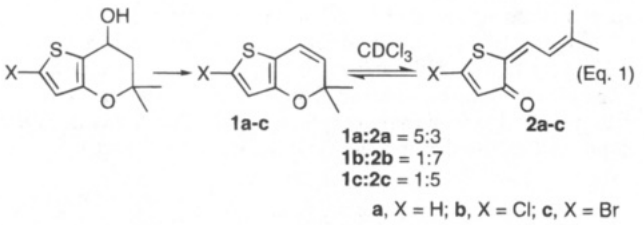
An Unusually Selective Diels–Alder Dimerization of a [4*n* + 2] Electrocyclic Ring-Opened Thieno[3,2-*b*]pyran†

Jeffery B. Press,*,‡ Kirk L. Sorgi,§
James J. McNally,|| and Gregory C. Leo||

The Medicinal Chemistry Department and the Chemical Development Department, The R. W. Johnson Pharmaceutical Research Institute, Spring House, Pennsylvania 19477

Received April 19, 1994

We recently reported the unexpected electrocyclic ring-opening of thieno[2,3-*b*]- and thieno[3,2-*b*]pyrans which are isosteres of chromenes.[1] These compounds arose as intermediates to a series of novel potassium channel openers discovered in our laboratories.[2–5] Of note, while thieno[2,3-*b*]pyrans completely ring-open, thieno[3,2-*b*]-pyrans **1a–c** develop an equilibrium over several hours to form **2a–c**. Both **1a–c** and **2a–c** could be isolated and characterized (eq 1). These compounds are stable



in solution in neutral solvents such as base-washed pentane for weeks, but re-form the same equilibrium mixture of **1**:**2** (determined by NMR) within 12 h in chloroform-*d*. These data suggest that this reaction is an acid-catalyzed equilibrium process, an unusual phenomenon for an electrocyclic reaction.

We now wish to report an additional unusual electrocyclic reaction discovered during the course of these studies. In contrast to the ring-opened thieno[2,3-*b*] analogues of **2** which underwent an *Z*- to *E*-isomerization upon exposure to acid or iodine,[1] **2a** did not isomerize to give isolable *Z*-trienones **4**. Instead, under these conditions, **2a** was converted in high yield to a single dimeric product, which was isolated and characterized by NMR, IR, MS, and combustion analysis. Furthermore the precursor alcohol, 6,7-dihydro-7-hydroxy-5,5-dimethyl-5*H*-thieno[3,2-*b*]pyran,[2] was converted in high yield to the same product upon prolonged exposure to catalytic acid under mild conditions, presumably through the intermediacy of **1a** and **2a.** The carbon spectrum of the product showed a doubling of the number of carbon resonances as compared to **1a**, the presence of three methyls and one methylene indicative of a dimeric material. NMR analysis of 2D carbon–carbon connectivity data indicated the product of **2a** was one of the four isomers arising from a Diels–Alder reaction, namely **5**, **6**, **7**, or **8** (Scheme 1). A relatively strong NOE observed between the H-6 (geminal to the hydroxyl thiophene) and H-10 (geminal to the isobutene) protons suggested the 1–3 diaxial arrangement of either **6** or **7**. The NOE's from the thienone ring protons were of no assistance in determining the stereochemistry of the thienone attachment but long-range proton–carbon couplings from the cyclohexenyl protons (H-6 and H-10) to the carbonyl carbon were small (<1.0 Hz), supporting a syn orientation between H-6 (or H-10) and carbonyl carbon C-4, as in **6**.

The structure of the product was ultimately determined by X-ray analysis of the crystal (Figure 1)[7] which identified the product as isomer **6**, the endo product of a

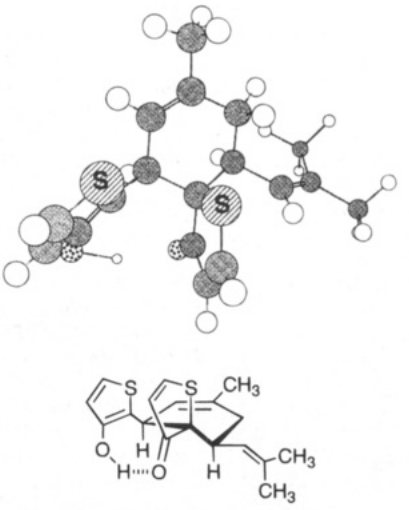
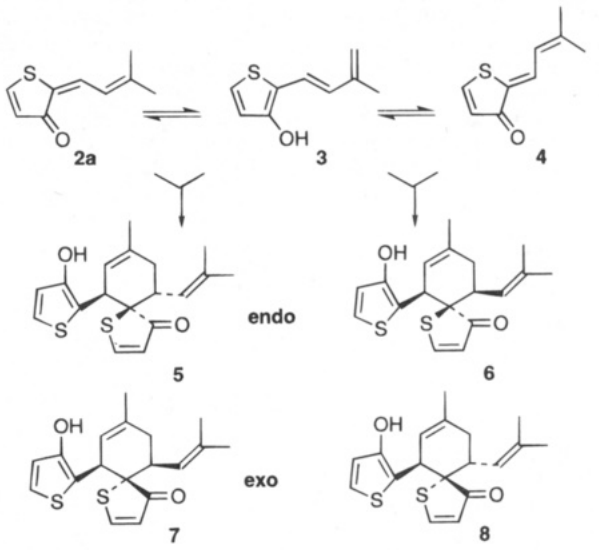


Figure 1. ORTEP representation of **6** showing position of heteroatoms.

Scheme 1



† This is the 17th paper in the series. For the previous paper see ref 5.

‡ Present afilliation Emisphere Technologies, Inc. Hawthorne, New York 10532.

|| Medicinal Chemistry Department.

§ Chemical Development Department.

