.

4-(2-Acetoxyethylthio)-1-naphthalenesulfonamide (9). A solution of 3.03 g (8.79 mmol) of **8** in 36 mL of anhydrous acetonitrile was placed in a 50-mL flask equipped with a magnetic stirrer, gas inlet, and balloon. The reaction mixture was cooled in an ice bath, and anhydrous NH_3 was added through the gas inlet. A precipitate (NH_4Cl) formed immediately, the ice bath was removed, and the mixture was stirred at room temperature for 2 h with periodic additions of NH_3 sufficient to keep the balloon slightly inflated. The reaction mixture was filtered (NH_4Cl = 0.44 g, 93.5%), and the acetonitrile solution was concentrated to 20 mL. Water was added to incipient turbidity, and the solution was allowed to cool, during which time **9** separated as colorless plates (2.56 g, 89.5%), mp 142–143 °C. The sulfonamide **9** exhibited another crystalline modification, mp 115–116°C, which reverted to the higher melting form when its solution in 95% ethanol was seeded with a crystal of **9**: mp 142–143 °C; IR (KBr) 3410 (NH), 3260 (NH), 1715 (C=O), 1325 ($ArSO_2NH_2$), 1255, 1225 (AcO), 1190, 1145, 1130, 1060 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.54–8.93 (6 H, m), 6.72 (2 H, s), 4.31 (2 H, t, J = 6.4 Hz), 3.43 (2 H, t, J = 6.4 Hz), 1.97 (3 H, s); ^{13}C NMR (Me_2SO-d_6) 170.4, 139.6, 136.9, 131.5, 128.1, 127.7, 127.3, 126.4, 126.1, 124.5, 122.3, 61.9, 30.4, 20.7.

Anal. Calcd for $C_{14}H_{15}NO_4S_2$: C, 51.69; H, 4.62; N, 4.31. Found: C, 51.70; H, 4.54; N, 4.21.

4-(2-Acetoxyethylsulfonyl)-1-naphthalenesulfonamide (10). A solution of 3.25 g (10 mmol) of **9** in 450 mL of anhydrous CH_2Cl_2 was added dropwise over a period of 1 h to a cold (ice bath) stirred solution of 4.5 g (22 mmol) of 85% *m*-chloroperoxybenzoic acid in 100 mL of dry CH_2Cl_2. The ice bath was removed after an additional 30 min of stirring, and stirring was continued at room temperature for another 2 h, after which time TLC showed the absence of **9** and the presence of **10** as a fluorescent spot at R_f 0.39. The reaction mixture was extracted twice with 5% $NaHCO_3$ (aq) and once with water. After drying the organic layer over anhydrous $MgSO_4$, the CH_2Cl_2 was removed on a steam bath, and the residue was crystallized from 95% ethanol to give 3.01 g (84%) of **10** as colorless prisms: mp 172–173 °C; IR (KBr) 3380 (NH), 3270 (NH), 1725 (C=O), 1335 ($ArSO_2R$), 1312 ($ArSO_2NH_2$), 1285, 1235 (AcO), 1185, 1155 ($ArSO_2R$), 1120 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) 169.7, 145.5, 138.8, 129.4, 129.3, 128.7, 128.5, 126.7, 125.2, 124.9, 58.7, 54.6, 19.9.

Anal. Calcd for $C_{14}H_{15}NO_6S_2$: C, 47.05; H, 4.23; N, 3.92. Found: C, 47.07; H, 4.34; N, 3.95.

4-(2-Hydroxyethylsulfonyl)-1-naphthalenesulfonamide (HO-ENS) (1). To a warm, stirred solution of 1.07 g (3 mmol) of **10**, mp 172–173 °C, in 50 mL of 95% EtOH was added 50 mL of 5% aqueous HCl. The solution was heated at 60–65 °C for 2.5 h, at the end of which time TLC showed that **10** had been completely converted to **1**. The reaction mixture was cooled, and the solvent was removed under reduced pressure on a rotary evaporator. The crystalline residue was triturated with water, filtered, washed with water, and dried in an evacuated desiccator to afford 0.90 g (95%) of HO-ENS (**1**) as colorless crystals, mp 208–209 °C. Recrystallization from 95% EtOH gave an analytical sample as colorless prisms: mp 208–209 °C; IR (KBr) 3570 (OH), 3420 (NH), 3290 (NH), 1325 ($ArSO_2R$), 1310 (Ar-

SO_2NH_2), 1290, 1190, 1165 ($ArSO_2R$), 1140 ($ArSO_2NH_2$), 1120 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) 145.0, 139.3, 129.1, 129.0, 128.4, 126.5, 125.2, 124.9, 58.1, 55.2.

