

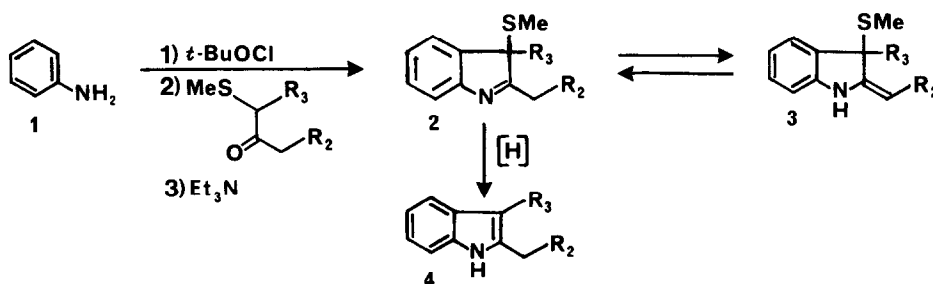
METHANESULFENYLATION OF 2,3-DIALKYLINDOLES: SYNTHESIS
AND REACTIONS OF 3-METHYLTHIOINDOLENINES

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3-Methylthioindolenines, readily prepared from 2,3-dialkylindoles and methanesulfonyl chloride, are heat and acid labile, yielding the parent indole and methyl disulfide as the major decomposition products, and are readily reduced to the parent indoles with mercaptoacetic acid.

Recent studies in our laboratory have been concerned with the development of new methods for synthetic elaboration of 2,3-dialkylindoles involving C-3-heteroatom substituted indolenines as intermediates¹. In this connection we became interested in the synthesis and chemical behaviour of 3-alkylthioindolenines. 3-Methylthioindolenines **2** have been isolated as intermediates in the synthesis of indoles from anilines devised by Gassman². A number of reductive reaction conditions were found to convert the indolenines **2** to the corresponding indoles **4**. An extremely unusual behaviour reported for these indolenines was a slow tautomerism to the enamine form **3** (as evidenced by the appearance of an N-H stretching band at 3400 cm⁻¹ in the infrared spectrum and an additional S-CH₃ signal in the proton nmr spectrum) which comprised up to 65% of the equilibrium mixture.

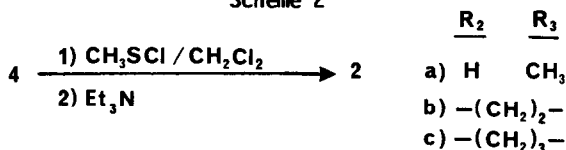
Scheme 1



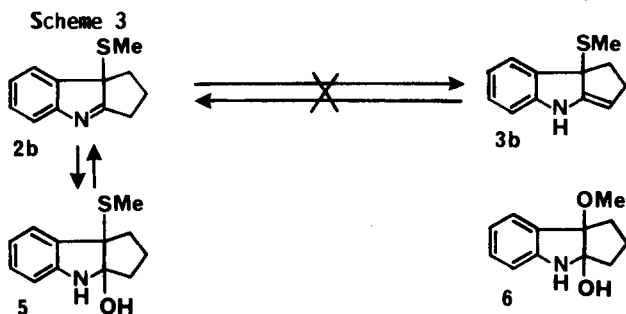
Although much of the chemistry of indolenines is best rationalized in terms of a tautomeric equilibrium with an enamine form³, it is clear from the study of a large number of indolenines, prepared recently in our laboratory⁴ or reported in the literature by others⁵, that such enamine forms are present in very small amounts, certainly below the detection limits of routine ¹H nmr spectrometers⁶. We report herein a study of the chemical properties of 3-methylthioindolenines which clarifies the apparently anomalous behaviour of these systems. Recently, we have described the preparation of 3-arylthioindolenines by reaction of a variety of 2,3-dialkylindoles with *o*-nitrophenylsulfonyl chloride in the presence of triethylamine^{4c}. We have found that

2,3-dialkylindoles react with methanesulfonyl chloride under similar conditions to give the corresponding 3-methylthioindolenines in excellent yield.^{7,8}

