

Synthesis of Unsymmetrical Dithioacetals: An Efficient Synthesis of a Novel LTD₄ Antagonist, L-660,711

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An efficient four-step synthesis of the potent LTD₄ antagonist L-660,711 (1) is described. The key step involves selective conversion of aldehyde 2 to the unsymmetrical dithioacetal 7, via *O*-trimethylsilyl hemithioacetal 10. This specific cleavage of the carbon-oxygen bond of a mixed *O,S*-acetal permits the unprecedented synthesis of unsymmetrical dithioacetals.

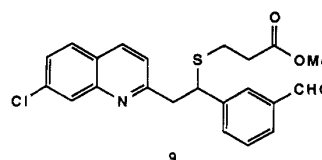
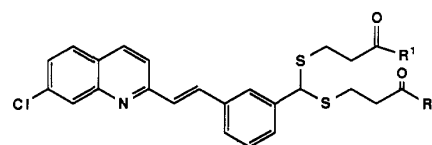
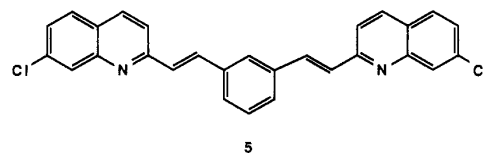
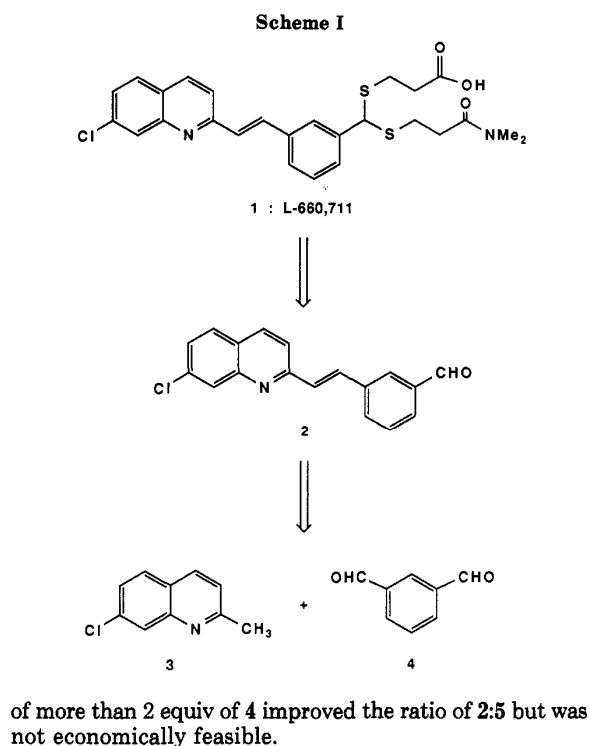
The important biological activity of the slow-reacting substance of anaphylaxis (SRS-A) has been attributed to the leukotrienes LTC₄, LTD₄, and LTE₄. Their potentially important role in the etiology of human asthma and other diseases suggests that leukotriene antagonists will offer effective new therapy. Thus, extensive efforts have been directed toward the discovery and synthesis of such agents.¹

L-660,711 (1) [5-(3-(2-(7-chloroquinolin-2-yl)ethenyl)phenyl)-4,6-dithianonedicarboxylic acid *N,N*-dimethylamide]² is a potent, orally active, specific LTD₄ antagonist. As part of our efforts on this important clinical candidate an efficient synthesis was designed. This paper details that synthesis.