(1) Turchi, I.; Press, J. B.; McNally, J. J.; Bonner, M. P.; Sorgi, K. L. *J. Org. Chem.* **1993**, *58*, 4629. See ref 6.

(2) Sanfilippo, P. J.; McNally, J. J.; Press, J. B.; Fitzpatrick, L. J.; Urbanski, M. J.; Katz, L. B.; Giardino, E.; Falotico, R.; Salata, J.; Moore, J. B. Jr.; Miller, W. *J. Med. Chem.* **1992**, *35*, 4425.

(3) McNally, J. J; Sanfilippo, P. J.; Fitzpatrick, L.; Press, J. B. *J. Heterocycl. Chem.* **1992**, *29*, 247.

(4) Sanfilippo, P. J.; McNally, J. J.; Press, J. B.; Falotico, R.; Giardino, E.; Katz, L. *Bioorg. Biomed. Lett.* **1993**, *3*, 1385.

(5) Press, J. B.; McNally, J. J.; Sanfilippo, P. J.; Addo, M. F.; Loughney, D.; Giardino, E.; Katz, L. B.; Damiano, B. P.; Falotico, R.; Haertlein, B. J. *Bioorg. Med. Chem.* **1993**, *1*, 423.

(6) For reviews of synthesis of chromenes, see: (a) Hepworth, J. D., Pyrans and Fused Pyrans: (iii) Synthesis and Applications. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 3, 737–874. (b) Schweizer, E. E.; Meeder-NYCZ, D. 2*H*- and 4*H*-Benzopyrans. *Chromenes, Chromanones and Chromones*, Ellis, G. P., Ed.; John Wiley & Sons: New York, 1977; Vol. 31, pp 11–140.

0022-3263/94/1959-5088$04.50/0

Diels–Alder reaction of **3** with **4**. The specificity of the reaction is quite remarkable; none of the other possible products are observed even in the crude reaction mixture. It is interesting to speculate that the formation of the single product **6** with such high selectivity might arise by intermolecular hydrogen bonding between the hydroxyl of **3** and the carbonyl of **4** (formed in situ) to establish proper spatial orientation prior to the [4*n* + 2] cyclization process. This would thus represent further exemplification of the recently reported diene–dienophile hydrogen bonding control in Diels–Alder reactions (Figure 2).[8]

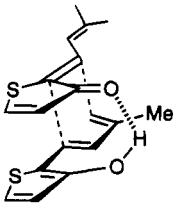


Figure 2.

The chemistry of the thienopyrans has proven to be extremely rich and surprisingly different from the known chemistry of the isosteric benzopyrans. Thieno[2,3-*b*]- and -[3,2-*b*]pyrans undergo an unusual 6π electrocyclic ring-opening with the latter being an equilibrium process as demonstrated by NMR.[1] Even more unusual, the ring-opened trienone **2a** forms the single dimeric product **6** under reaction conditions which causes only *E*- to *Z*-isomerization in the isomeric thieno[2,3-*b*]pyran series.

(7) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(8) (a) Tripathy, R.; Carroll, P. J.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 7630. (b) Tripathy, R.; Carroll, P. J.; Thornton, E. R. *J. Am. Chem. Soc.* **1990**, *112*, 6743.

Experimental Section

[5*S*-(6*S*,10*R*)]-6-(3-Hydroxythiophen-2-yl)-8-methyl-10-(2-methylpropenyl)-1-thiaspiro[4.5]deca-2,7-dien-4-one (6). From 2a. A catalytic amount of iodine was added to a solution of **2a**[1] (0.50 g, 3.0 mmol) in CH_2Cl_2 and stirred at rt for 2 h. The solution was poured onto a column of silica gel, and the product was eluted with CH_2Cl_2 to give 0.4 g of an orange solid **6**. The product was recrystallized from hexanes to give 0.199 g (40%) of a colorless solid: mp 136–137 °C; a second crop of crystals contained an additional 0.197 g (39%). IR (KBr): 3450–3150, 1656, and 1209 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.61 (s, 3H), 1.65 (s, 3H), 1.76 (s, 3H), 2.08–2.20 (m, 2H), 3.27–3.37 (m, 1H), 4.59 (br s, 1H), 4.92 (d, J = 9.5 Hz, 1H), 5.52 (d, J = 1.3 Hz, 1H), 5.96 (d, J = 6.0 Hz, 1H), 6.04 (s, 1H, exchangeable), 6.54 (d, J = 5.3 Hz, 1H), 6.97 (d, J = 5.3 Hz, 1H), and 8.27 (d, J = 6.0 Hz, 1H); ^{13}C NMR δ 18.6, 22.7, 25.8, 36.7, 41.4, 41.9, 72.5, 115.2, 119.1, 121.2, 122.4, 123.9, 124.5, 135.5, 136.2, 150.9, 166.4, and 211.6; MS *m*/*z* 333 (MH^+). Anal. Calcd for $C_{18}H_{20}O_2S_2$: C, 65.03; H, 6.06. Found: C, 64.87; H, 5.98.

From 6,7-Dihydro-7-hydroxy-5,5-dimethyl-5*H*-thieno-[3,2-*b*]pyran. A catalytic amount of *p*-toluenesulfonic acid was added to a solution of 6,7-dihydro-7-hydroxy-5,5-dimethyl-5*H*-thieno[3,2-*b*]pyran (2.3 g, 12.5 mmol) in methylene chloride (100 mL) and stirred at rt overnight. The solution was washed with saturated aqueous sodium bicarbonate and dried over sodium sulfate. The solvent was evaporated in vacuo, and the residue was purified by flash chromatography on silica gel using 10% ethyl acetate in hexane to give the product, 1.25 g (60%) of a colorless solid, identical in all aspects to the above product.