Alkylation and Ring Contraction of 11-Oxo-6,11-dihydrodibenzo[*b,e*]thiepins[1]

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The ready availability and remarkable physiological properties of a number of substituted dibenzo[*b,e*]thiepins have stimulated much interest in this area. The tricyclic ring system is invariably synthesized by cyclization of an ortho-substituted arylthiomethylbenzoic acid or acid chloride. Loss of a proton from the resulting 11-oxodibenzo[*b,e*]thiepin, e.g., **1** (Scheme I), would give the mesomeric anion **2a** ↔ **2b.** This is of particular interest as the anion is fully conjugated, and 16π antiaromatic systems of this type are unknown. In addition, alkylation at C-6 would offer a rapid and direct route to a variety of substituted dibenzothiepins.

Treatment of a solution of the thiepin **1** in methanol-d_4 with a trace of sodium hydride resulted in a deep red solution and disappearance of the NMR signal (δ 4.1) attributed to the protons at C-6. The mass spectrum of the recovered thiepin showed a molecular ion (*m/e* 289) and fragmentation pattern consistent with the incorporation of five deuterium atoms (two at C-6 and three from ester exchange). The demonstrated acidity of the protons at C-6 suggested that the anion **2a** ↔ **2b** could be prepared and perhaps alkylated.

Treatment of a cooled (ice–salt bath) solution of **1** in *N*-methylpyrrolidone with sodium hydride gave a deep red solution which was largely decolorized on addition of methyl iodide. Analysis of the reaction mixture showed the presence of unreacted **1** and three new products (two major and one minor) which were isolated by column chromatography. NMR, mass spectral, and elemental analyses of the first two components eluted from the column established that the compounds were isomeric and that each contained two methyl groups in addition to the methyl ester function. The least polar isomer displayed a blue fluorescence in dilute solution and a UV spectrum closely matching that seen in many anthracene derivatives.[2,3] In addition, the IR spectrum (showing no absorption attributable to a diarylcarbonyl moiety) was consistent with the structure (**4**) assigned to the new compound.

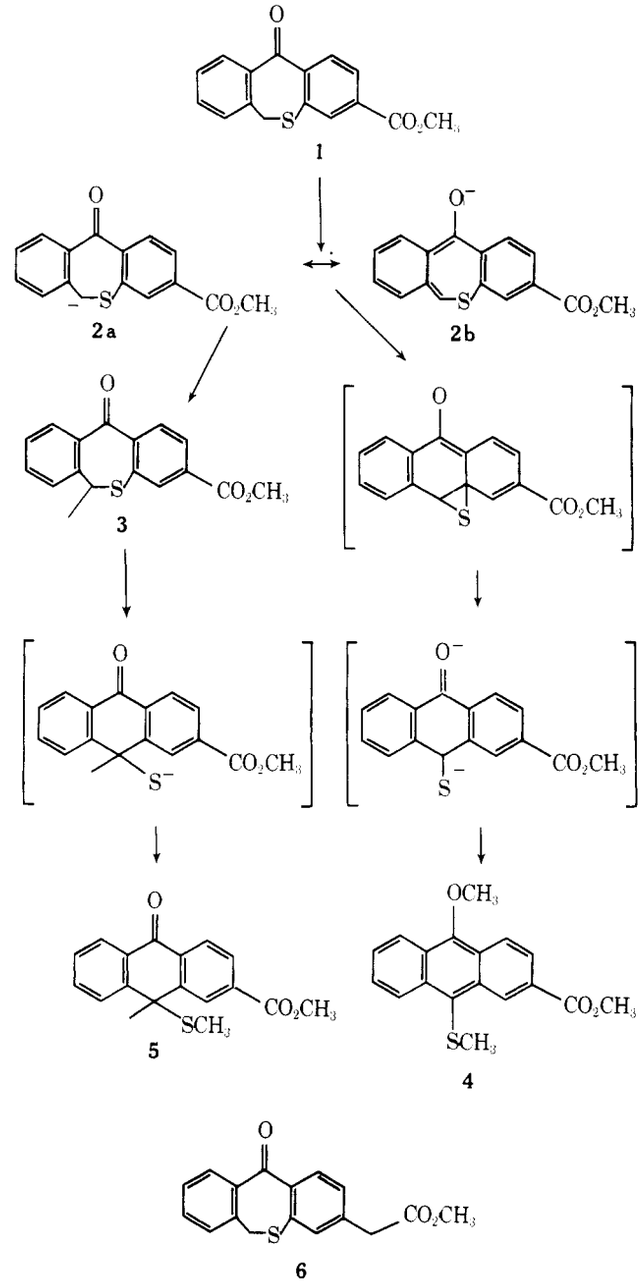
The transformation of **1** into **4** can be accounted for in terms of a thiepin rearrangement, analogous to that observed with benzo[*b*]thiepins[4] and benz[*b*]oxepins,[5] followed by methylation of the intermediate anthracenethiol (Scheme I). A related thermal rearrangement in the benzothiepin series has also been noted by Reinhoudt and Kouwenhoven.[6] The spectral data of the second major component were fully consistent with those expected for the tricyclic ketone **5**, which undoubtedly arises by a similar pathway. In this case, C-methylation of the mesomeric anion **2a** ↔ **2b** to give the 6-substituted derivative **3** is followed by proton loss, rearrangement, and finally C-methylation. The spectra of the minor component showed it to be the thiepin **3**, postulated as being intermediary in the formation **5.** This was confirmed by showing that **3,** on treatment with sodium hydride and subsequent methylation, gave **5.**

