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THE ACETYLATION OF 2-METHYL-Δ^2-THIAZOLINE*[1]

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Abstract—Some of the products of the reaction of 2-methyl-Δ^2-thiazoline with acetyl chloride in anhydrous acetonitrile are N,S-diacetylcysteamine **6** (30–35%), the dimer **1** (16%) and the cyclic trimer **3** (7%). Inclusion of small amounts of water in the reaction solvent diverts the course of the reaction to the exclusive production of diacetylcysteamine. The transient formation of the reactive N-acetylthiazolinium ion **5** is proposed to account for these observations.

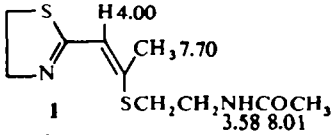
INTRODUCTION

DIVERSE compounds have been encountered in reactions of Δ^2-thiazolines with acid chlorides or anhydrides. These include the products (a) of cycloaddition to the imine function;[2-4] (b) of ring opening, yielding derivatives of cysteamine;[5, 6] (c) of substitution on an exocyclic 2-Me function,[7] and (d) of substitution on ring nitrogen accompanied by double bond migration.[8]

In the course of an investigation of the nucleophilic reactivity of Δ^2-thiazolines, two unexpected substances were isolated from the reaction of 2-methyl-Δ^2-thiazoline with acetyl chloride. The present report describes the elucidation of their structures, and offers a mechanistic hypothesis to account for their genesis, as well as that of the major reaction product, N,S-diacetylcysteamine. The two new compounds are designated the "thiazoline dimer" and the "thiazoline trimer", respectively, in what follows.

The "thiazoline dimer"

Examination of the UV absorption spectra of reaction mixtures consisting of equimolar quantities of 2-methyl-Δ^2-thiazoline and acetyl chloride in anhydrous acetonitrile disclosed the slow appearance of a striking absorption maximum at about 330 mμ. The substance responsible for this characteristic spectrum was found to be a base, $C_{10}H_{16}N_2OS_2$, m.p. 77–77·5°, which could be isolated in yields of about 16% as the picrate or salt with 2-nitroindane-1,3-dione. The free base had λ_{max} 283 mμ (ε_{max} 18,500) in 95% ethanol–water, and maximal absorption shifted to 333 mμ (ε_{max} 28,600) on acidification with 0·01 N HCl. Spectrophotometric or potentiometric titration indicated the presence of a single ionizable group, pK_a 5·94. On the basis of the spectral and other data presented below, it is proposed that the dimer is the substituted Δ^2-thiazoline **1**, formally derived from 2 moles of 2-methylthiazoline and one mole of acetyl chloride.†



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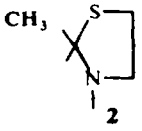

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* This work is taken from a dissertation presented by L.V.G. in partial fulfillment of the requirements for the Ph.D. degree, Yale University, 1967.

† The geometry of the substituents attached to the olefinic bond is not known.

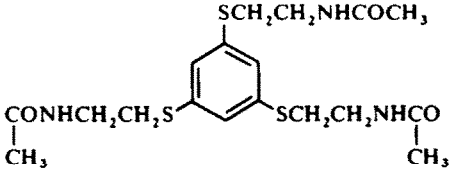
Both the positions and extinction coefficients of the absorption maxima, and the bathochromic shift on protonation resemble those of Δ^2-thiazolines bearing conjugated substituents in the 2-position,[9] although no close analogue of the proposed chromophore is known.* The dimer is somewhat more basic than 2-methylthiazoline (pK_a 5·25 in 10% ethanol–water),[9] a finding in qualitative agreement with the expected effect of a 2-substituent capable of electron donation. Infrared spectral data (Experimental) provided evidence for the presence of the—NH—and amide functions: absorption at 6·23μ was consistent with the known behaviour of simple Δ^2-thiazolines.†[11]

The NMR spectrum strengthens the proposed structural assignment and serves to rule out isomeric structures; in particular, the downfield positions of the two Me groups (8·01 and 7·70 τ) effectively eliminates isomers containing the 2-methylthiazolidine function (**2**).

Δ^2-Thiazolines exhibit bell-shaped pH-rate profiles for hydrolysis, one limb of which results from the fact that the protonated species of the substrate undergoes hydrolysis, while its conjugate base does not.[9, 12–14] At pH >4, the pH-rate profile for the disappearance of the dimer in 10% ethanol–water at 100° is in accord with expectation for the hydrolysis of a weak acid of pK_a *ca* 5·8.

