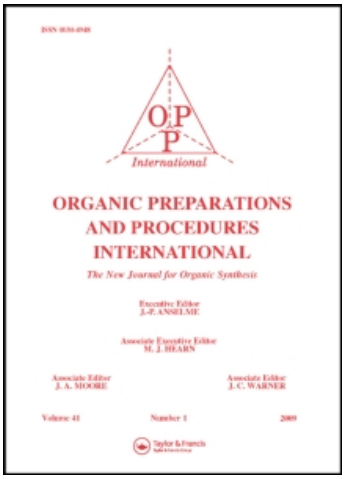

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SYNTHESIS OF 2-[4-METHOXY-2-[2-(METHYLSULFINYL)ETHOXY]PHENYL]-1H-IMIDAZO[4, 5-b]PYRIDINE, A POTENT NONGLYCOSIDE INHIBITOR OF Na^+, K^+-ATPASE

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8. Amberlyst-15, sulfonated, bead-form resin, was a gift from Rohm and Haas Co., Philadelphia, PA 19105.

9. R. D. Haworth, J. Chem. Soc., 1125 (1932).

10. 5% Carbowax 20 M on Chromosorb W, 1/8" x 6' at 200°C, with 4 preceding 5.

11. 3-Methylphenanthrene (5) was subjected to GC/MS using a 60-m DB-5 capillary column operated from 70° to 120° 10°/min, from 120 to 200° at 2°/min, and from 200 to 350° at 12°/min. We thank D. R. I. McNeil, Shell Development Company for these studies.

12. L. F. Fieser and C. C. Price, J. Am. Chem. Soc., 58, 1838 (1936).

13. W. M. Harms and E. J. Eisenbraun, Org. Prep. Proced. Int., 4, 67 (1972).

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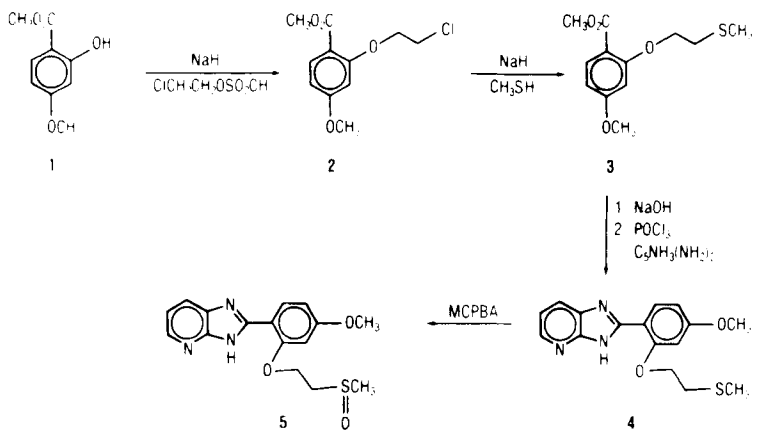
AR-L 100 (compound 5, 2-[4-methoxy-2-[2-(methylsulfinyl)ethoxy]-phenyl]-1H-imidazo[4,5-b]pyridine) is one of the few potent, nonglycoside inhibitors of Na^+, K^+-ATPase.[1,2] We now describe our synthesis of this important pharmacological tool as shown below. Since acid-catalyzed

esterification of 2-hydroxy-4-methoxybenzoic acid was surprisingly difficult, the carboxylate anion, generated from reaction with potassium carbonate in DMSO, was alkylated with dimethyl sulfate in 88% yield; no alkylation of the phenol was observed. The chloroethyl group was introduced by alkylation of the phenol anion with 2-chloroethyl methanesulfonate; although this reaction was sluggish, a 59% yield of 2 was obtained

Scheme



following purification by HPLC. The intermediate 3 was obtained by reaction of 2 with methyl mercaptan; only one equivalent was used to preclude nucleophilic dealkylation of the ester or ether moieties. Base-catalyzed hydrolysis provided the benzoic acid corresponding to ester 3. The overall yield for these final two steps was 88%.

Formation of the imidazo[4,5-b]pyridine ring system was effected in 61% yield by refluxing a mixture of the acid and 2,3-diaminopyridine (DAP) in phosphorus oxychloride.[3] Finally, low-temperature (-40 to -70°) oxidation of the sulfide with m-chloroperbenzoic acid (MCPBA) gave 5; only minor quantities of starting material and sulfone by-product were observed.