Anal. Calcd for $C_{12}H_{13}NO_5S_2$: C, 45.71; H, 4.13. Found: C, 45.70; H, 4.24.

2-(1-Naphthalenethio)ethyl Chloride (11). To a stirred solution of **4** (11.9 g, 58 mmol) in 5 mL of dry $CHCl_3$ was added dropwise (10 min) a solution of 4.35 mL (59.8 mmol) of $SOCl_2$ in 5 mL of dry $CHCl_3$. The reaction mixture was warmed to 40–50 °C for 5 min and then stirred for an additional 10 min at room temperature, at which point the reaction was complete (TLC). The excess $CHCl_3$ and $SOCl_2$ were removed at reduced pressure, and the residual oil amounted to 12.9 g (quant): IR (neat) 3050 (CH_2Cl), 1500, 1380, 1210, 1200 cm^{-1}; ^1H NMR (CCl_4) δ 6.92–8.40 (7 H, m), 2.81–3.51 (4 H, m).

1-Naphthylvinyl Sulfide (12). To a stirred solution of 10.6 g (47.6 mmol) of **11** in 15 mL of 95% EtOH was added a solution of 3.3 g of KOH (85%) in 15 mL of 95% EtOH. The mixture was stirred under reflux for 2.5 h, after which time **11** was completely consumed (TLC). The reaction mixture was cooled and the precipitated KCl filtered (3.3 g, 44 mmol). The ethanol was removed on a steam bath, water was added, and the insoluble oil was extracted into ether. The ether solution was washed three times with water and dried over $MgSO_4$. The ether was removed and the residue distilled at reduced pressure, affording 7.12 g (81%) of **12** as a colorless liquid: bp 106–108 °C at 0.35 mm; IR (neat) 3080, 1720, 1580, 1560, 1500, 1380, 1260, 1200, 1020, 975, 955, 870 cm^{-1}; ^1H NMR (CCl_4) δ 6.95–8.20 (7 H, m), 6.26 (1 H, d of d, J_{cis} = 10 Hz, J_{trans} = 16 Hz), 5.04 (1 H, d, J_{cis} = 10 Hz), 4.90 (1 H, d, J_{trans} = 16 Hz); ^{13}C NMR ($CDCl_3$) 133.9, 133.0, 131.9, 130.9, 130.3, 128.7, 128.4, 126.6, 126.2, 125.6, 125.2, 114.3.

Anal. Calcd for $C_{12}H_{10}S$: C, 77.42; H, 5.38. Found: C, 77.31; H, 5.38.

