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SYNTHESIS, STRUCTURE, AND CHEMISTRY OF A 1-THIA-4-AZANAPHTHALENE

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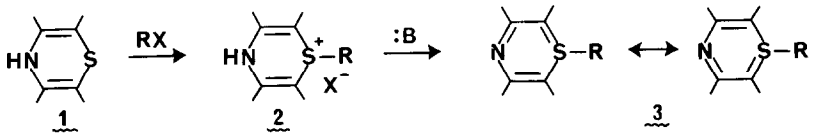
Summary: From a crystal structure determination and thermal rearrangement studies, it is evident that 1-methyl-2-carbethoxy-3-phenyl-1-thia-4-azanaphthalene is an alias for a molecule more properly represented by a name emphasizing its zwitterionic character.

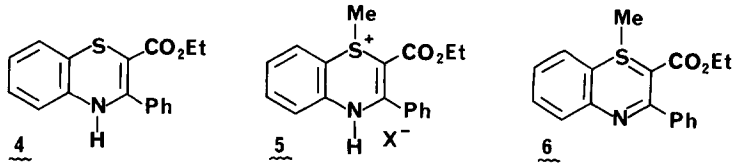
The premise that 1-thia-4-azabenzenes (3) could be made by alkylation of 4H-[1,4]-thiazines (1) at sulfur (→ 2) followed by deprotonation at nitrogen prompted the work reported here. In the proposed scheme, the NH proton would serve the dual role of N-protection during alkylation and of the charge lost to give the neutral 3. The opportunity to study the sulfur valence changes involved in the conversion of 1 to the formally tetravalent 3 in conjunction with an equilibrium pK_a measurement (2 ⇌ 3) seemed particularly attractive. Promising early



1 2 3

experiments with phenothiazines were discontinued because of the intractability of the dibenzo-analogues of 3.[1] Efforts then were diverted to the synthesis of 5 which already was known in the literature as the perchlorate salt.[2]

Condensation of 2-aminothiophenol with ethyl 2-chlorobenzoylacetate gave 2-carbethoxy-3-phenyl-4H-[1,4]-benzothiazine[2] (4, IR 1710 and 1680 cm^{-1}) which on methylation with methyl triflate in CH_2Cl_2 produced the sulfonium salt (5, X = CF_3SO_3, mp 186-188 °C,[3] IR[4] 1675 cm^{-1}, ^1H NMR S-Me at 2.97 δ) in 76% yield. Treatment of 5 in CH_2Cl_2 with 1 M aqueous Na_2CO_3 followed by evaporation of the organic phase and crystallization of the residue from EtOH-H_2O afforded the desired thiazanaphthalene[3] (6) as a yellow solid (mp 186-189 °C, IR 1675 and 1640 cm^{-1}, ^1H NMR S-Me at 2.23 δ) in 87% isolated yield.



4 5 6

The platelets (6) are stable to air and light and do not absorb CO_2 or moisture. Temperatures above 120 °C are required for thermal decomposition in solution (vide infra). These observations along with the measured pK_a of 12.4±0.3 (1:1 MeOH-H_2O, 28 °C) for the transformation, 5 ⇌ 6, all testify to the exceptional stability of the ring system (6). To determine the causes of this stability, the structure was investigated by X-ray crystallography.[5]

The structure (Fig 1) is certainly not that anticipated from formulation (6). Instead of being in the ring plane as expected for a classical aromatic structure, the S-methyl sits 2.25 Å above plane I defined by the four ring carbons (C1, C2, C7, C8) and the S-Me bond is almost orthogonal to plane I (87°, slight lean to N). Moreover, the dihydrothiazine ring has a boatlike conformation with its prow-S higher than its stern-N (0.46 vs. 0.11 Å above plane I). The sulfur is pyramidal with C-S-C angles less than tetrahedral. The smallest angle is C1-S-C8 (100.3°) because of the constraints put on the ring by the long C-S bonds and the greater ease of squeezing the angle of a higher row element.[6] The sulfur electron pair must be in a quasi-equatorial position (staggered vs. methyl H's). The data are consistent with a sulfonium ylid structure with much of the minus charge divided between C8 (7) and N (8).