A retrosynthetic analysis of 1 is outlined in Scheme I, the key step being the construction of the unsymmetrical dithioacetal 1 from aldehyde 2. In order to achieve this transformation in a *selective* manner, novel methodology was required. The intermediate aldehyde 2 would come from the coupling of two readily available fragments: 7-chloroquinaldine (3)³ and 1,3-benzenedicarboxaldehyde (4).⁴

Results and Discussion

Aldehyde Synthesis. Aldehyde 2 was prepared by condensation of 7-chloroquinaldine (3) with 1.5 equiv of 1,3-benzenedicarboxaldehyde (4) in the presence of acetic anhydride (3 equiv).⁵ A major byproduct, bis-adduct 5, was produced to the extent of ca. 20%. The crude product was isolated as a 4:1 mixture of 2:5 in 90% yield by filtration. Purification was effected by digestion of the crude product in hot ethyl acetate, removal of the extremely insoluble bis-adduct 5 by filtration, and crystallization. In this manner ≥98% pure aldehyde 2 was obtained in 65% overall yield. Use of less than 1.5 equiv of 1,3-benzenedicarboxaldehyde (4) in the condensation reaction gave unacceptably high levels of bis-adduct 5. Conversely, use



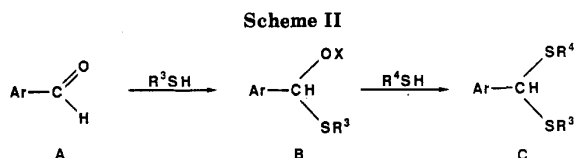
(1) Young, R. N.; Guindon, T. R.; Jones, A. W.; Ford-Hutchinson, P.; Belanger, P.; Champion, E.; Charette, L.; DeHaven, R. N.; Denis, D.; Fortin, R.; Frenette, R.; Gauthier, J.-Y.; Gillard, J. W.; Kakushima, M.; Letts, L. G.; Masson, P.; Maycock, A.; McFarlane, C.; Piechuta, H.; Pong, S. S.; Rosenthal, A.; Williams, H.; Zamboni, R.; Yoakim, C.; Rokach, J. *Advances in Prostaglandin, Thromboxane, and Leukotriene Research*; Raven Press: New York, 1986; Vol. 16, p 37.

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Dithioacetal Synthesis. Our initial attempts to prepare a symmetrical dithioacetal **6** via aldehyde **2** by reaction with methyl 3-mercaptopropionate were unsuccessful. Reaction of **2** with 2.0 equiv of methyl 3-mercaptopropionate and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) in refluxing benzene gave adduct **9**, which arises from conjugate addition of the thiol to the unsaturated quinoline. Lewis acids such as zinc halides also led to conjugate addition. Boron trifluoride etherate, however, was found to be an ideal Lewis acid, effecting the desired conversion of aldehyde **2** to dithioacetals without promoting conjugate addition. For example, treatment of **2** with 2.0 equiv of methyl 3-mercaptopropionate and 2.0 equiv of boron trifluoride etherate in anhydrous methylene chloride at 0 °C gave dithioacetal **6** in 87% yield. It should be noted that at least 2 equiv of boron trifluoride etherate were required for this reaction; presumably 1 equiv complexes with the quinoline nitrogen and is unavailable to activate the aldehyde.⁶ This result also implies that boron trifluoride etherate is less activating than protic acids (such as PPTS) for conjugate addition to the unsaturated quinoline.

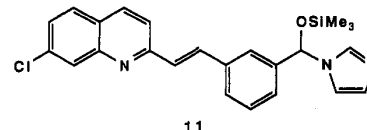
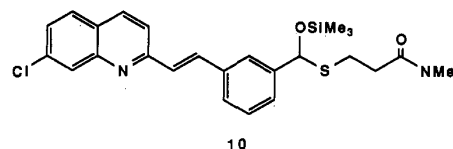
A modification of this procedure led to a straightforward preparation of the required unsymmetrical dithioacetal **7**. Thus, treatment of **2** with 1 equiv of methyl 3-mercaptopropionate, 1 equiv of *N,N*-dimethyl-3-mercaptopropionamide⁷ and 3 equiv of boron trifluoride etherate in anhydrous acetonitrile at 0 °C gave approximately the statistical distribution (1:2:1) of diester **6**, desired ester amide **7**, and diamide **8** in >95% yield. The analytically pure unsymmetrical ester amide **7** was isolated in 49% yield after simple silica gel chromatography and crystallization.