The thiepin rearrangement was effectively suppressed by carrying out the alkylation at lower temperature (−20 to −40 °C) using a reverse addition technique in which a solution of potassium *tert*-butoxide in *tert*-butyl alcohol was added to a solution of **1** containing excess methyl iodide in *N*-methylpyrrolidone. No dialkylation was observed, and the 6-methylated thiepin **3** was obtained in high yield.

The propensity of thiepins to rearrange is determined, in part, by the antiaromaticity (i.e., formal antiaromatic character) of the system. Electron-withdrawing groups exert a stabilizing effect[6] by reducing the electron density and thereby the antiaromaticity of the ring. On the other hand, enolate anions derived from 11-oxodibenzo[*b,e*]thiepins are electron-rich species which rearrange especially rapidly; however, the ease with which the anion **2a** ↔ **2b** is generated and alkylated suggests that these reactions are fairly general. A noteworthy exception is methyl 11-oxo-6,11-dihydrodibenzo[*b,e*]thiepin-3-acetate (**6**), which does not rearrange on treatment with sodium hydride. In this case, a proton is lost from the side chain at C-3, giving a stable enolate which is easily alkylated.[7]

In general, thiepin[8] and benzothiepin *S,S*-dioxides[9] are more stable than the unoxidized systems. Methyl 11-oxo-6,11-dihydrodibenzo[*b,e*]thiepin-3-carboxylate *S,S*-dioxide (**7**) was prepared by oxidation of **1** with 2 equiv of *m*-chloroperbenzoic acid. The dioxide formed a stable anion upon treatment with sodium hydride in *N*-methylpyrrolidone. Treatment of the anion with methyl iodide gave methyl 6-

Scheme I



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methyl-11-oxo-6,11-dihydrodibenzo[*b,e*]thiepin-3-carboxylate *S,S*-dioxide (**8**) in high yield.

Experimental Section

Melting points were determined with a Mel-Temp apparatus and are not corrected. The IR spectra were measured with a Perkin-Elmer Model 237B spectrophotometer in chloroform solution or as solids in potassium bromide discs. The UV spectra were recorded in methanol solution with a Cary 14 recording spectrophotometer. Proton NMR spectra were measured with a Varian HA100 spectrometer in $CDCl_3$ or Me_2SO-d_6. Chemical shifts are expressed in parts per million (δ) from internal Me_4Si. The mass spectra were obtained with an Atlas CH-4 mass spectrometer. The spectral data for all new compounds were consistent with the assigned structures. Satisfactory analytical data (±0.4%) were reported for all new compounds except for **3**, which was fully characterized as the free acid.

Methyl 11-Oxo-6,11-dihydrodibenzo[*b,e*]thiepin-3-carboxylate (1). A solution of 11-oxo-6,11-dihydrodibenzo[*b,e*]thiepin-3-carboxylic acid chloride[10] (5 g) in methanol (50 mL) was heated under reflux for 1h. The reaction mixture was cooled to 0 °C, and the product was collected by filtration: yield 4.0 g (81%); mp 150–151 °C; UV (dioxane) 246, 280, 371 nm (ϵ 27 000, 10 000, 3400); NMR ($CDCl_3$) δ 3.88 (s, 3 H), 4.03 (s, 2 H), 7.12–7.48 (m, 4 H), 7.57 (dd, J_1 = 8 Hz, J_2 = 1.5 Hz, 1 H), 7.81 (dd, J_1 = 8 Hz, J_2 = 1.5 Hz, 1 H), 7.97 (d, J = 1.5 Hz, 1 H), 8.20 (d, J = 8 Hz, 1 H). Anal. ($C_{16}H_{12}O_3S$) C, H.