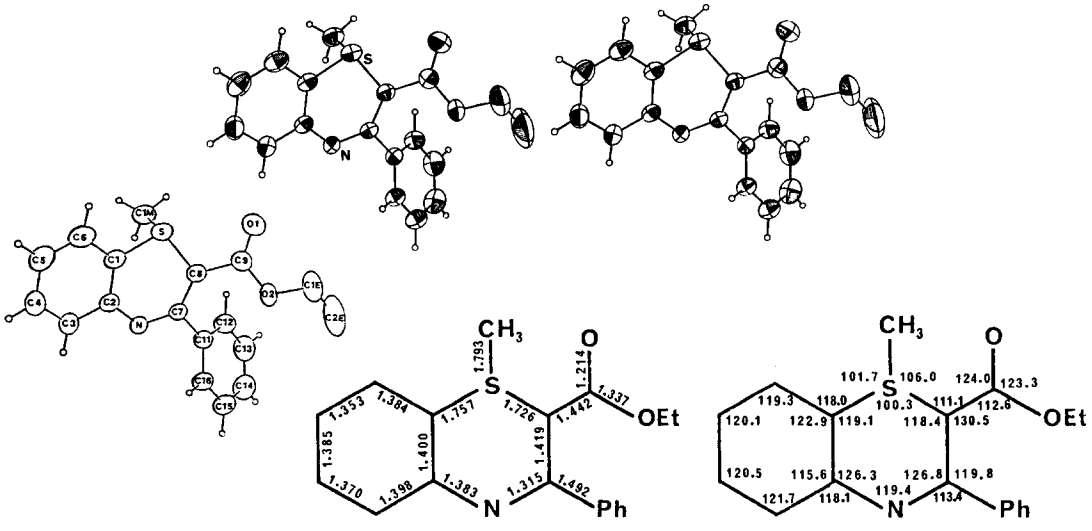
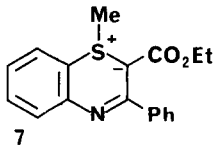


Figure 1. Top: Stereoscopic view of 1-methyl-2-carbethoxy-3-phenyl-1-thia-4-azanaphthalene. Thermal ellipsoids for non-H atoms represent 35% probability. Bottom: Important bond distances (Å) and angles (°) with crystallographic numbering system (e.s.d. ranges: 0.005-0.009 Å and 0.2-0.6°). Both benzene rings (including directly attached atoms) are planar.



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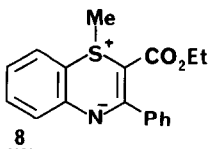

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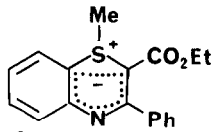

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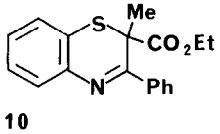
Since C8-S is shorter than C1-S, less charge must be on C1 than on C8 (with its stabilizing CO_2Et). (Both bonds are so close to the length of the internal model, S-CM, that no contribution from C=S- containing structures is evident.) Although C8, C9, O1, and O2 are in the same plane, little of the minus charge seems to have found its way to the ester oxygen (C=O distance normal). While C1, C2, N, C7, and C8 are nearly in the same plane suggesting substantial delocalization, it is unlikely that much overlap of the kind defined by the homoaromatic structure (9) is present. The C1-C8 distance is just too long (2.68 Å).[7] The structure found for 6 is in accord with recent conclusions that thiabenzenes and thianaphthalenes are best represented as sulfonium ylids.[8,9]

The zwitterionic character of 6 is confirmed by investigations of its thermal decomposition. When 6 was heated neat for 10 min at 210 °C, two rearrangement products were found: the 1,6- or 1,2-methyl shift product (10, 49% yield, mp 51-54 °C,[3] IR 1730 cm^{-1}, ^1H NMR C-Me at 1.65 δ) and the 4H-[1,4]-benzothiazine from methyl migration to nitrogen (11, 40% yield, oil,[3] IR 1680 cm^{-1}, ^1H NMR N-Me at 2.87 δ). Both products formally are the consequences of successful efforts by a zwitterion (7 ↔ 8) to internally neutralize itself.