Selective Unsymmetrical Dithioacetal Synthesis. Obviously, a *selective* method to prepare the unsymmetrical dithioacetal **7** from aldehyde **2** was desired. To the best of our knowledge, no synthetic method to effect this transformation has been reported.⁸ The plan to achieve this goal is outlined in Scheme II. It consists of formation of a mixed *O,S*-acetal (**B**) followed by selective carbon-oxygen bond cleavage to produce the unsymmetrical dithioacetal (**C**).

Evidence that supports this proposal was obtained as follows: Treatment of aldehyde **2** with 1 equiv of methyl 3-mercaptopropionate and 2 equiv of boron trifluoride etherate in anhydrous methylene chloride at -50 °C for 30 min led to a ca. 50% yield of diester **6** with a recovery of ca. 50% of **2**. Thus, rupture of the carbon-oxygen bond in presumed intermediate **B** where X = BF₃ is relatively fast, even at -50 °C. Secondly, treatment of diester **6** with 1 equiv of *N,N*-dimethyl-3-mercaptopropionamide and 3 equiv of boron trifluoride etherate in either anhydrous methylene chloride or ethyl acetate at -50 °C for 12 h gave

only trace amounts (≤5%) of thiol-exchanged compounds **7** and **8**. This implies that cleavage of the carbon-sulfur bonds in diester **6** is relatively slow, in contrast to the rupture of the carbon-oxygen bond in **B**.

Thus, we turned our attention to the preparation of an unsymmetrical hemithioacetal intermediate of type **B**. Noting earlier reports of *O*-trimethylsilyl hemithioacetals, we chose to investigate the preparation of compound **10**. However, due to the sensitive nature of substrate **2**, precisely defined conditions for its conversion to **10** were required. Application of Evans⁹ and Chan's¹⁰ conditions were unsatisfactory due to competitive conjugate addition of the thiol to the unsaturated quinoline (cf. **9** above). This problem was averted by a modification of Glass's procedure,¹¹ the net result being facile preparation of the desired *O*-trimethylsilyl hemithioacetal **10**. Treatment of aldehyde **2** with 1.06 equiv of *N,N*-dimethyl-3-mercaptopropionamide and 1 molar equiv of 1,1,1,3,3,3-hexamethyldisilazane in the presence of 10 mol % imidazole in anhydrous methylene chloride with a nitrogen sweep to remove the ammonia afforded very clean conversion to **10** with ≤5% remaining starting aldehyde. It is interesting to note that attempted formation of **10** using stoichiometric 1-(trimethylsilyl)imidazole as the silylating agent led to significant 1,2-addition of 1-(trimethylsilyl)imidazole to the aldehyde to give the corresponding *N,O*-trimethylsilyl acetal **11**.¹²



The conversion of *O*-trimethylsilyl hemithioacetal **10** to the unsymmetrical dithioacetal **7** was then investigated. Treatment of **10** with 1.10 equiv of methyl 3-mercaptopropionate and 3.0 equiv of boron trifluoride etherate in anhydrous methylene chloride at -55 °C gave **7** with good selectivity, the relative distribution of the desired unsymmetrical ester amide **7**:diamide **8**:diester **6** being > 8:1:1. In situ ¹H NMR studies showed that at temperatures above -40 °C boron trifluoride etherate begins to cleave the *O*-silylated hemithioacetal **10** and produce aldehyde **2**. Under these conditions (with both thiols present) **2** was converted to a statistical mixture of dithioacetals **6**, **7**, and **8**, the result being a compromise of overall selectivity. At lower temperatures decomposition of **10** was prevented and high selectivity was achieved.

The key ratio of amide-ester **7** to diester **6** was further improved by either direct crystallization of crude **7** or by a simple silica gel chromatography. In this way **7** was isolated with ≤1% diester **6** present. To our knowledge, this is the first report of a practical, selective synthesis of unsymmetrical dithioacetals.

