Novel Alkaline Ring Cleavage of 2-Phenyl-3-hydroxythieno[2,3-*b*]quinoline 1,1-Dioxide, a Potent Inhibitor of Cyclic Adenosine 5′-Monophosphate Phosphodiesterase[1a]

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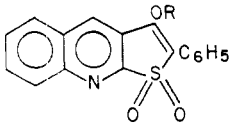
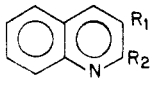
The sodium salt (**1b**) of the potent cyclic AMP phosphodiesterase inhibitor 2-phenyl-3-hydroxythieno-[2,3-*b*]quinoline 1,1-dioxide (**1a**) has been shown to undergo a novel, high-yielding ring cleavage to benzyl 3-(2-methoxyquinolyl) ketone (**5**) and sulfur dioxide when treated with sodium methoxide in refluxing methanol. Conditions used for this transformation are somewhat more vigorous than those employed earlier for the preparation of **1b**. Formation of **5** from **1b** or benzyl 2-[3-(carbomethoxy)quinolyl)] sulfone (**4**), which is initially converted to **1b** under the reaction conditions, appears to proceed with loss of sulfur dioxide from an intermediate sulfinic acid which, in turn, is presumably formed by nucleophilic attack of methoxide ion on **1b**, followed by ring opening. Additional reactions of the system studies are described.

Recently, we reported[2] a potent new class of cyclic AMP phosphodiesterase inhibitors of which 2-phenyl-3-hydroxythieno[2,3-*b*]quinoline 1,1-dioxide (**1a**) was the



1a, R = H
1b, R = Na

prototype in the series synthesized. Synthesis of **1a** proceeded from quinoline via the readily available benzyl 2-(3-formylquinolyl) sulfide (**2**) by using a novel sodium



2, R_1 = CHO, R_2 = $SCH_2C_6H_5$
3, R_1 = CO_2H, R_2 = $SO_2CH_2C_6H_5$
4, R_1 = CO_2CH_3, R_2 = $SO_2CH_2C_6H_5$
5, R_1 = $COCH_2C_6H_5$, R_2 = OCH_3
6, R_1 = $CHOHCH_2C_6H_5$, R_2 = OCH_3
11, R_1 = CO_2H, R_2 = OCH_3
12, R_1 = CO_2CH_3, R_2 = OCH_3

chlorite oxidation of **2** directly to acid **3** followed by cyclization of the corresponding ester **4** and acidification. The cyclization of **4** to the freely water-soluble **1b** occurred in nearly quantitative yield, using 1.1 equiv of sodium methoxide in refluxing methanol for 15–30 min (Scheme I).

We now find that when **1b** or **4** is refluxed with excess sodium methoxide, the intense orange color of **1b** (which is initially formed from **4**) gradually fades and, after 8 h, has essentially disappeared. As indicated by TLC analysis, the alkaline solution consisted nearly exclusively of a neutral substance which could be readily isolated in at least 92% yield. The elemental analysis and mass spectrum of this material were consistent with a structure which would result from addition of methanol to and loss of sulfur dioxide from **1a** (or formally with loss of sulfur dioxide from **4**). In addition to the molecular ion, the mass spectrum also showed an ion consistent with loss of a benzyl moiety as the base peak. The compound gave a positive test with 2,4-dinitrophenylhydrazine reagent and the intense IR absorption at 1675 cm^{-1} suggested the presence of an aromatic ketone function. In view of the susceptibility of 2-methanesulfonylquinoline to attack by methoxide ion[3] and the data described above, the structure of the material was formulated as benzyl 3-(2-methoxyquinolyl) ketone (**5**), which can be formally viewed as resulting from interchange of the benzyl and methoxy groups in the starting ester **4**, with loss of sulfur dioxide. This structural assignment was supported by the NMR spectrum which confirmed the presence of methoxy and benzyl groups, as well as the required number of aromatic protons in **5**. Additional confirmation of the structure of **5** was obtained by reduction with sodium borohydride to the corresponding alcohol **6** for which the expected spectral and analytical data were obtained. The IR spectrum of **6** showed the expected loss of the aromatic ketone function and appearance of a hydroxyl absorption. The NMR spectrum of **6** was also revealing, and when it was recorded at 220 MHz, the coupling constants for the three-spin benzylic system could readily be obtained and were of the magnitude expected: J_{gem} = 14.0 Hz and J_{vic} = 4.0 and 8.5 Hz.