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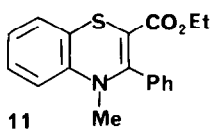

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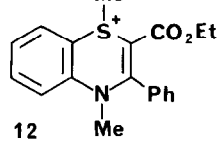

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Evidence that the two rearrangements are mechanistically independent was obtained from solution studies. In 1,2,4-trichlorobenzene at 210 °C, 10 was formed in 80% yield compared with only 9% for 11. At 140 °C in the same solvent, however, 11 was the dominant product. For example, after 4 hr with a 20% initial concentration of 6, the product mixture contained 5% 6, 12% 10, and 62% 11. Thus it is unlikely that both processes have a common intermediate. The transformation, 6 → 10, can be likened to a Stevens type rearrangement. Since that reaction is Woodward-Hoffmann disallowed (with retention of configuration) for 6, the normal Stevens rearrangement mechanism - a homolytic dissociation-recombination in a solvent cage[10] - should be favored. The N-methyl product (11) probably arises from a precedented[11] intermolecular S_N2 mechanism with the cation (12) as the key chain carrying intermediate. If 11 is generated by an intermolecular pathway while 10 is formed intramolecularly, the rate of production of 11 should decrease in more dilute solution while formation of 10 becomes more competitive as is found: after 4 hr at 140 °C with 6 at 5% initial concentration, the product

mixture contained 33% 6, 17% 10, and 38% 11. The reversal in preferred reaction with temperature is consistent with literature data on Stevens rearrangements.[12]

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3. New compound; spectral and analytical data (including high resolution mass spectra for 6, 10, and 11) confirm the structures proposed for all new compounds.

4. ^{13}C NMR spectral comparisons (ppm, $CDCl_3$ [CD_3CN for 5]): CO_2Et: 4 163.5, 60.4, 13.7; 5 160.1, 63.5, 14.1; 6 165.6, 60.3, 13.9; 10 171.1, 60.2, 13.3; 11 163.7, 60.2, 13.3. Me: 5 34.4; 6 31.2; 10 21.8; 11 37.8. Benzo-C-H's: 4 129.5, 127.2, 126.7, 114.9; 5 135.1, 134.8, 134.5, 122.9; 6 134.2, 130.9, 130.7, 124.8; 10 129.4, 127.9, 127.2, 126.7; 11 129.0, 128.9, 128.9, 114.2. S,N-ring C's: 4 152.7, 139.6, 120.5, 91.1; 5 163.8, 138.1, 119.5, 107.2; 6 163.4, 145.9, 123.5, 108.9; 10 160.6, 141.5, 128.3, 47.4; 11 157.5, 145.3, 127.9, 125.5.

5. Crystals from EtOH-water; monoclinic, $P2_1/c$, Z = 4, a = 10.609(2), b = 9.492(3), c = 16.236(4) Å, β = 101.84(2)°, V = 1600(2) Å^3, d_x = 1.27 g/cm^3; structure solved from 1322 reflections of $I>2\sigma(I)$ measured on an Enraf-Nonius CAD-4 automated diffractometer (Mo K_α radiation); anisotropic refinement of all non-H atoms and isotropic refinement of H's (B_{iso} = 5 Å^2) converged at R = 0.046 and R_w =0.045 (esd of obs of unit weight = 1.11). Atomic coordinates for this work are available from the Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK. Any request should be accompanied by the full literature citation for this communication. Supplementary data available: structure factors, complete bond distances and angles, thermal parameters, and useful least-squares planes; see Announcement to Authors, Tetrahedron Letters, 47, 5154 (1983).

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