Ester Hydrolysis. Ester-amide **7** was then hydrolyzed to L-660,711 (**1**) under basic conditions. Treatment of a tetrahydrofuran solution of **7** with aqueous lithium hy-

(6) For the coordination of boron trifluoride etherate with imines, see: Ryan, K. M.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* 1987, 28, 2103.

(7) Durden, J. A. U.S. Patent 4,454,134, 1984. See the Experimental Section for our modified preparation of this compound.

(8) For a recently discovered alternative synthesis of unsymmetrical dithioacetals, see: Gauthier, J. Y.; Henien, T.; Lo, L.; Therien, M.; Young, R. N. *Tetrahedron Lett.* 1988, 29, 6729. Therien, M.; Gauthier, J. Y.; Young, R. N. *Tetrahedron Lett.* 1988, 29, 6733. See also Young, R. N.; Gauthier, J. Y.; Therien, M.; Zamboni, R. *Heterocycles* 1989, 28, 967 (and reference 6 therein).

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dioxide (1.05 equiv, -3°C to 2°C , 4.5 h) followed by acidic workup produced crystalline **1** in 88% yield. During the workup any residual diamide **8** is removed in the neutral organic layer leaving $\geq 98\%$ pure L-660,711 (**1**).

Conclusion

The selective cleavage of the carbon-oxygen bond of a mixed *O,S*-acetal has been used to permit the conversion of an aldehyde to an unsymmetrically substituted dithioacetal. This novel and practical chemistry has resulted in the efficient synthesis (four steps, 34% overall yield) of the pharmacologically important LTD₄ antagonist L-660,711 (**1**) and will be widely applicable to this exciting class of compounds.

Experimental Section

Proton NMR spectra were measured on a Bruker WM-250, AM-250, or AM-300 spectrometer with 0.5 Hz/Pt digital resolution or better. Spectra are referenced to the solvent (CHCl_3 $\delta = 7.27$ ppm; DMSO $\delta = 2.50$ ppm). Assignments were made by using COSY (2D) and NOE difference experiments. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Microanalyses were obtained on a Control Equipment Model 240X elemental analyzer. 7-Chloroquinoline (**3**) was obtained from Trans World Chemicals, Inc. (Rockville, MD). 1,3-Benzenedicarboxaldehyde (**4**) was obtained from Lancaster Synthesis, Ltd. Methyl 3-mercaptopropionate was obtained from Aldrich.

Aldehyde 2. 7-Chloroquinoline (**3**) (3000 g, 16.89 mol), 1,3-benzenedicarboxaldehyde (**4**) (3398 g, 25.34 mol), and acetic anhydride (4.69 L, 49.7 mol) were suspended in xylene (16 L) and heated to reflux for 7 h with mechanical stirring. The reaction mixture was allowed to cool to ca. 40°C overnight, and hexane (16 L, precooled to 5°C) was added with stirring. After being cooled to 21 – 23°C , the reaction mixture was filtered, and the collected solid was rinsed with hexane (16 L). Overnight drying in vacuo gave the crude product (4470 g).

Half of the crude product was suspended in EtOAc (40 L) and heated to reflux. The insoluble bis-adduct **5** was removed by hot filtration through a preheated, jacketed, sintered-glass funnel. The filtrate was concentrated in vacuo at $\leq 40^{\circ}\text{C}$ to ca. 15 L, heated to reflux, and cooled to ambient temperature overnight. The resulting slurry was cooled to 0°C , stirred for 2 h, and filtered. The filter cake was washed with cold EtOAc (ca. 5 L) and then dried overnight in vacuo at 45°C . The other half of the crude product was processed as above to afford crystalline aldehyde **2** (total = 3228 g, 65%). An analytical sample was prepared by recrystallization from EtOAc: mp 156 – 157°C ; $^1\text{H NMR}$ (CDCl_3) δ 7.46 (d, $J = 16.1$ Hz, 3'-CH=), 7.48 (dd, $J = 8.3$, 2.0 Hz, 6-H), 7.59 (t, $J = 7.8$ Hz, 5'-H), 7.65 (d, $J = 8.3$ Hz, 3-H), 7.74 (d, $J = 8.3$ Hz, 5-H), 7.80 (d, $J = 16.1$ Hz, 2-CH=), 7.86 (dt, $J = 7.8$, 2.0 Hz, 6'-H), m.90 (dt, $J = 7.8$, 2.0 Hz, 4'-H), 8.10 (d, $J = 2.0$ Hz, 8-H), 8.14 (d, $J = 8.3$ Hz, 4-H), 8.15 (t, $J = 2.0$ Hz, 2'-H), 10.08 (s, CH). Anal. Calcd for $\text{C}_{19}\text{H}_{12}\text{ClNO}$: C, 73.59; H, 4.12; Cl, 12.07; N, 4.77. Found: C, 73.52; H, 4.17; Cl, 12.25; N, 4.70.