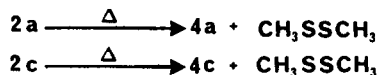
Scheme 2



As described by Gassman and coworkers², these compounds undergo a slow reaction on standing as evidenced by the spectroscopic changes alluded to above. For **2b** the new compound which formed slowly on standing was found to comprise 95% of the mixture when a sample of the indolenine, freed of triethylamine *in vacuo*, was treated with water. That this new product was the hydrate **5** and not the enamine **3b** was readily apparent from the mass spectrum which indicated a compound of molecular weight equal to 227 and from the ¹H nmr spectrum which bore a striking resemblance to that of the hydrate **6** previously prepared in this laboratory.^{4b}

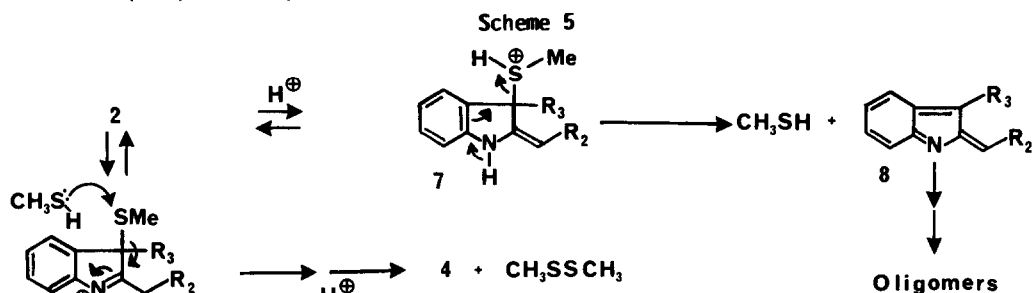


Scheme 4



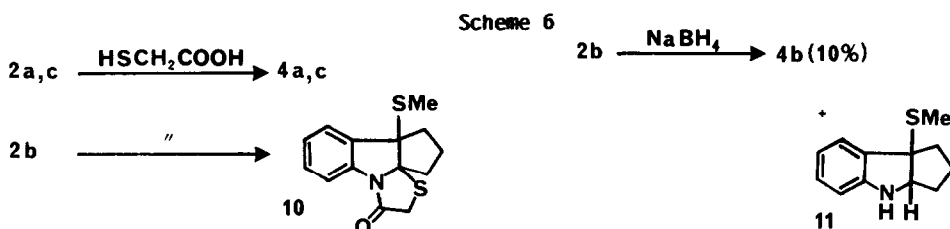
Since examination of a variety of indolenines in our laboratory had shown that the tendency to form stable hydrates was limited to indolenines derived from 2,3-cyclopentanoindoles, it seemed unlikely that the hydration phenomenon would explain the apparent imine-enamine tautomerism reported for other 3-methylthioindolenines. In our hands, samples of **2a** or **2c** upon standing neat at room temperature or upon heating (140°) underwent a reaction characterized in each case by the appearance of a new S-CH₃ signal at 2.30 ppm in the ¹H nmr spectrum. The reaction was also found to be markedly accelerated by acids such as trifluoroacetic acid. It was soon found that after such a sample had been subjected to high vacuum, the signal in the ¹H nmr spectrum, previously assigned to an S-CH₃ group of the enamine form was absent and no other alteration of the ¹H nmr spectrum was noted. In each case it was found by hplc analysis that the volatile component was simply methyl disulfide and the major non-volatile component was the parent indole **4**.¹⁰ The indoles could be isolated from the mixture by preparative tlc and their presence in such decomposed samples of the indolenines **2** explain the appearance of an N-H signal in the infrared spectrum.¹¹ These observations prompted us to speculate concerning the possible mechanism of this decomposition process as shown in Scheme 5. Nucleophilic attack of methanethiol (generated by elimination from an enamine tautomer) at sulfur of an N-protonated indolenine would generate the observed products, indole **4** and methyl disulfide. The unstable elimination product might give rise to higher molecular weight oligomeric products which have not been characterized. Although these mechanistic proposals were highly speculative, they proved to be very useful in that they led us to argue