The "thiazoline trimer"

The second compound isolated (*ca* 7% yield) from the reaction of acetyl chloride with 2-methylthiazoline was a sparingly soluble neutral substance, m.p. 181–182°, of elemental composition corresponding to C_6H_9NOS and with UV absorption (λ_{max} 255 mμ) unaffected by acidification. The NMR spectrum gave unambiguous testimony for the presence of the following types and numbers of protons: methyl (**3**), methylene (**4**), methine or aromatic (**1**), and amide nitrogen (**1**). The chemical stability of the unknown substance, coupled with the deceptively simple NMR spectrum, proved uninterpretable until the mass spectrum disclosed, *via* a molecular ion at *m/e* 429, that the empirical formula of the material must be $C_{18}H_{27}N_3O_3S_3$. The high symmetry revealed by the NMR spectrum was readily accommodated by the structure **3**, derived from 3 molecules of each of the reactants.



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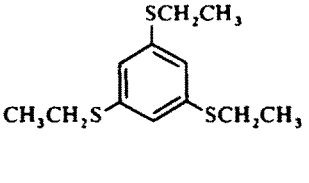

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Convincing support for the proposed structure **3** was obtained by comparison of the UV spectrum of the trimer (λ_{max} 255 mμ, ε_{max} 34,000) to that of 1,3,5-tris(ethylthio)benzene **4** (λ_{max} 255 mμ, ε_{max} 32,000).‡[15, 16] The two spectra were found to

* In 10% ethanol–water 2-(*p*-methoxyphenyl)-Δ^2-thiazoline shows λ_{max} 270 mμ (ε_{max} 18,600), which is shifted to λ_{max} 327 mμ (ε_{max} 25,600) on protonation.[9] The enolized form of 2-acetonylthiazoline, whose absorption spectrum might be expected to be intermediate between that of dimer and protonated dimer, has λ_{max} 312 mμ in methanol.[10]

† Absorption bands at 6·10 μ and 6·20 μ have been reported[11] for 2-methyl- and 2-phenylthiazoline, respectively.

‡ We are indebted to Dr. W. Reifschneider, of the Dow Chemical Company, for the generous gift of a sample of **4**.

be nearly identical throughout the wavelength region of 230 to 310 mμ. Finally, major fragments in the mass spectrum were seen at *m/e* 370, 311 and 252, which, together with the expected metastable ions, indicated the consecutive loss of three CH_3CONH_2 molecules.

N,S-*Diacetylcysteamine*

The predominant product of the reaction is N,S-diacetylcysteamine **6**, whose formation in 30–35% yield was shown by gas chromatography of reaction mixtures. The material whose retention time corresponded to that of the cysteamine was collected after chromatography and found to be identical in m.p., IR and UV spectra to authentic **6**. The

TABLE 1. ACETYLATION OF 2-METHYLTHIAZOLINE IN $CH_3CN—H_2O$[a]

Expt. No.	Solvent, % CH_3CN v/v	CH_3COCl M	Thiazoline M	Yield of Diacetylcysteamine[b] %
1[c]	99·5	0·25	0·25	57 ± 0·3
2[d]	99·5	0·25	0·50	76·5 ± 1·3
3[e]	99·5	0·025	0·050	95·0 ± 2
4[f]	98·0	0·025	0·060	99·5 ± 0·5
5[f]	95·0	0·025	0·060	84 ± 0·4
6[f]	90·0	0·025	0·050	35 ± 0·7
7[f]	80·0	0·025	0·050	4·3

[a] Room temperature.
[b] Measured by gas chromatography and based on CH_3COCl.
[c] Reaction time 26 min
[d] Reaction time 30 min, but 90% of final yield reached in 3 min.
[f] Reaction time 1 hr.

rate of appearance of **6** is rapid and could not be accurately estimated. With 0·25 M reactants, 90% of the eventual yield is reached within one minute after mixing. In contrast, dimer formation, as measured by the increase of absorbance at 330 mμ, is half-complete in 45 min and reaches its maximum in about 4 hr.