An analytical sample of the bis-adduct **5** was prepared by slurrying **5** (obtained as described above) in hot EtOAc followed by filtration and rinsing the filter cake with hot EtOAc: mp 266 – 267°C ; $^1\text{H NMR}$ (CDCl_3) δ 7.44 (d, $J = 16.9$ Hz, 1'-CH=), 7.47 (overlapping m, 6-H, 5'-H), 7.62 (b d, $J = 8$ Hz, 4'-H), 7.67 (d, $J = 9.1$ Hz, o-H), 7.77 (overlapping doublets, $J \approx 16$, 8 Hz, 2-CH=, 5-H), 7.93 (b s, 2'-H), 8.10 (d, $J = 1.8$ Hz, 8-H), 8.14 (d, $J = 8.1$ Hz, 4-H). Anal. Calcd for $\text{C}_{28}\text{H}_{18}\text{Cl}_2\text{N}_2$: C, 74.18; H, 4.00; Cl, 15.64; N, 6.18. Found: C, 74.02; H, 4.09; Cl, 15.59; N, 6.16.

Diester 6. To a stirred solution of aldehyde **2** (3.00 g, 10.2 mol) and methyl 3-mercaptopropionate (2.26 mL, 20.4 mol) in anhydrous CH_2Cl_2 (150 mL) at -5°C was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (2.52 mL, 20.4 mol) dropwise. After 2 h at -5 to 0°C , the reaction mixture was poured into a stirred solution of 15% aqueous Na_2CO_3 (200 mol) and extracted with CH_2Cl_2 (200 mL). The organic layer was washed with 10% aqueous Na_2CO_3 (100 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo to give the crude product, which was purified by silica gel (SG) chromatography (60 g SG, elution with 25% EtOAc in hexane) to give diester **6** (4.58 g, 87%),

which slowly crystallized on standing. An analytical sample was prepared by recrystallization ($2\times$) from hexane-EtOAc: mp 54 – 56°C ; $^1\text{H NMR}$ (CDCl_3) δ 2.6 (t, $J = 7.3$ Hz, 2 CCH_2), 2.86 (m, 2 SCH_2), 3.69 (s, 2 OCH_3), 5.04 (s, Ar-CH), 7.39 (d, $J = 16.1$ Hz, 3'-CH=), 7.40 (overlapping m, 5'-H, 6'-H) 7.45 (dd, $J = 8.8$, 2.0 Hz, 6-H), 7.56 (dt, $J = 7.1$, 2.0 Hz, 4'-H), 7.65 (d, $J = 8.8$ Hz, 3-H), 7.70 (d, $J = 16.1$ Hz, 2-CH=) 7.72 (d, $J = 8.8$ Hz, 5-H), m.74 (b t, $J = 2.0$ Hz, 2'-H), 8.07 (d, $J = 2.0$ Hz, 8-H), 8.11 (d, $J = 8.8$ Hz, 4-H). Anal. Calcd for $\text{C}_{28}\text{H}_{28}\text{ClN}_2\text{O}_4$: C, 61.29; H, 5.52; Cl, 6.70; N, 5.30; S, 12.12. Found: C, 61.30; H, 5.57; Cl, 6.65; N, 5.23; S, 12.10.