The formation of **5** from **1b** (and from **4** via **1b**) can be rationalized as shown in Scheme I. Intramolecular cyclization of **4** followed by attack of methoxide ion on **1b** would generate resonance-stabilized **7** which could undergo ring opening to the sulfinate ion **8** by a process which resembles the mechanism formulated[4a] for the methoxide ion induced transformation of methyl *N*-tosyl-3,4-dehydroproline to methyl pyrrole-2-carboxylate and *p*-toluenesulfinate ion.[4b] Desulfination of **9**, the monoprotonated keto form of **8**, would then yield the enolate ion **10** of the observed product **5** by a process similar to decarboxylation of β-keto acids. Nucleophilic displacements of sulfone groups to give stable sulfinic acids have been reported, including the well-known Smiles[5] and Truce–Smiles[5] rearrangements, which are intramolecular

(1) (a) Presented in part at the 29th Southeast Regional Meeting of the American Chemical Society, Tampa, Fla., November 1977; Abstract 229. (b) Guest worker on sabbatical leave from the Department of Chemistry, The Pennsylvania State University, York Campus, York, Pa.

(2) E. A. Harrison, Jr., K. C. Rice, and M. E. Rogers, *J. Heterocycl. Chem.*, 14, 909 (1977).

(3) G. B. Barlin and W. V. Brown, *J. Chem. Soc.* B, 736 (1967).

(4) (a) A. V. Robertson, J. E. Francis, and B. Witkop, *J. Am. Chem. Soc.*, 84, 1709 (1962). (b) We formulated the sequence **1b** → **9** in Scheme I as proceeding through enolates **7** and **8** in view of the apparent preference[2] of the conjugate acid of **1b** to exist as the enol form and the strongly basic reaction conditions utilized. This sequence could also be written (and may take place) through the keto forms of **1b** and **7**.

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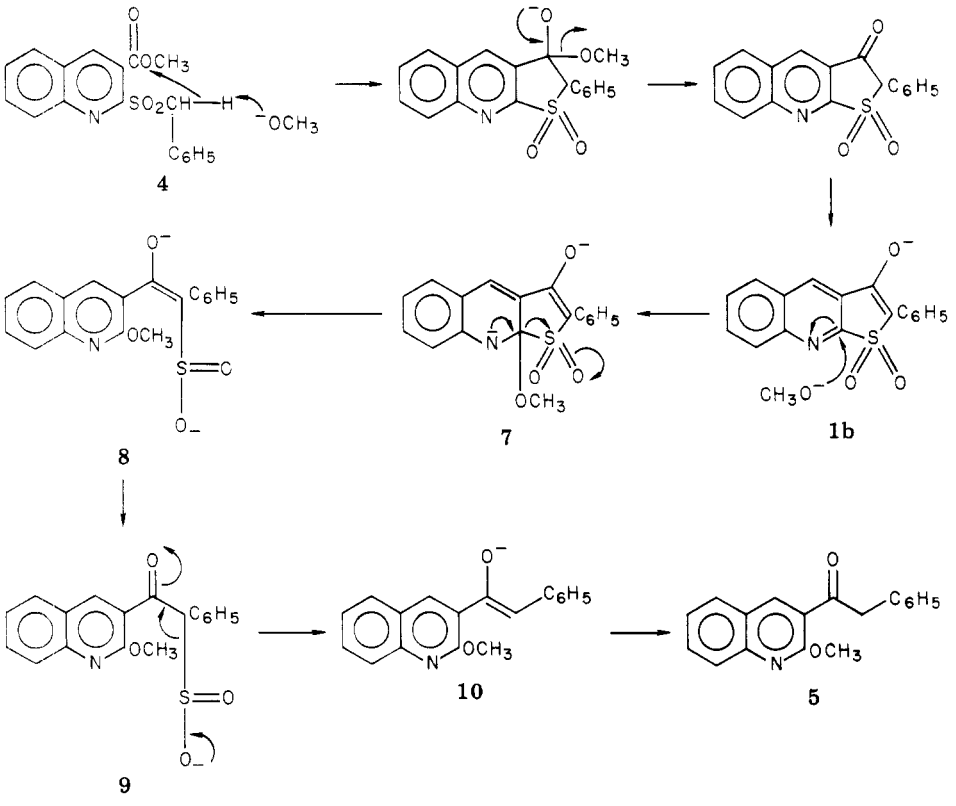
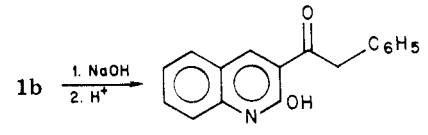
Scheme I



examples of such a displacement; however, loss of sulfinyl groups is known to occur in basic solution and to proceed more readily when the resulting carbanion can be stabilized as in **10**.[6] For example, desulfination of 2,4-dinitrobenzenesulfinic acid has been reported to occur at a much lower temperature than that of *o*- or *p*-nitro compounds.[7] In accordance with this postulated route for formation of **5**, the alkaline reaction mixture released large quantities of sulfur dioxide upon acidification.