EXPERIMENTAL SECTION

Mps were determined on a Thomas-Hoover capillary melting point apparatus and were not corrected. Proton magnetic resonance (^{1}H-NMR) spectra were

obtained with a Bruker WM-270 spectrometer. Chemical shifts are reported in ppm downfield from a tetramethylsilane internal standard (δ scale). ^{1}H-NMR data are presented in the form: (solvent in which spectra were taken), δ value of signal (peak multiplicity, integrated numbers of protons, and assignment). Mass spectra were recorded from a Varian MAT CH-5 spectrometer at the ionization voltage expressed in parentheses. Only peaks of high relative intensity or of diagnostic importance are presented in the form: m/e (intensity relative to base peak). Microanalytical data were provided by the Physical Chemistry Department of the Lilly Research Laboratories. Except where noted, a standard procedure was used for product isolation. This involved quenching by addition to water, filtration or exhaustive extraction with a solvent (washing of extract with aqueous solutions, on occasion), drying over an anhydrous salt, and evaporation of solvent under reduced pressure. Particular solvents, aqueous washes (if needed), and drying agents are mentioned in parentheses after the phrase "product isolation".

Methyl 2-Hydroxy-4-methoxybenzoate (1).- Potassium carbonate (233.6 g, 1.69 mol) was added in portions to a solution of 2-hydroxy-4-methoxybenzoic acid (423.4 g, 2.52 mol) in 500 mL of anhydrous DMSO at 0°. After gas evolution ceased, dimethyl sulfate (238.9 mL, 2.52 mol) was added dropwise. After stirring the reaction overnight at room temperature, product isolation (ether, water, brine, $MgSO_4$) provided 405.5 g (88%) of homogeneous 1, mp. 37.5-39.0°. An analytical sample was obtained by recrystallization from methanol, mp. 39-41°.

^{1}H-NMR ($CDCl_3$): δ 3.82 and 3.91 (each s, each 3, ester and ether CH_3's), 6.30-6.53 (m, 2, ArH), 7.71 (d, 1, ArH ortho to carbomethoxy); MS (70 eV): m/e (rel intensity) 182 (35, M^+), 150 (100).

Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53

Found: C, 59.09; H, 5.40

Methyl 2-(2-Chloroethoxy)-4-methoxybenzoate (2).- Sodium hydride (6.6 g of a 60% dispersion in oil, 165 mmol) was added in portions to a solution of 1 (20 g, 110 mmol) in 100 mL of DMF. After hydrogen evolution ceased, 2-chloroethylmethanesulfonate (25.0 mL, 220 mmol) was added in one portion. The reaction was heated at 80° overnight. Product isolation (water, ethyl acetate, brine, $MgSO_4$) and preparative HPLC (silica gel, 0-25% ethyl acetate in hexane gradient) provided 15.9 g (59%) of 2 as a colorless oil that was homogeneous by TLC and NMR.

^{1}H-NMR ($CDCl_3$): δ 3.80-3.96 (m, 8, CH_3's and CH_2 α to Cl), 4.27 (t, 2, CH_2 α to O), 6.48 (s, 1, ArH ortho to chloroethoxy), 6.55 (d, 1, ArH para to chloroethoxy), 7.86 (d, 1, ArH ortho to carbomethoxy); MS (70 eV): m/e (rel intensity) 246 (21, M^+), 244 (87, M^+), 151 (100).

Anal. Calcd for $C_{11}H_{13}O_4Cl$: C, 54.00; H, 5.36; Cl, 14.49

Found: C, 54.22; H, 5.24; Cl, 14.29

Methyl 2-[2-(Methylthio)ethoxy]-4-methoxybenzoate (3).- Methanethiol (132 mL, 196 mmol) was added dropwise to a suspension of sodium hydride (2.74 g of a 60% dispersion in oil, 68.4 mmol) in 100 mL of DMF at 0°. After hydrogen evolution ceased, a solution of 2 (15.94 g, 65.2 mmol) in 100 mL of DMF was added rapidly. The reaction was stirred 2 hrs at room temperature. Product isolation (water, ethyl acetate, brine, Na_2SO_4) provided 16.6 g of 3 as a yellow oil that was essentially homogeneous by tlc and was used without purfication.

^{1}H-NMR ($CDCl_3$): δ 2.23 (s, 3, SCH_3), 2.94 (t, 2, CH_2S), 3.84 (s, 6, OCH_3's), 4.20 (t, 2, OCH_2), 6.46-6.54 (m, 2, ArH), 7.84 (d, 1, ArH ortho to carbomethoxy); MS (70 eV): m/e (rel intensity) 256 (1, M^+), 225 (22), 182 (100).