***N,N*-Dimethyl-3-mercaptopropionamide.** *N,N*-Dimethylacrylamide (1.24 L, 12.0 mol) was cooled to -5°C , and thioacetic acid (0.850 L, 12.0 mol) was added dropwise over ca. 2 h with stirring while the temperature was maintained at $\leq 5^{\circ}\text{C}$ (exothermic). The reaction mixture was allowed to warm to ambient temperature over 12 h, and then MeOH (6 L) was added. The reaction mixture was cooled to -5°C , and 3 N aqueous NaOH (6 L) was added dropwise with stirring at $\leq 5^{\circ}\text{C}$. After 2 h at $\leq 10^{\circ}\text{C}$ the pH was adjusted to 7.5 with concentrated HCl (ca. 1.3 L) while the temperature was maintained at $\leq 10^{\circ}\text{C}$. The reaction mixture was concentrated in vacuo in order to remove the MeOH, and the residual aqueous concentrate was extracted with CH_2Cl_2 (4×1 L). The combined extracts were washed with brine (2 L), dried over MgSO_4 , filtered, and concentrated in vacuo to an oil, which was vacuum distilled (bp 101 – 104°C at 2.5 mm) to give pure *N,N*-dimethyl-3-mercaptopropionamide (1342 g, 84%) after a ca. 80 g forerun: $^1\text{H NMR}$ (CDCl_3) δ 1.77 (t, $J = 8.3$ Hz, SH), 2.65 (t, $J = 6.7$ Hz, CH_2C), 2.81 (m, CH_2S), 2.96, 3.00 (2 s, $\text{N}(\text{CH}_3)_2$).

Hemithioacetal 10. A 500-mL three-necked flask was equipped with a rubber septum containing a nitrogen inlet needle, a mechanical stirrer, and a drying tube containing CaCl_2 . 1,1,1,3,3,3-Hexamethyldisilazane (7.2 mL, 17 mmol), *N,N*-dimethyl-3-mercaptopropionamide (4.51 mL, 36.0 mmol), and imidazole (0.23 g, 3.4 mmol) were added to a suspension of aldehyde **2** (10.0 g, 34.0 mmol) in anhydrous CH_2Cl_2 (100 mL). The reaction mixture was stirred under a gentle nitrogen sweep (in order to remove NH_3), which caused the internal temperature to drop to 12 – 14°C . Additional anhydrous CH_2Cl_2 was added periodically in order to maintain the initial volume of the reaction mixture. After 24 h $^1\text{H NMR}$ analysis indicated high conversion to the *O*-silylated hemithioacetal **10** with $\leq 5\%$ remaining **2**. The reaction mixture was filtered and concentrated in vacuo at $\leq 25^{\circ}\text{C}$ to give crude **10** as an oil. Anhydrous CH_2Cl_2 solutions of **10** are stable for at least 3 weeks at room temperature: $^1\text{H NMR}$ (CDCl_3) δ 0.20 (s, $\text{OSi}(\text{CH}_3)_3$), 2.49 (m, CH_2C), 2.85 (m, CH_2S), 2.90, 2.92 (i s, $\text{N}(\text{CH}_3)_2$), 6.07 (s, Ar-CH), 7.36 (t, $J = 7.5$ Hz, 5'-H), 7.38 (d, $J = 16.1$ Hz, 3'-CH=), 7.44 (overlapping m, 6-H, 6'-H), 7.53 (dt, $J = 7.5$, 1.5 Hz, 4'-H), 7.65 (d, $J = 8.5$ Hz, 5-H), 7.72 (d, $J = 8.8$ Hz, 3-H), 7.72 (d, $J = 16.1$ Hz, 2-CH=), 7.75 (b s, 2'-H), 8.06 (d, $J = 2.0$ Hz, 8-H), 8.11 (d, $J = 8.8$ Hz, 4-H).