Treatment of sulfone acid **3** with excess sodium methoxide in methanol also resulted in displacement of the sulfonyl group affording, after acidification, 2-methoxyquinoline-4-carboxylic acid (**11**), the product expected since acid **3** cannot cyclize to **1b**. Methylation of **11** with diazomethane gave ester **12** which was only observed (GLC and TLC) in trace amounts as a side product in the conversion of **1b** and **4** to **5**. Formation of **12** during the conversion of **4** to **5** could occur by methoxide ion displacement of the benzylsulfonyl moiety prior to cyclization of **4** and from **1b** by reversion to **4** (via attack of methoxide ion on the keto form of the conjugate acid of **1b**) and displacement. Cleavage of the putative sulfinate ion **9** in a manner similar to the alkaline cleavage of β diketones is also a possible mode of formation of **12** during conversion of **1b** to **5**. From the data accumulated in this study, it is not possible to offer a definitive explanation for the appearance of **12** as a side product in the reactions discussed; however it is clear that cyclization of **4** is many times faster than attack of methoxide ion to give **12**.

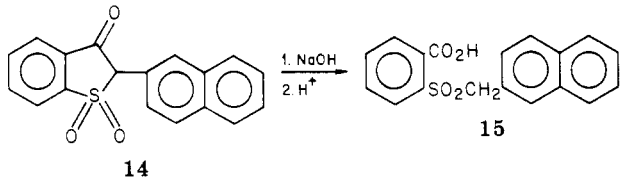
When **1b** was treated with excess aqueous sodium hydroxide followed by acidification, sulfur dioxide and a new substance, formulated as **13**, on the basis of spectral and analytical data, were produced. Although this reaction



(1)

13

is analogous to the reaction of **1b** and methoxide ion, it is interesting in view of the results Lamberton[8] obtained with the closely related, but nonnitrogenous, benzo[*b*]thiophene **14**. He found the sulfone carboxylic acid **15**



14 **15**

(2)

was the only product observed when **14** was treated with base under the conditions used by us for the conversion of **1b** to **13**.

In the benzo[*b*]thiophene 1,1-dioxide **14**, ring cleavage occurs in a manner similar to alkaline cleavage of β diketones, probably because a resonance-stabilized intermediate similar to **7** is not possible in this nonnitrogenous system and nucleophilic displacement of the sulfone group is energetically less favorable than the observed reaction pathway.

Experimental Section

Melting points (corrected) were determined in open capillary tubes with a Thomas-Hoover apparatus. Microanalyses were

(5) For reviews, see: W. E. Truce, E. M. Kreider, and W. W. Brand, *Org. React.*, **18**, 99 (1971); H. J. Shine, "Aromatic Rearrangements", American Elsevier, New York, N.Y., 1967, p 307; T. S. Stevens and W. E. Watts, "Selected Molecular Rearrangements", Van Nostrand Reinhold, London, 1973, p 81; J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951).

(6) For a review of the chemistry of sulfinic acids see: C. J. M. Sterling, *Int. J. Sulfur Chem., Part B*, **6**, 277 (1971).

(7) N. Kharasch, W. King, and T. Bruice, *J. Am. Chem. Soc.*, **77**, 931 (1955).

(8) A. H. Lamberton and J. E. Thorpe, *J. Chem. Soc. C*, 2571 (1967).

performed by the Laboratory's Section on Microanalytical Services and Instrumentation. IR and mass spectra (70 EV) were determined by using Perkin-Elmer 257 and Hitachi Perkin-Elmer RMU-6E instruments, respectively. NMR spectra were obtained with either a Varian A-60 or HR-220 spectrometer with Me_4Si as the internal reference. Silica gel GF plates for TLC were purchased from Analtech, Inc.

