Acidic Cyclization of a 2,3,4,5-Tetrahydrobenzo[*b*]thiepin-5-ylidenemalononitrile

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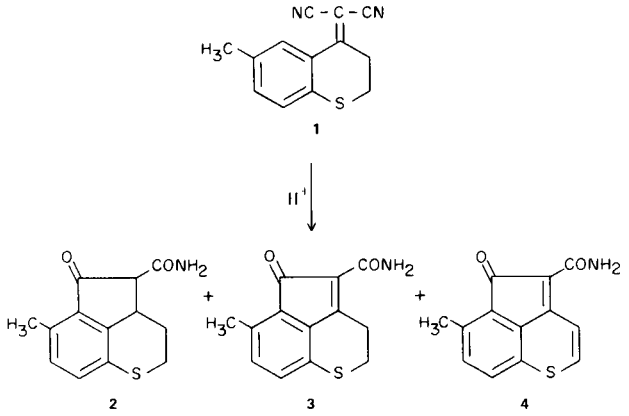
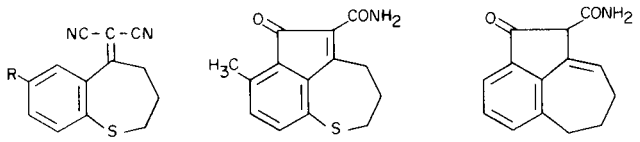
Treatment of 6-methylthiochroman-4-ylidenemalononitrile (**1**) with concentrated sulfuric acid has been shown (2) to result in three tricyclic ketoamides (**2**, **3**, and **4**) possessing varying degrees of unsaturation. It has been



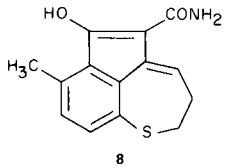
speculated (2), along with some supporting evidence, that this reaction involves initial formation of **3** (*cf.*, the α-tetralone analog (3)) which disproportionates to **2** and **4** *via* a hydride transfer involving the hydrogens on the carbon *alpha* to the sulfur of **3**. The driving force for this behavior is believed to be the formation of the highly conjugated **4**. Therefore, if such a situation is involved, subjecting the seven-membered analog (**5**), in which such conjugation would no longer be attainable, to similar cyclization conditions should only yield the product analogous to **3**.



Compound **5**, which was readily available (2) from the corresponding ketone, underwent a series of color changes (yellow to orange to red to deep blue) similar to **1** when treated with concentrated sulfuric acid at room temperature. Quenching the reaction by pouring over ice previous to the blue color resulted in uncyclized unidentifiable materials. However, quenching after the blue color had remained for one hour (total of two hours reaction time) and subsequent column chromatography produced **6** in near quantitative yield.

The structure of **6** was based on several lines of evidence: (a) dark red color analogous to that of **3** (2) and in contrast to indanone-like structures (*e.g.*, **7**) which are colorless (4); (b) infrared bands in chloroform at ν 1684 cm^{-1} (ketone carbonyl) and ν 1650 cm^{-1} (amide carbonyl) which are in agreement with that reported (2,3,4) for other amidoindenones; (c) ultraviolet absorptions at 253 nm and 277-284 nm similar to those for **3** (2); and (d) pmr spectral peaks at τ 2.91 (quartet, 2H, aromatic), τ 6.28 (broadened triplet, 2H, allylic C-H or C-H *alpha* to sulfur), τ 6.95 (broadened triplet, 2H, allylic C-H or C-H *alpha* to sulfur), and τ 7.28-7.67 (methyl singlet at τ 7.5 superimposed on a broad multiplet, 5H, CH_2 *beta* to sulfur and aromatic methyl).

The formation of **6** possessing the double bond endocyclic to the five-membered ring is surprising in view of the exocyclic product (**7**) from the corresponding carbocyclic ylidenemalonitrile (4). Attempts (3) to isomerize **6** to exocyclic (indanone) isomer have failed but the infrared spectrum suggests an enolization of **6** (*e.g.*, **8**) does exist, a phenomenon not observed for **7** (4). Application of the sulfur acid conditions to **9**, likewise available



from the ketone (5), formed only water soluble products (possibly a 7-sulfonated cyanoamide as reported for the six-membered series (2)) and, thereby, necessitated the aromatic methyl blocking group as with **1**.

Compound **6** provides additional evidence for the disproportionation scheme for **1** and is now being exploited as a starting point for a series of potential chemotherapeutic (6) agents.

EXPERIMENTAL (7)

2,3,4,5-Tetrahydrobenzo[*b*]thiepin-5-ylidenemalononitriles.

The method employed has been previously described (2) and used xylene as the condensing solvent and either 7-methyl-2,3,4,5-tetrahydrobenzo[*b*]thiepin-5-one or 2,3,4,5-tetrahydrobenzo[*b*]-thiepin-5-one (5) as the starting ketones.

7-Methyl-2,3,4,5-tetrahydrobenzo[*b*]thiepin-5-ylidenemalononitrile (**5**).

This compound was realized in 38% yield as yellow crystals from 95% ethanol, m.p. 109-110°, ir ν max (chloroform) 2220 cm^{-1} (CN).

Anal. Calcd. for $C_{14}H_{12}N_2S$: C, 69.96; H, 5.03. Found: C, 70.18; N, 5.19.

2,3,4,5-Tetrahydrobenzo[*b*]thiepin-5-ylidenemalononitrile (**9**).

This compound was obtained in 45% yield as light yellow crystals from absolute ethanol, m.p. 76-77°; ν max (chloroform) 2222 cm^{-1} (CN).

Anal. Calcd. for $C_{13}H_{10}N_2S$: C, 68.99; H, 4.45. Found: C, 68.89; H, 4.49.

Cyclization of 7-Methyl-2,3,4,5-tetrahydrobenzo[*b*]thiepin-5-ylidenemalononitrile (**5**).

A 60 ml. concentrated sulfuric acid solution containing 2.40 g. (0.01 mole) of **5** was stirred at room temperature until the blue color had persisted for one hour (total reaction time two hours). The solution was then warmed on a steam bath for 30 minutes and poured into a 1 l. beaker of ice. After standing for several days, the brownish product was filtered and air dried. Thin layer chromatography on silica gel with ethyl acetate-benzene (1:2) showed one major product and two extremely minor constituents. Following column chromatography on silica gel employing ethyl acetate-benzene (1:9) **6**, m.p. 175°, was obtained in near quantitative yield (based on isolated material) as red prisms recrystallizable from absolute ethanol.

Anal. Calcd. for $C_{14}H_{13}NO_2S$: C, 64.86; H, 5.02. Found: C, 64.73; H, 5.05.

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(7) Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The nmr spectrum was obtained on a Varian A60 spectrometer. The ultraviolet absorption spectrum was determined with a Cary Model 14 recording spectrophotometer using 1-cm sample cells. Ir spectra were recorded on a Perkin-Elmer Model 225 spectrophotometer. The microanalyses were performed by Meade Microanalytical Laboratories, Amherst, Massachusetts and Galbraith Laboratories, Knoxville, Tennessee.