Ester-Amide 7. From Aldehyde 2. To a suspension of aldehyde **2** (1200 g, 4.08 mol) in anhydrous CH_3CN (9.5 L) was added *N,N*-dimethyl-3-mercaptopropionamide (533 mL, 4.28 mol) and methyl 3-mercaptopropionate (430 mL, 3.88 mol). The reaction mixture was cooled to -10°C , and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.50 L, 12.2 mol) was added dropwise with stirring over 1.5 h while the temperature was maintained at $\leq 3^{\circ}\text{C}$. After 2 h at -8°C to 2°C the reaction mixture was poured into a stirred solution of 15% aqueous Na_2CO_3 (38 L). EtOAc (24 L) was added, and after mixing and separation the organic product layer was washed with 5% aqueous Na_2CO_3 (24 L). Concentration in vacuo at $\leq 30^{\circ}\text{C}$ gave the crude product as an oil, which was adsorbed on silica gel (1.5 kg) by evaporation of a CH_2Cl_2 solution (6 L). The resulting "dry pack" of the crude compound on silica gel was purified by chromatography on silica gel (8 kg of silica gel, elution with a gradient of 25% EtOAc in hexane to EtOAc: R_f values in 1:1 hexane-EtOAc aldehyde **2**, 0.9; diester **6**, 0.85; ester-amide **7**, 0.4; diamide **8**, 0.1) to give ester-amide **7**, which crystallized on standing. Slurrying in warm 2:1 hexane-EtOAc (8 L) followed by cooling to 5°C , filtration, rinsing with hexane (6 L), and drying in vacuo for 24 h afforded pure **7** (1058 g, 49%): mp 108 – 109°C ; $^1\text{H NMR}$ (CDCl_3) δ 2.6 (overlapping m, CH_2C), 2.85, (overlapping m, 2 CH_2S), 2.90 (s, $\text{N}(\text{CH}_3)_2$), 3.58 (s, OCH_3), 5.06 (s, Ar-CH), 7.3–8.2 (aromatic and olefinic protons are essentially identical

with assignments for 7). Anal. Calcd for $C_{27}H_{29}ClN_2S_2O_3$: C, 61.29; H, 5.52; Cl, 6.70; N, 5.30; S, 12.12. Found: C, 61.30; H, 5.57; Cl, 6.65; N, 5.23; S, 12.10.

From O-Silylated Hemithioacetal 10. The O-silylated hemithioacetal reaction mixture as described above (ca. 34 mmol of 10) was filtered, and the resulting CH_2Cl_2 solution was cooled to $-50^\circ C$. Methyl 3-mercaptopropionate (4.33 mL, 39.1 mmol) was added followed by dropwise addition of $BF_3 \cdot Et_2O$ (21.0 mL, 170 mmol) with mechanical stirring at $<-45^\circ C$. The reaction mixture was stirred at $-50^\circ C$ for 16 h and then was quenched by addition to a stirred solution of 15% aqueous Na_2CO_3 (200 mL). Additional CH_2Cl_2 (100 mL) was added, and the resulting organic layer was separated, washed with brine (150 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo at $\leq 30^\circ C$ to give the crude product as a 8:1:1 mixture of 7:8:6. Purification as described above gave ester-amide 7 (10.9 g, 61%).

L-660,711 (1). Ester-amide 7 (746 g, 1.41 mol) was dissolved in warm THF (8.8 L) and cooled to $-3^\circ C$. A solution of 1.00 N aqueous LiOH (1.48 L, 1.48 mol) was added dropwise with mechanical stirring over ca. 1.2 h at $\leq 0^\circ C$. After an additional 2 h at -1 to $1^\circ C$, extra 1.00 N aqueous LiOH (70 mL, 0.070 mol) was added. After a total reaction time of 4.5 h at -3 to $2^\circ C$, water (12 L; precooled to $5^\circ C$) was added and the THF was removed in vacuo at $\leq 20^\circ C$. The resulting aqueous concentrate was extracted with EtOAc (2×4.5 L) and transferred to a round-bottomed flask equipped with a mechanical stirrer. 2-Propanol