Potassium 4-(Vinylthio)-1-naphthalenesulfonate (14). To a cold (ice bath) stirred solution of 12.9 g (58.0 mmol) of crude **11** in 65 mL of dry $CHCl_3$ was added dropwise 6.76 g (58.0 mmol) of $ClSO_3H$ in 95 mL of dry $CHCl_3$. The solution turned a pale yellow-green, and after 5 min a colorless solid separated. The addition was complete in 50 min, and the reaction mixture was stirred for an additional 30 min. The colorless solid was collected, washed with cold $CHCl_3$, and dried at 50 °C at reduced pressure to give 13.09 g (75%) of 4-(2-chloroethylthio)-1-naphthalenesulfonic acid (**13**), mp 122–128 °C. The crude acid **13** was directly dissolved in 65 mL of 95% EtOH and to this solution was added a solution of 6 g of KOH (85%) in 65 mL of 95% EtOH. The resulting slurry was stirred at reflux for 2 h, during which time an additional 30 mL of 95% EtOH was added to aid stirring (TLC showed a single spot at R_f 0.73, 95% EtOH–EtOAc, 1:1). The reaction mixture was cooled and the precipitate was collected, digested with hot 95% EtOH, filtered (to remove KCl), and allowed to cool, whereupon **14** separated as glistening plates (4.31 g). An additional 1.20 g of **14** was obtained from the mother liquor. The solid presumed to be KCl from the original digestion with 95% EtOH contained additional **14**. This was dissolved in hot water and, upon cooling, an additional 4.23 g of **14** was obtained to make the total yield 9.74 g (70%). A small sample was recrystallized from 95% EtOH to give an analytical sample of **14** as glistening colorless plates: IR (KBr) 3570 (OH), 3470, 1640, 1585, 1565, 1500, 1365, 1200 ($ArSO_3^-$·H_2O), 1160 ($ArSO_3^-$·H_2O), 1060 ($ArSO_3^-$·H_2O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.8–8.4 (6 H, m), 6.05 (1 H, d of d, J_{cis} = 10 Hz, J_{trans} = 16 Hz), 4.75 (1 H, d, J_{cis} = 10 Hz), 4.54 (1 H, d, J_{trans} = 16 Hz), 2.74 (2 H, s).

Anal. Calcd for $C_{12}H_9O_3KS_2$·H_2O: C, 44.70; H, 3.44. Found: C, 44.73; H, 3.35.

4-(Vinylthio)-1-naphthalenesulfonamide (16). To a cold (ice bath) solution of 3.87 g (12 mmol) of **14** in 24 mL of dry DMF was added 1.7 mL (24 mmol) of $SOCl_2$. The solution was stirred for 3.5 h, after which time TLC showed a major spot at R_f 0.84 (benzene) plus several other minor spots. The reaction mixture was poured over ice/H_2O, and the oily product was extracted with benzene. The benzene layer was washed with H_2O, followed by saturated NaCl (aq), and dried over $MgSO_4$. Removal of the benzene on a rotary evaporator afforded 3.18 g of crude **15** as a yellow oil which failed to crystallize. This was chromatographed on silica gel using benzene as the eluent, and the fraction containing only material of R_f 0.83 (benzene) was rotary-evaporated to give 2.68 g (78%) of **15** as a yellow oil which was directly dissolved in 35 mL of dry acetonitrile and treated with excess NH_3 gas as described in the synthesis of **9**. After stirring for 1 h at room temperature, TLC showed a major spot at R_f 0.67 along with minor spots. The acetonitrile was evaporated on a steam bath, water was added, and the straw-colored solid obtained was collected, washed with water, and dried at reduced pressure to give 2.41 g (97%) of crude **16**, mp 143–149 °C. ^{13}C NMR (Me_2SO-d_6) showed that this crude product was essentially **16** along with a small amount of unidentified impurity. Recrystallization of the crude product from 95% EtOH afforded 1.69 g (68%) of tan crystals, mp 153.5–155.0 °C. Further crystallization from 95% EtOH gave an analytical sample of **16** as buff crystals: mp 156–157 °C; TLC R_f 0.70; IR (KBr) 3430 (NH), 3335 (NH), 1560, 1500, 1325 ($ArSO_2NH_2$), 1260, 1200, 1160, 1140 ($ArSO_2NH_2$), 910 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) 138.4, 137.9, 131.5, 129.1, 128.3, 128.0, 127.6, 126.6, 126.1, 125.1, 124.8, 119.8.

Anal. Calcd for $C_{12}H_{11}NO_2S_2$: C, 54.32; H, 4.18; N, 5.28. Found: C, 54.46; H, 4.21; N, 5.33.