Reaction of 1 with Sodium Hydride and Methyl Iodide. A mixture of the ester **1** (3.2 g) and sodium hydride (57% in oil, 0.5 g) in *N*-methylpyrrolidone (50 mL) was cooled in an ice–salt bath, stirred for 30 min, and then treated with methyl iodide (0.7 mL, 1.7 g). The reaction mixture was allowed to warm to room temperature and stirred for a further 18 h, whereupon it was diluted with ice, aqueous ammonium chloride solution, and ethyl acetate. The organic layer was separated, washed, dried, and evaporated to yield an oil which was chromatographed through silica gel (500 g) eluting with hexane–ether (20:1 → 10:1). The fractions containing pure material were evaporated to give (a) methyl 9-thiomethyl-10-methoxyanthracene-2-carboxylate (**4**; 450 mg) [mp 131–132 °C (ethyl acetate–hexane); UV (MeOH) 265, 285, 331, 352, 372, 396, 417 nm (ϵ 78 000, 67 000, 1700, 3000, 4900, 6400, 6600); IR ($CDCl_3$) 1720 cm^{-1}; NMR ($CDCl_3$) δ 2.36 (s, 3 H), 3.99 (s, 3 H), 4.10 (s, 3 H), 7.51–7.71 (m, 2 H), 8.04 (dd, J_1 = 9 Hz, J_2 = 1.5 Hz, 1 H), 8.35 (d, J = 9 Hz, 1 H), 9.00–9.16 (m, 1 H), 9.73 (brd s, 1 H). Anal. ($C_{18}H_{16}O_3S$) C, H.], (b) methyl 9-methyl-9-thiomethyl-10-oxo-9,10-dihydroanthracene-2-carboxylate (**5**; 425 mg) [mp 121 °C (methanol); UV (MeOH) 272, 313 sh nm (ϵ 21 000, 4200); IR ($CHCl_3$) 1720, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.36 (s, 3 H), 2.01 (s, 3 H), 3.96 (s, 3 H), 7.35–8.43 (m, 6 H), 8.72 (d, J = 1.5 Hz, 1 H). Mass spectrum (molecular ion) theoretical, *m/e* 312; found, *m/e* 312, 265 (100, $M^+ - 47$). Anal. ($C_{18}H_{16}O_3S$) C, H.], and (c) methyl 6-methyl-11-oxo-6,11-dihydrodibenzo[*b,e*]thiepin-3-carboxylate (**3**) as a pale yellow oil (180 mg) [UV (MeOH) 245, 280 sh, 372 nm (ϵ 2600, 10 000, 3400); IR ($CHCl_3$) 1720, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.74 (d, J = 7 Hz, 3 H), 3.88 (s, 3 H), 4.32 (q, J = 7 Hz, 1 H), 7.20–7.59 (m, 4 H), 7.81 (dd, J_1 = 8 Hz, J_2 = 1.5 Hz, 1 H), 7.97 (d, J = 1.5 Hz, 1 H), 8.20 (d, J = 8 Hz, 1 H). Mass spectrum (molecular ion) theoretical, *m/e* 298; found, *m/e* 298.].

Hydrolysis of the ester **3** with aqueous methanolic sodium hydroxide gave, after acidification and crystallization from ethyl acetate, 6-methyl-11-oxo-6,11-dihydrodibenzo[*b,e*]thiepin-3-carboxylic acid: mp 184–185 °C; NMR (Me_2SO-d_6) δ 1.67 (d, J = 7 Hz, 3 H), 4.62 (q, J = 7 Hz, 1 H), 7.32–8.27 (m, 7 H). Anal. ($C_{16}H_{12}O_3S$) C, H.

Methyl 6-Methyl-11-oxo-6,11-dihydrodibenzo[*b,e*]thiepin-3-carboxylate (3). A 9.0-mL amount of a 1 N solution of potassium *tert*-butoxide in *tert*-butyl alcohol was slowly added to a stirred solution of **1** (2.0 g) in dry *N*-methylpyrrolidone containing methyl iodide (3.0 mL, 6.9 g). During the addition the reaction mixture was cooled in a dry ice–acetone bath, the temperature of which was gradually reduced from −20 to −40 °C during the course of the reaction. The mixture was quenched by addition of saturated aqueous ammonium chloride solution (5 mL) and worked up as described above to yield the ester **3** as a pale yellow oil (1.8 g, 86%).