(13 L) was added, and the pH was adjusted to 6.0 with concentrated HCl. Seed crystals of 1 (ca. 7 g) were added, and the pH was adjusted to 3.5 with 2 N aqueous HCl. After being stirred for 16 h at ambient temperature, the resulting product was filtered, rinsed with 2-propanol (7 L), and dried in vacuo at $50^\circ C$ overnight to give crystalline 1 (639 g, 88%; $\geq 97\%$ pure by HPLC). An analytical sample was prepared by recrystallization from 2-butanone: mp $161.5-163^\circ C$; 1H NMR (DMSO- d_6) δ 2.5-3.4 (overlapping multiplets, 4 CH_2), 2.79, 2.89 (2 s, $N(CH_3)_2$), 5.32 (s, Ar-CH), 7.44 (m, 5'-H, 6'-H), 7.47 (d, $J = 16.5$, 3'-CH=), 7.59 (dd, $J = 8.7, 2.3$ Hz, 6-H), 7.67 (m, 4'-H), 7.80 (b s, 2'-H), 7.87 (d, $J = 16.5$ Hz, 2-CH=), 7.95 (d, $J = 8.6$ Hz, 3-H), 8.00, 8.03 (overlapping doublets, 5-H, 8-H), 8.40 (d, $J = 8.6$ Hz, j-H), 12.3 (broad, CO_2H). Anal. Calcd for $C_{26}H_{27}ClN_2S_2O_3$: C, 60.63; H, 5.28; Cl, 6.88; N, 5.44. Found: C, 60.68; H, 5.36; Cl, 6.98; N, 5.35.

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Reactivity of Biologically Important Reduced Pyridines. 4. Effect of Substitution on Ferricyanide-Mediated Oxidation Rates of Various 1,4-Dihydropyridines[†]

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The effect of substitution on the rate of ferricyanide-mediated oxidation of various dihydropyridines was examined. 1-Alkyl-, 1-aryl-, 1-aryl-, and 6-substituted 1-methyl-1,4-dihydropyridines, 3-substituted 1-methyl-1,4-dihydropyridines, and quinoline and isoquinoline derivatives were subjected to ferricyanide oxidation. Increasing the *n*-alkyl chain of 1-methyl-1,4-dihydropyridine acted to slowly decrease the rate of oxidation. The 1-cyclopropyl-1,4-dihydropyridine was shown to be unusually stable compared to the 1-isopropyl derivative due presumably to the electron-withdrawing nature of the π -like substituent. 1-(4-Substituted phenyl)-1,4-dihydropyridines over the range of *p*-NO₂ ($\sigma = 0.778$) to *p*-N(CH₃)₂ ($\sigma = 0.83$) generated a linear Hammett plot ($r = 0.9994$) with a reaction constant of $\rho = 2.76$, consistent with an initial electron removal in the rate-determining step of oxidation. When substitutions at the 3-position are considered, the rank order of stability was CHO > CN > COCH₃ > COOCH₃ > CONH₂ > CONHR > CONR₂ and is related to the electron-withdrawing potency of the moiety. Finally the 1-methyl-1,4-dihydro-3-quinolinecarboxamide was found to be much more stable than the 2-methyl-1,2-dihydro-4-isoquinolinecarboxamide.

Introduction

The occurrence of dihydropyridine partial structures in biologically important coenzymes such as NADH and NADPH has made these compounds an appealing subject for study.¹ Of particular importance is the mechanism

of oxidation of substituted dihydropyridines. The classical work of Abeles and Westheimer suggested that the oxidation of various dihydropyridines by thiobenzophenones was mediated by concerted hydride transfer.² Later, discrepancies between kinetic isotope effects and product isotope compositions indicated that intermediates existed on the reaction coordinate for this process.³ Postulated intermediates included radical cations which can be formed

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