4-(Vinylsulfonyl)-1-naphthalenesulfonamide (17). A. From 4-(Vinylthio)-1-naphthalenesulfonamide (16). A mixture of 0.27 g (1 mmol) of **16**, 1.5 mL of HOAc, 0.2 mL of 90% H_2O_2, and 0.8 mL of H_2O was heated on a steam bath for 1 h. The resulting solution was cooled in an ice bath, and the colorless solid which crystallized was collected, washed with water, and dried to give 0.26 g (87%) of 4-(vinylsulfonyl)-1-naphthalenesulfonamide (**17**) as colorless crystals: mp 158–159 °C; R_f 0.53, fluorescent; IR (KBr) 3430 (NH), 3340 (NH), 1540, 1510, 1330 ($ArSO_2R$), 1190, 1160 ($ArSO_2R$), 1135 ($ArSO_2NH_2$), 990 cm^{-1}; ^{13}C NMR (Me_2SO-d_6) 145.4, 138.4, 138.3, 130.9, 129.2, 128.8, 128.6, 128.4, 126.5, 125.3, 124.8.

Anal. Calcd for $C_{12}H_{11}NO_4S_2$: C, 48.47; H, 3.73; N, 4.71. Found: C, 48.36; H, 3.82; N, 4.82.

B. From 4-(2-Acetoxyethylsulfonyl)-1-naphthalenesulfonamide (10). To 0.35 g (1 mmol) of **10** was added 1.2 mL of 10% NaOH (aq) and 1.2 mL of H_2O. A pale yellow solution resulted and, after 1 min at room temperature, the solution was added to 3 mL of 5% HCl (aq). The white gummy precipitate that formed was washed with H_2O by decantation and dissolved in Me_2SO-d_6 for a ^{13}C NMR spectrum which showed the presence of **17** along with small amounts of impurities, none of which were either **10** or **1** as shown by the absence of upfield resonances at 58.7, 54.6, 19.9 (**10**), or 58.1, 55.2 (**1**). The Me_2SO solution was added to H_2O, and 0.23 g (79%) of impure **17** was obtained: mp 150–153 °C; TLC R_f 0.50, fluorescent.

Reaction of 4-(Vinylsulfonyl)-1-naphthalenesulfonamide (17) with Aqueous Sodium Hydroxide. A. A sample of **17** was dissolved in 5% NaOH (aq) and, after standing for 2 h, ^{13}C NMR showed the presence of all ten bands corresponding to an authentic sample of **1** in aqueous NaOH: ^{13}C NMR (H_2O, OH^-) (sample from **17** in parentheses) 149.7 (149.7), 136.7 (136.7), 130.5 (130.4), 129.9 (129.8), 129.2 (129.1), 127.8 (127.8), 124.9 (124.9), 124.5 (124.5), 58.4 (58.4), 56.1 (56.1).

B. A sample of **17** was dissolved in 6 drops of 10% NaOH (aq) and, after standing at room temperature for 1 h, the solution was acidified with 5% HCl. The precipitate that formed was shown to be HO–ENS (**1**): mp 207–208 °C; TLC R_f 0.12 (major), 0.47 (trace).

C. A sample of 0.15 g of **17** was dissolved in 2.5 mL of 5% NaOH (aq). After standing at room temperature for 1 h, the solution was acidified with 5% HCl, and the precipitate was collected and dried (quant). ^{13}C NMR (Me_2SO-d_6) showed the product to be mainly **1** with small amounts of impurity.

^{13}C NMR Spectra of 4-Ethylsulfonyl-1-naphthalenesulfonamide (2) and 4-Ethylthio-1-naphthalenesulfonamide (18). The ^{13}C NMR spectra of these compounds (**2** and **18**) were not reported in the earlier paper[2] and were determined as part of the current work for comparison purposes to allow assignment of the compounds in this paper as belonging to the ENS (**2**) series: ^{13}C NMR (**2**) (Me_2SO-d_6) 145.2, 137.6, 129.4, 129.2, 128.6, 128.4, 126.5, 125.1, 124.9, 49.7, 7.2; ^{13}C NMR (**18**) (Me_2SO-d_6) 141.1, 136.2, 131.2, 128.0, 127.8, 127.1, 126.6, 126.1, 124.4, 120.9, 25.5, 13.6.