2-[2-(Methylthio)ethoxy]-4-methoxybenzoic Acid.- Sodium hydroxide (65.2 mL of a 5 N solution, 326 mmol) was added to a solution of ester (3) in 200 mL of methanol at room temperature. The reaction was stirred for 2 hrs and then solvent was removed under reduced pressure. The residue was dissolved in water and washed with hexane (discarded). The aqueous solution was then acidified with concentrated hydrochloric acid. Product isolation (ethyl acetate, water, brine, $MgSO_4$) provided 13.9 g (88% over 2 steps) of homogeneous product as a white solid. An analytical sample was prepared by recrystallization from THF/hexane to provide the product 6 as white crystals, mp. 76-77°.

^{1}H-NMR ($CDCl_3$): δ 2.20 (s, 3, SCH_3), 3.00 (t, 2, CH_2S), 3.88 (s, 3, OCH_3), 4.36 (t, 2, OCH_2), 6.53 (s, 1, ArH ortho to both esters), 6.67 (d, 1, ArH para to methylthioethoxy), 8.15 (d, 1, ArH ortho to carboxy); MS (70 eV): m/e (rel intensity) 168 (39), 75 (100).

Anal. Calcd for $C_{11}H_{14}O_4S$: C, 54.53; H, 5.82

Found: C, 54.25; H, 5.84

2-[4-Methoxy-2-[2-(methylthio)ethoxy]phenyl]-1H-imidazo[4,5-b]pyridine (4).- An intimate mixture of 2-[2-(methylthio)ethoxy]-4-methoxybenzoic acid (12.98 g, 53.6 mmol) and 2,3-diaminopyridine (5.85 g, 53.6 mmol) was added to 250 mL of phosphorus oxychloride. The reaction was heated at reflux for 5 h and then the phosphorus oxychloride was removed under reduced pressure. Water was slowly added to the residue, followed by 5 N sodium hydroxide until the pH was 8 (**CAUTION**: Aqueous decomposition of phosphorus oxychloride can be violent!). The precipitated product was chromatographed (silica gel, 0-3% methanol in methylene chloride) to provide 10.3 g (61%) of homogeneous 4 as a tan solid.

^{1}H-NMR (DMSO-d_6): δ 2.14 (s, 3, SCH_3), 3.07 (t, 2, CH_2S), 3.87 (s, 3, OCH_3), 4.44 (t, 2, OCH_2), 6.77, 7.96, 8.22, and 8.32 (each d, each 1, ArH) 6.82 (s, 1, ArH), 7.21 (dd, 1, ArH); MS (70 eV): m/e (rel intensity) 315 (21, M^+), 241 (100). The hydrochloride salt was prepared and recrystallized from ethanol, mp. 203°.

Anal. Calcd for $C_{16}H_{18}ClN_3O_2S$: C, 54.62; H, 5.16; N, 11.94; Cl, 10.08

Found: C, 54.56; H, 5.22; N, 12.14; Cl, 10.19

2-[4-Methoxy-2-[2=(methylsulfinyl)ethoxy]phenyl]-1H-imidazo[4,5-b]pyridine (5).- The sulfide 4 (4.22 g, 13.4 mmol) was suspended in ca. 100 mL of chloroform; sufficient methanol was added to achieve homogeneity, and the solution was maintained between -40 and -70°. A solution of MCPBA (3.73 g, 13.4 mmol) in ca. 40 mL of methanol was added dropwise over a 1 hr period. The reaction was stirred at room temperature overnight. Removal

of solvent under reduced pressure and flash chromatography (silica gel, 0-4% methanol in methylene chloride gradient) provided 3.3 g (74%) of homogeneous product. Recrystallization from THF/methanol/methylene chloride provided 2.66 g of 5 as light yellow crystals, mp. 195-196°.

^{1}H-NMR (DMSO-d_6): δ 2.81 (s, 3, SCH_3), 3.30-3.56 (m, 2, CH_2S), 3.90 (s, 3, OCH_3), 4.64-4.88 (m, 2, OCH_2), 6.76-6.90, 7.18, and 8.32 (m, 6, ArH); MS (70 eV): m/e (rel intensity) 331 (3, M^+), 241 (100).

Anal. Calcd for $C_{16}H_{17}N_3O_3S$: C, 57.99; H, 5.17, N, 12.68

Found: C, 58.23; H, 5.30; N, 12.68

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REFERENCES

1. W. Diederen and R. Kadatz, Arzneim.-Forsch., 31, 141 (1981).

2. J. S. Hayes, V. L. Wyss, H. C. Wilson, D. W. Robertson and R. F. Kauffman, J. Pharmacol. Exp. Ther., 239, 375 (1986).

3. D. W. Robertson, E. E. Beedle, J. H. Krushinski, G. D. Pollock, H. Wilson, V. L. Wyss and J. S. Hayes, J. Med. Chem., 28, 717 (1985).