Methyl 11-Oxo-6,11-dihydrodibenzo[*b,e*]thiepin-3-carboxylate *S,S* Dioxide (7). A solution of the ester **1** (0.8 g) in dichloromethane (20 mL) was treated with a solution of *m*-chloroperbenzoic acid (1.2 g) in the same solvent (10 mL). After 10 min, the reaction mixture was washed with sodium bisulfite solution and then with sodium carbonate solution. The organic layer was dried and evaporated, and the residue was crystallized from ethyl acetate–hexane to yield **7**: 650 mg; mp 166–167 °C; IR 1725, 1655, 1325 cm^{-1}; NMR ($CDCl_3$) δ 3.97 (s, 3 H), 4.80 (s, 2 H), 7.22–7.63 (m, 3 H), 7.97 (d, J = 9 Hz, 1 H), 8.07 (dd, J_1 = 8 Hz, J_2 = 1.5 Hz, 1 H), 8.35 (dd, J_1 = 8 Hz, J_2 = 1.5 Hz, 1 H), 8.70 (d, J = 1.5 Hz, 1 H). Anal. ($C_{16}H_{12}O_5S$) C, H.

Methyl 6-Methyl-11-oxo-6,11-dihydrodibenzo[*b,e*]thiepin-3-carboxylate *S,S* Dioxide (8). A solution of methyl 11-oxo-6,11-dihydrodibenzo[*b,e*]thiepin-3-carboxylate *S,S*-dioxide (630 mg) in dry *N*-methylpyrrolidone was treated with sodium hydride (45 mg) and stirred for 18 h at room temperature. The solution was decolorized by addition of methyl iodide (0.14 mL) and quenched with water. The oily product was filtered and crystallized from ether–hexane to yield **8**: 480 mg; mp 151–153 °C; IR (KBr) 1725, 1655 cm^{-1}; NMR ($CDCl_3$) δ 1.53 (d, J = 7 Hz, 3 H), 3.96 (s, 3 H), 4.70 (q, J = 7 Hz, 1 H), 7.20–8.08 (m, 5 H), 8.34 (dd, J_1 = 8 Hz, J_2 = 1.5 Hz, 1 H), 8.64 (d, J = 1.5 Hz, 1 H). Anal. ($C_{17}H_{14}O_5S$) C, H.

Registry No.—**1**, 67667-05-4; **3**, 68002-09-5; **4**, 68002-10-8; **5**, 68002-11-9; **7**, 68002-12-0; **8**, 68002-13-1; 11-oxo-6,11-dihydrodibenzo[*b,e*]thiepin-3-carboxylic acid chloride, 61220-66-4; 6-methyl-11-oxo-6,11-dihydrodibenzo[*b,e*]thiepin-3-carboxylic acid, 68002-14-2.

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Studies on Sulfur-Containing Peptides: *tert*-Butyloxycarbonylsulfenyl and Benzyloxycarbonylsulfenyl Derivatives as Protecting Groups for Cysteine[1]

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A heterolytic fragmentation route from sulfenyl thiocarbonates to unsymmetrical disulfides was reported by Brois et al.[3]

$$R_1OCOSCl \xrightarrow{+R_2SH} R_1OCOSSR_2$$

$$\xrightarrow{+R_3SH} R_2SSR_3 + COS + R_1OH \quad (I)$$

This disulfide-forming reaction was applied by Kamber[4] to the synthesis of the disulfide-linked insulin fragment A20-B19 using the methoxycarbonylsulfenyl group[5] (R_1 = CH_3). The SCM group as a SH protecting group for cysteine has also been reported by Hiskey et al.[6]

The present report concerns our studies with two alkyloxycarbonylsulfenyl groups, *tert*-butyloxycarbonylsulfenyl (SCB) and benzyloxycarbonylsulfenyl (SZ), and their use as a thiol protection for peptide synthesis.

1. SCB Derivatives. Sulfenyl chloride **1** (R_1 = $(CH_3)_3C$; SCB-Cl) was synthesized from *tert*-butyl alcohol by reaction with chlorocarbonylsulfenyl chloride.[7] SCB-Cl is stable for more than 1 year at −25 °C. Unlike SMC-Cl, SCB-Cl failed to react with the *S*-Trt-cysteine derivatives Boc-Cys(Trt)-

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