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Registry No.—**1**, 23043-35-8; **2**, 842-00-2; **3**, 529-36-2; **4**, 17225-94-4; **5**, 67761-05-1; **7**, 67761-06-2; **8**, 67761-07-3; **8a**, 67774-29-2; **9**, 67784-59-2; **10**, 67761-08-4; **11**, 35374-48-2; **12**, 67761-09-5; **13**, 67761-10-8; **14**, 67761-11-9; **15**, 67761-12-0; **16**, 67761-13-1; **17**, 67761-14-2; **18**, 28177-06-2; 2-chloroethanol, 107-07-3; **7** free acid, 67761-06-2.

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New Approaches to the Pyrrolizidine Ring System: Total Synthesis of (±)-Isoretronecanol and (±)-Trachelanthamidine[1,2]

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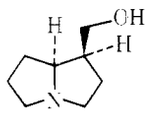
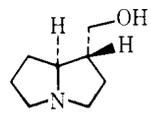
The family of alkaloids containing the pyrrolizidine ring system is attracting much attention[3] because of the wide range of physiological properties exhibited by these compounds.[4] We report the total synthesis of the two simplest members of this series of alkaloids: the diastereomers of 1-hydroxymethylpyrrolizidine, isoretronecanol (1), and trachelanthamidine (2).

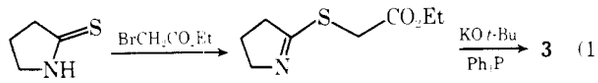


1



2

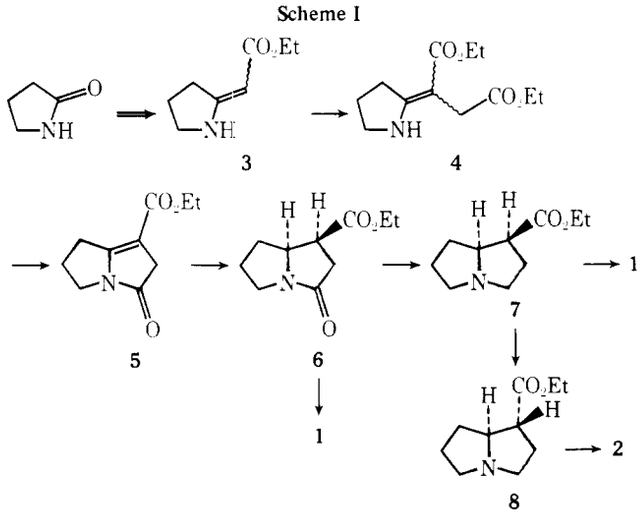
The basic strategy for the syntheses is outlined in Scheme I. Thus, pyrrolidone is converted into thiopyrrolidone which yields the enamine ester **3** by the two-step procedure developed by Eschenmoser[5] (eq 1). Reaction of compound **3** with



(1)

lithium diisopropylamide (LDA) in tetrahydrofuran (THF) followed by ethyl bromoacetate gives the diester **4** in 74% yield.[6] Cyclization with potassium hydride at 0 °C in THF affords the lactam **5** in nearly quantitative yield. Conversion

Scheme I



of this unsaturated lactam into the key intermediate **7** requires reduction of the lactam carbonyl as well as the enamine double bond; however, direct reduction of the lactam carbonyl proves difficult. Fortunately, catalytic reduction proceeds smoothly to give lactam ester **6** which undergoes further reduction with excess lithium aluminum hydride ($LiAlH_4$) to give isoretronecanol.

Selective reduction of lactam **6** would give ethyl isoretronecanolate (**7**) which is reported to epimerize upon heating with base to give the more stable diastereomer **8**[7] which will yield trachelanthamidine after reduction with $LiAlH_4$. Several attempts to carry out this selective reduction (**6** → **7**) with diborane[8] were complicated by the difficulty in destroying the amine–boron complex after the reduction was complete. In every attempt much product was lost during the workup. By using phosphoryl chloride/sodium borohydride[9] instead of diborane, however, this problem was circumvented and **6** was reduced to ester **7** in 66% yield. This completes a formal synthesis of trachelanthamidine.