Benzyl 2-[3-(Carbomethoxy)quinolyl] Sulfone (4). Esterification of **3** as described below by the method of Riegl and Harrison[9] provided **4** much more conveniently on a large scale than by the CH_2N_2 method previously described.[2] A mixture of 3.27 g (10.0 mmol) of crude acid **3**, 1.48 g (20.0 mmol) of Li_2CO_3, 2.52 g (20.0 mmol) of Me_2SO_4, and 30 mL of dry DMF was stirred at 25 °C for 2.5 h, heated at 60–70 °C for 20 min, cooled, and slowly diluted with 125 mL of H_2O. The crystalline **4** that separated was filtered, washed well with H_2O, and dried at 50 °C in vacuo overnight to give 3.35 g of **4**; mp 151.5–154 °C (turbid melt). This material was dissolved in 25 mL of $CHCl_3$ and filtered to remove a small amount of $CHCl_3$-insoluble material. Evaporation of the solvent left 3.20 g (94%) of **4** which showed one spot on TLC (isopropyl ether); mp 152.5–154 °C (lit.[2] mp 152.5–153.5 °C).

Benzyl 3-(2-Methoxyquinolyl) Ketone (5). A. From 4. To a solution of $NaOCH_3$, prepared under N_2 by dissolving 805 mg (35.0 mg-atom) of clean Na in 100 mL of dry methanol, was added 1.20 g (3.50 mmol) of ester **4**. The reaction mixture was heated to reflux and the orange color of **1b** developed rapidly. This color gradually faded and after 9.0 h of reflux a light yellow solution that contained solid material resulted. The mixture was cooled and evaporated to a semisolid which was partitioned between 90 mL of Et_2O and 20 mL of H_2O. The Et_2O was removed and the aqueous phase was extracted with 2 × 30 mL of Et_2O. Acidification of the aqueous phase with 37% HCl produced evolution of SO_2. Drying ($MgSO_4$) of the combined Et_2O extracts and evaporation left 891 mg (92%) of a slightly off-white crystalline residue of **5**, mp 87–89 °C, which was essentially homogeneous on TLC (hexane–isopropyl ether). Recrystallization of this material from MeOH gave 796 mg (82%) of pure **5**: mp 88–89.5 °C; mass spectrum m/e 277 (M^+), 186 ($M^+ - CH_2C_6H_5$); IR ($CHCl_3$) 1688 (ArC=O), 1622, 1400, 1344 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 4.16 (s, 3, OCH_3), 4.33 (s, 2, CH_2), 7.08–7.98 (m, 9), 8.40 (s, 1, C-4 H). GLC and TLC (hexane–isopropyl ether) analysis of the mother liquor from recrystallization of **5** revealed only traces of **12**.

Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.89; H, 5.58; N, 5.00.

B. From 1b. Addition of 1.38 g (3.50 mmol) of **1b**·$2CH_3OH$[10] to a solution of $NaOCH_3$ prepared exactly as described in **A** above gave an orange solution which was refluxed for 8.0 h, cooled, evaporated to a syrup, and partitioned between 20 mL of H_2O and 100 mL of Et_2O. The aqueous layer was removed and extracted with 3 × 25 mL of Et_2O, and the combined Et_2O extracts were washed with 3 × 5 mL of H_2O, dried ($MgSO_4$), and evaporated to give 983 mg of nearly pure (TLC), crystalline **5**; mp 85–87 °C. Recrystallization of this material from 7 mL of CH_3OH (cooling to −10 °C) gave 892 mg (92%) of pure (TLC) **5**; mp 87.5–89 °C. Acidification of the aqueous phase from the Et_2O extraction above produced evolution of SO_2. TLC and GLC of the mother liquor from recrystallization of **5** showed the presence of trace amounts of **12**.

α-Benzyl-2-methoxyquinoline-3-methanol (6). A stirred slurry of 454 mg (1.64 mmol) of ketone **5** in 10 mL of 8:2 2-propanol–H_2O at 25 °C was treated with 100 mg (2.64 mmol) of solid $NaBH_4$ in one portion. After 1.5 h of stirring, the essentially homogeneous solution was diluted with 50 mL of Et_2O. The Et_2O was washed with 3 × 20 mL of H_2O and evaporated to an oil that crystallized. Drying under high vacuum left 443 mg (97%) of **6** as cotton-like microneedles, mp 93–95 °C, that was chromatographically homogeneous on TLC (hexane–isopropyl ether, 1:1). Recrystallization from petroleum ether (bp 60–90 °C)–isopropyl ether gave an analytical sample of **6** as stout prisms: mp 112–113.5 °C: mass spectrum m/e 280 (M + 1), 279 (M^+), 188 ($M^+ - CH_2C_6H_5$); IR ($CHCl_3$) 3600 (OH), 1630 cm^{-1}; NMR ($CDCl_3$, 220 MHz) δ 2.51 (s, 1, OH, exchanges with D_2O), 2.82 (dd, 1, J = 8.5 and 14.0 Hz), 3.20 (dd, J = 4.0 and 14.0 Hz), 4.10 (s, 3, OCH_3), 5.11 (dd, 1, J = 4.0 and 8.5 Hz), 7.00–7.41 (m, 6, ArH), 7.40–7.68 (m, 2, ArH), 7.86 (d, 1, J = 8 Hz, ArH), 7.95 (s, 1, C-4 H).

