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REACTIONS OF SULFUR YLIDS WITH HETEROCYCLIC SALTS

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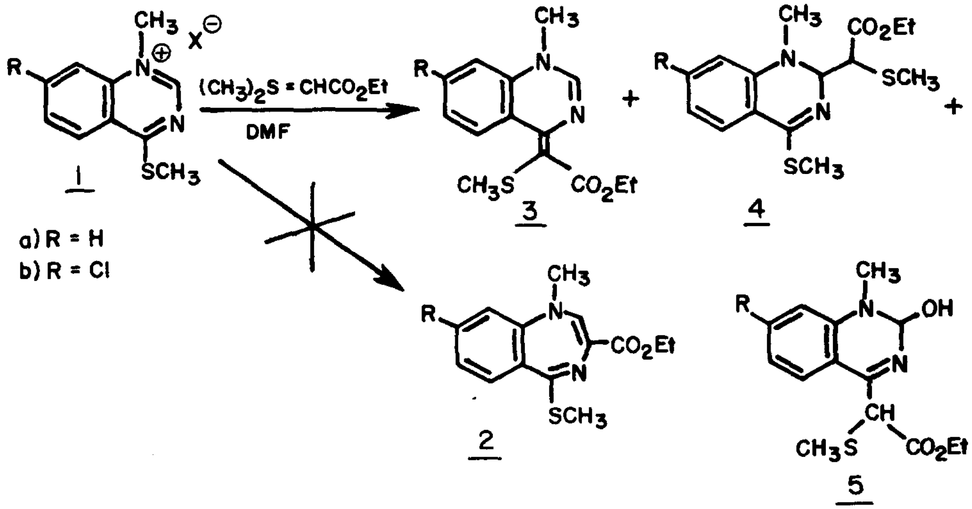
Nucleophiles such as hydride and hydroxide have previously been shown to readily react with pyrimidinium salts, and the products of these reactions can be rationalized on the basis of nucleophilic attack at the 2-position of the heterocycle (1,2,3).

In the present work we have studied the reactions of carbonyl-stabilized sulfur ylids as nucleophiles (4) with quinazolinium salts in an attempt to obtain 1,4-benzodiazapines *via* ring expansion of the C-2 adduct. However, reaction of ethyl dimethylacetylsulfurane, for example, with 1, did not furnish the desired product 2, but a variety of unexpected new compounds. As shown below, products 3 and 4 were obtained in yields that depended on the nature of the anion associated with the starting salt. With hydroxide (generated in situ) as the anion, 4 (R=Cl) was the major product (80% yield), whereas nitrate as the anion afforded predominately 3 (90% yield), but no 4 (*vide infra*). Compound 5 was isolated in small amounts in both cases. Spectral evidence and the chemical transformations described below form the basis for the structural assignments.



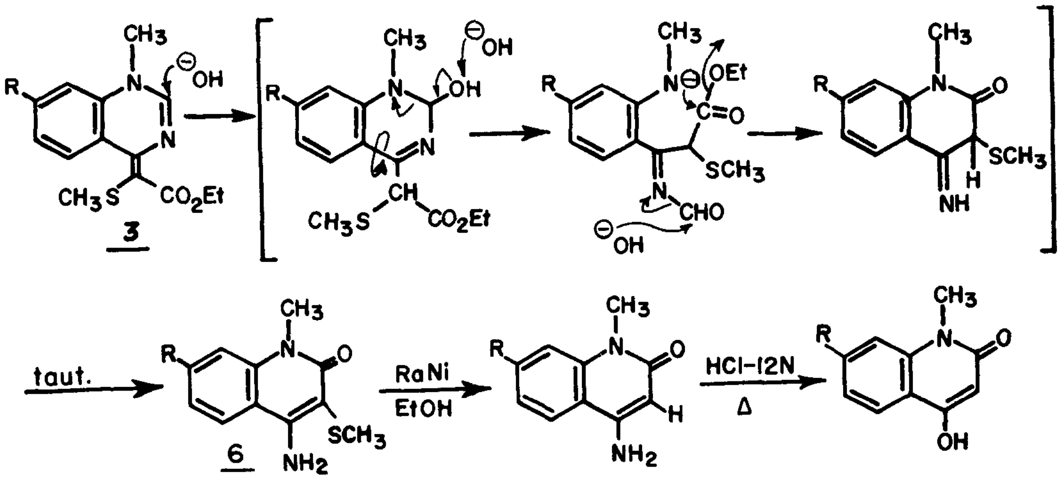
<u>Compound 4</u>: Valuable information was derived from the mass spectrum of this compound. Base peak at m/e 191, indicating the loss of 133 mass units ($CH_3S-CHCO_2Et$). NMR spectrum of 4a ($CDCl_3$): 75 H_z (triplet, 3H); 121 H_z (singlet, 3H); 140 H_z (singlet, 3H); 190 H_z (singlet, 3H); 201 H_z (doublet, 1H, J = 10 H_z); 148 H_z (quartet, 2H); 326 H_z (doublet, 1H, J = 10 H_z); 430 H_z (multiplet, 4H). Since the C-4 methylthio group is intact, and an AX pattern can arise only from adjacent protons, structure <u>4a</u> (R = H or Cl) best fits these data: <u>Anal</u>. Calcd. for $C_{15}H_{19}O_2N_2S_2Cl$ (R = Cl): C, 50.21; H, 5.34; N, 7.81; S, 17.85; Cl, 9.88. Found: C, 50.24; H, 5.45; N, 8.00; S, 17.59; Cl, 9.62.