Experimental Section

Proton nuclear magnetic resonance spectra were recorded on a Varian T-60 instrument. Carbon 13 nuclear magnetic resonance spectra were recorded on a JEOL PFT-100 spectrometer. All chemical shifts are reported in ppm downfield from tetramethylsilane (0.0) as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrometer and are reported in cm^{-1} (calibration with 1601 cm^{-1} polystyrene peak). Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

Reagent grade THF was distilled from potassium prior to use. Other anhydrous solvents were distilled from CaH_2 and stored over 4A molecular sieves until use.

Combustion analyses were performed by Atlantic Microlabs, Atlanta, Ga.

Preparation of Thiopyrrolidone. Phosphorus pentasulfide (24.4 g, 110 mmol) and 300 mL of anhydrous xylene were mixed in a 1000-mL flame-dried three-neck flask equipped with an efficient mechanical stirrer. Pyrrolidone (42.5 g, 500 mmol) was added in one portion and the solution was allowed to stir at room temperature for 20 min. A dark brown oil separated after the reaction mixture was heated at 130 °C for 30 min with vigorous stirring. The hot solution was filtered through a coarse sintered glass funnel. White crystals formed immediately in the filtrate. Fresh xylene (100 mL) was added to the oily residue and heated to 130 °C for 20 min followed by a hot filtration. This process was repeated once more and the combined xylene was allowed to cool. White crystals were collected by filteration and air dried to give 32.2 g (64%) of thiopyrrolidone: mp 114–115 °C (lit.[5] mp 114–115 °C) after recrystallization from $CHCl_3$/hexane; NMR ($CHCl_3$) 1.95–2.5 (2 H, m), 2.85 (2 H, unsym t, J = 8 Hz), 3.7 (2 H t, J = 8 Hz), 8.5 (1 H, br s); IR (NaCl) 3415 (sharp), 3120 (broad), 1547, 1520 cm^{-1}.

Alkylation of Thiopyrrolidone with Ethyl Bromoacetate. Ethyl bromoacetate (53.2 g, 319 mmol) was added dropwise to thiopyrrolidone (32.2 g, 319 mmol) dissolved in 250 mL of CH_2Cl_2 at 0–10 °C. The reaction mixture was allowed to warm gradually to room temperature and was stirred for 4 h. Solid $NaHCO_3$ was added in portions until further addition did not cause CO_2 evolution. The CH_2Cl_2 solution was washed with saturated $NaHCO_3$ and water, dried over $MgSO_4$, and concentrated to give the thioimino ester (60.0 g, 100%): bp 115–120 °C (1.2 mm); NMR ($CDCl_3$) 1.3 (3 H, t, J = 7 Hz), 1.8–2.4 (2 H, m), 2.5–2.9 (2 H, m), 3.7–4.1 (4 H, m and s), 4.3 (2 H, q, J = 7 Hz); IR (NaCl) 2950, 2850, 1735, 1580 cm^{-1}.

Preparation of Enamine Ester 3. The thioimino ester (60.0 g, 319 mmol), triphenylphosphine (334 g, 1.28 mol), and 550 mL of anhydrous xylene were combined in a flame-dried 1000-mL three-neck flask. A solution of KO-*t*-Bu (3.57 g, 32.0 mmol) in 20 mL of *tert*-butyl alcohol was added dropwise and the reaction mixture was stirred at room temperature for 4 h and then refluxed for 60 h. This was cooled and extracted with 150 mL of 10% HCl three times. The combined aqueous extracts were washed with 50 mL of ether three times, neutralized with solid $NaHCO_3$, and extracted with four 100-mL portions of CH_2Cl_2. The combined CH_2Cl_2 layers were washed twice with 80 mL of brine, dried over $MgSO_4$, and concentrated to give a crude brown solid which was sublimed (40 °C, 0.1 mm) to yield **3** (37.6 g, 76%): mp 62–63 °C; NMR ($CDCl_3$) 1.25 (3 H, t, J = 7 Hz), 2.0 (2 H, t, J = 6 Hz), 2.6 (2 H, t, J = 7 Hz), 3.6 (2 H, t, J = 6 Hz), 4.2 (2 H, q,

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