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.14; N, 5.01. Found: C, 77.10; H, 6.38; N, 5.11.

2-Methoxyquinoline-3-carboxylic Acid (11) and Methyl Ester 12. To a solution of NaOMe prepared under N_2 by dissolving 690 mg (30.0 mg-atom) of clean Na in 75 mL of dry methanol was added 981 mg (3.0 mmol) of solid **3**. The mixture was stirred under N_2 and refluxed for 9.0 h, cooled, and treated with 3.0 mL of AcOH. Evaporation of the solvent left a white solid that was heated to solution in 20 mL of H_2O. Acidification to pH 4.0 (Hydrion paper) with 37% HCl gave crystalline solid. Cooling the slurry to 0 °C, filtering, washing the precipitate with cold H_2O, and drying gave 583 mg (95.6%) of essentially pure **11**; mp 184.5–186.5 °C. Recrystallization from methanol gave pure **11**: mp 185–187 °C; mass spectrum m/e 203 (M^+); IR ($CHCl_3$) 3312, 1740, 1610, 1604 cm^{-1}; NMR (Me_2SO-d_6, 220 MHz) δ 3.82 (br s, OH), 4.04 (s, 3, OCH_3), 7.36–7.64 (m, 1, ArH), 7.73–7.95 (m, 2, ArH), 8.05 (d, 1, J = 7.9 Hz, ArH), 8.75 (s, 1, C-4 H).

Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.86; H, 4.64; N, 6.86. Acid **11** was treated with excess CH_2N_2 in Et_2O to give the ester **12**; mp 55–56.5 °C. (lit.[11] mp 52–53 °C).

Benzyl 3-(2-Hydroxyquinolyl) Ketone (13). To a solution of 400 mg (10.0 mmol) of NaOH in 15 mL of H_2O was added 331 mg (1.0 mmol) of **1b**. The mixture was refluxed 2.0 h during which time **1b** dissolved and solid material separated from the solution. The hot slurry was treated with 4.0 mL of EtOH, cooled, and rendered acidic with 37% HCl, which produced evolution of SO_2. The slurry of yellow solid was filtered, washed with H_2O, and dried at 100 °C in vacuo to give 245 mg (93%) of nearly pure **13**; mp 249–251 °C. Recrystallization of this material by dissolving in a minimum amount of warm Me_2SO and diluting with MeOH gave pure **13**: mp 255–256.5 °C; mass spectrum m/e 263 (M^+), 172 (M^+–$CH_2C_6H_5$); IR ($CHCl_3$) 3400, 1689, 1600 cm^{-1}; NMR (Me_2SO-d_6, 220 MHz) δ 4.46 (s, 2, CH_2), 7.14–7.46 (m, 7, ArH), 7.55–7.71 (m, 1, ArH), 7.89 (d, 1, J = 8.1 Hz, ArH), 8.50 (s, 1, C-4 H), 12.21 (s, 1, exchanges with D_2O, OH).

Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.61; H, 4.86; N, 5.31.

Acknowledgments. The authors thank Mr. William Landis for determination of the mass spectra and Mrs. Alice Wong for combustion analyses. We also thank Dr. E. L. May for his encouragement during this work and Drs. L. A. Cohen and C. W. Jefford for helpful discussions concerning this work. E.A.H. thanks Dr. May for the opportunity to spend a sabbatical year in his laboratory.

Registry No. **1a**, 65764-38-7; **1b**, 65764-33-2; **3**, 65764-23-0; **4**, 65764-28-5; **5**, 70659-27-7; **6**, 70659-28-8; **11**, 70659-29-9; **12**, 16498-75-2; **13**, 70659-30-2; sodium methoxide, 124-41-4.

(9) I. T. Harrison and S. Harrison, "Compendium of Organic Synthetic Methods", Vol. 2, Wiley, New York, N.Y., 1974, p 110.

(10) Only unsolvated **1b** was previously described[2] in detail. The degree of solvation of this material (obtained by recrystallization from CH_3OH) was determined by drying the air-dried substance to constant weight at 160 °C under high vacuum. Calculated weight loss for **1b**·$2CH_3OH$: 16.21%. Found: 16.54%.

(11) K. Shimizu, I. Sakamoto, and S. Fukushima, *Yakugaku Zasshi*, 87, 672 (1967).