further that if the indolenines **2** were susceptible to nucleophilic attack at sulfur as suggested, then complete conversion of these systems to the parent indoles might be effected by other sulfur nucleophiles. This prediction was borne out by the observations that heating methylene chloride solutions of **2a** and **2c** briefly (30 min) with excess mercaptoacetic acid at reflux yielded the indoles **4a** and **4c** in 93 and 100% isolated yield respectively. Excess mercaptoacetic acid and the byproduct disulfide were removed simply by washing the crude reaction mixture with aqueous base. This mild efficient reductive process offers a potentially useful alternative to the reducing conditions developed previously² for conversion of 3-methylthioindolenines to indoles.



The anomalous reduction of **2b** with sodium borohydride, which gave only 10% of the indole **4b** and mostly (43%) the indoline **11**, is worthy of mention. It was argued that **2b** gives **4b** whereas

11 arises by reduction of **3b**. A more plausible explanation in light of our observations concerning the reactivity of **2b** is that **4b** and **11** arises from **2b** (in equilibrium with **5**) the former via nucleophilic attack by hydride at sulfur (analogous to the suggested mode of attack by sulfur nucleophiles which leads to indoles from 3-methylthioindolenines) and the latter via nucleophilic attack, by hydride at the C=N bond. The tendency of the C=N bond of **2b** to be especially prone to undergo nucleophilic attack in preference to attack at sulfur is supported by the formation of **10** quantitatively from **2b** under conditions which lead to clean reduction of other 3-methylthioindolenines to indoles.



Experiments aimed at exploiting the potential synthetic utility of 3-methylthioindolenines are reported in the accompanying communication.

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5. See for example: A.H. Jackson and A.E. Smith, Tetrahedron, **1965**, 21, 989; R.J. Owellen, J. Org. Chem., **1974**, 39, 69; P.G. Gassman, G.A. Campbell and G. Mehta, Tetrahedron, **1972**, 28, 2749; S. McLean and G.I. Dmitrienko, Can. J. Chem., **1971**, 49, 3642; M.E. Kuehne, T.H. Matisko, J.C. Bohnett and C.L. Kirkeny, J. Org. Chem., **1979**, 44, 1063; V. Dave and E.W. Warnhoff, Can. J. Chem., **1976**, 54, 1015.
6. Exceptions to this generalization occur with indolenines bearing a carboalkoxy group at the α -carbon at C-2, in which case the enamine form, a resonance stabilized β -anilinoacrylate system, predominates. This system is found in certain alkaloids of the aspidosperma class. For a recent review see G.A. Cordell in "The Alkaloids"; R.H.F. Manske and R. Rodrigo, Eds.; Academic Press; New York, **1979**, Vol. XVII.
7. To our knowledge this is the first report of the reaction of an alkylsulfenyl chloride with a 2,3-dialkylindole. For a summary of sulfenylation reactions of indoles reported before 1980 see M. Raban and L.J. Chern, J. Org. Chem., **1980**, 45, 1688.
8. In a typical experiment, a cold solution of methane sulfenyl chloride⁹ (3.4 mmole) in methylene chloride (3.7 ml) was added dropwise to a solution of the indole (3.4 mmole) in methylene chloride (10 ml) at -50° in a dry nitrogen atmosphere. Triethylamine (5 ml) was added and the mixture allowed to warm to room temperature. Aqueous work up and removal of solvent in vacuo from the dried organic phase yielded the methylthioindolenine **2** as a pale yellow oil containing traces of triethylamine. Pure **2** was obtained by rapid chromatography on silica gel with elution by ether.
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10. Hplc analyses were performed on a Varian Model 5000 using a 30 cm x 4 mm μ Pac-MCH-10 column and an elution gradient from 50% acetonitrile/water solvent system to 100% acetonitrile over 10 minutes. Under these conditions the retention times for methyl disulfide, 2,3-dimethylindole and tetrahydrocarbazole were 32.5, 40 and 51 minutes respectively.
11. In light of these observations, prompt reduction of the methylthioindolenines generated by Gassman's method is strongly recommended. Triethylamine should be included with samples that are to be stored for any length of time.

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