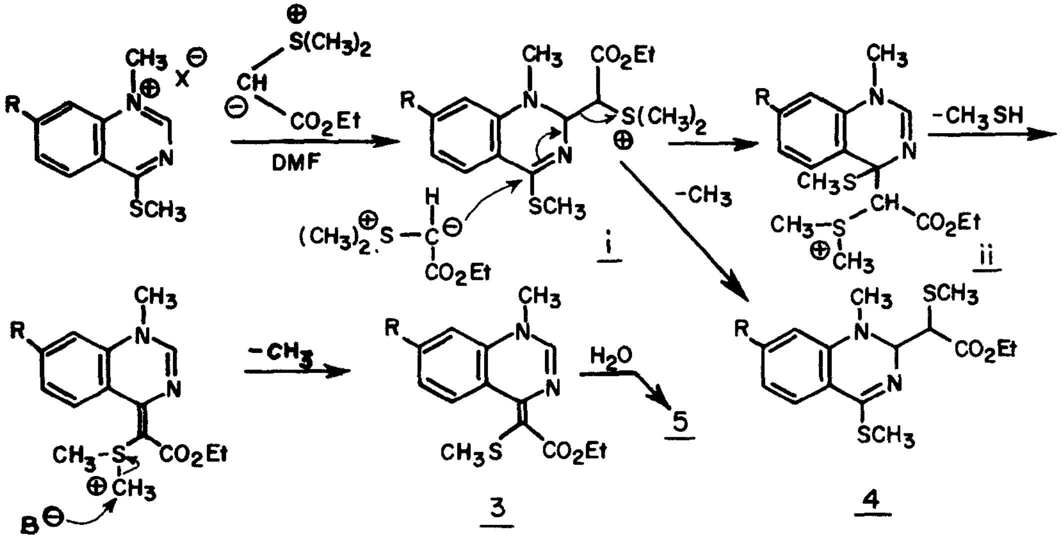
<u>Compound 5</u>: NMR spectrum (D_6MSO): 72 H_z (triplet, 3H); 108 H_z (singlet, 3H); 185 H_z (singlet, 3H); 247 H_z (quartet, 2H); 445 H_z and 492 H_z (multiplet, 7H); one proton in the 445 H_z multiplet exchanged upon D_2O addition. Mass spectrum: molecular ion at m/e 294, and base peak at m/e 161. The loss of 133 mass units is again consistent with loss of an ethyl thioglycolate side chain; the M-18 peak at m/e 276 (M* @ 259.1) indicates loss of H_2O.

A unifying mechanism which accounts for the formation of the observed products by initial nucleophilic attack of the ylid at C-2 of the heterocycle is presented below. Displacement of both the methylthio group and the initially added ylid from <u>i</u> by a second mole of ylid, then loss of a methyl group from <u>ii</u>, furnishes <u>3</u>. The formation of <u>4</u> can be rationalized by nucleophilic attack of the anion present in the reaction medium on a methyl group attached to the positive sulfur of intermediate <u>i</u>. This is supported by the observation that the yield of <u>4</u> increases with increasing nucleophilicity of the anion, i.e., from 0-5% for nitrate to 80% for hydroxide. That the methylthio group of <u>3</u> is indeed derived from the ylid is indicated by the finding that reaction of 4-phenoxy or 4-methoxy derivatives of <u>1</u> with ethyl dimethylacetylsulfurane likewise resulted in <u>3</u> as the major product. Compound <u>5</u> is apparently generated by addition of H_2O to <u>3</u>. Assignment of a 2-OH rather than a 4-OH adduct is supported by the fact that <u>5</u> upon treatment with ethanolic NaOH afforded exclusively <u>6</u>; no N-methyl-4(1H)quinazolinone was detected by thin layer chromatography.

Compound 3: NMR spectrum ($CDCl_3$): 76 H_z (quartet, 3H) 136 H_z (doublet, 3H); 197 H_z (doublet 3H); 256 H_z (5 lines, 2H) 440 H_z (multiplet, 4H); 506 H_z (doublet, 1H). The intensity ratios of the methyl doublets was reversed in D_6MSO. These doublets and the unusual multiplicities of the ethyl group are attributed to cis/trans isomerism around the exocyclic double bond. Variable temperature NMR spectroscopy afforded solvent dependent resolution of the carbethoxy group. Solute-solvent complexes may play a role in this behavior (5,6,7). Ultraviolet spectrum: λ_{max}^{EtOH} 363 mμ (ε = 26,400), 272 mμ (ε = 15,250); 250 mμ (ε = 18,800); the very broad band at or near 360 mμ ($\delta_{1/2}$ = 110 mμ) is characteristic for all of these compounds. Mass spectrum: base peak and molecular ion at m/e 276.0965 (8); loss of SH rather than SCH_3 as a major fragment has precedent in the fragmentation of various aromatic and aliphatic thioethers (9,10). Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.80; H, 5.80; N, 10.30; S, 11.50. Found: C, 60.78; H, 5.86; N, 10.30; S, 11.76.

Reaction of 3 with ethanolic sodium hydroxide gave 6 (mp 198°) in 60-70% yield (Anal. Calcd. for $C_{11}H_{12}N_2OS$: C, 60.00; H, 5.45; N, 12.70; S, 14.50. Found: C, 60.11; H, 5.61; N, 12.73; S, 14.20), which upon desulfurization with RaNi, followed by hydrolysis with conc. hydrochloric acid, gave the known N-methyl-4-hydroxy-2(1H)-quinolinone (11).





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