Reaction in partially aqueous media

Since it was suspected that the formation of diacetylcysteamine in reactions carried out in "anhydrous" acetonitrile was the result of adventitious traces of water, the effect of the addition of small amounts of water was examined (Table 1). It is clear that, in the presence of excess thiazoline, as little as 0·5% water diverts the course of the acetylation reaction quantitatively to the production of diacetylcysteamine (expt. 3). Higher concentrations of water lead to a decrease in the yield of acetylated product, presumably owing to competing hydrolysis of acetyl chloride. When equimolar reagents are used (expt. 1), gas chromatography showed that about half of the initial thiazoline remained unreacted, probably being protected as its conjugate acid.

In none of the experiments reported in Table 1 was any spectral evidence obtained for the formation of dimer.

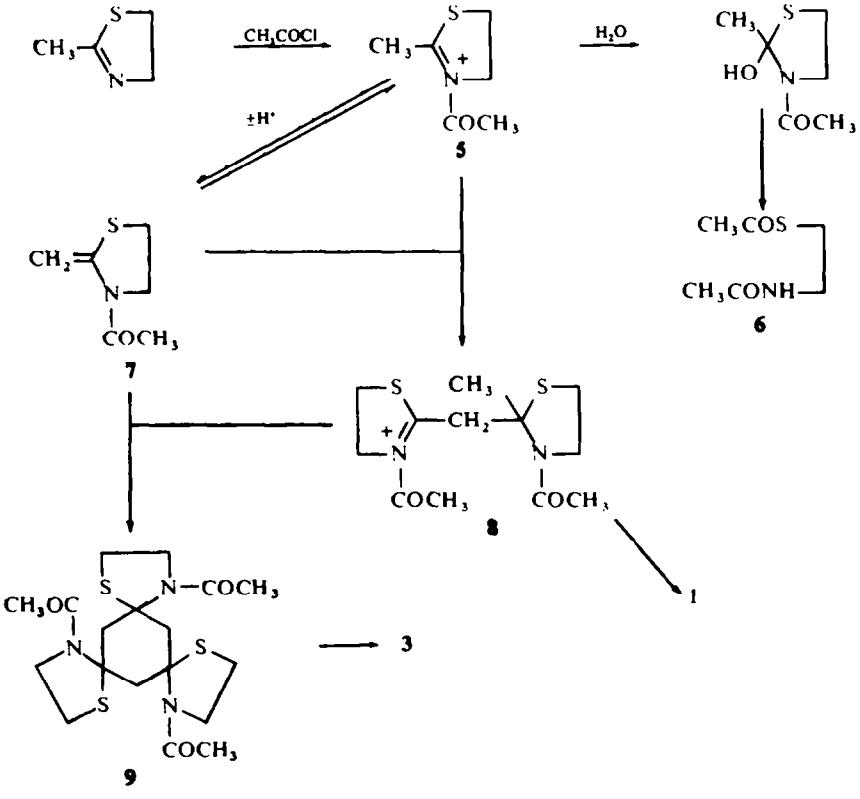
DISCUSSION

The primary feature of the reaction mechanism offered to account for the present findings is the formation of the N-acetylthiazolinium ion **5** (Scheme 1). In the presence of water, this highly electrophilic intermediate suffers rapid hydration at C-2 and yields the ring-opened cysteamine **6**. In anhydrous solvents of low nucleophilicity, deprotonation of the exocyclic methyl group produces the ketene-S,N-acetal **7**. Condensation of **7** with **5** may yield a dimeric intermediate **8**, which is readily transformed to the isolated dimer **1** by β-elimination and deacetylation. Alternatively, repeated attack of **7** on **8** could produce the cyclic trimer **9** easily aromatized to **3**.

Several simple ketene-S,N-acetals have been prepared in recent years,[17] and their reactivity with electrophilic reagents is well established.[17b, 18] In 1956, Sheehan *et al.*[8] assigned the structure of an N-acylated ketene-S,N-acetal to a rather unstable substance isolated from the reaction of 2-methylthiazoline with phthaloylglycyl chloride, and another example of this class has been reported recently.[19]

Dimerization mechanisms fundamentally similar to the above may be written for a number of known reactions, in which the β-C atom of an enamine function carries out nucleophilic attack on the α-C atom of its conjugate, C-protonated, species. These include the dimerization of enamines,[20] imide chlorides,[21] amides,[22] and enamides.[23] An instance particularly relevant to the present case is found in the product of alkali treatment of 2,3-dimethylbenzthiazolium salts, first thought to be a methylene base of

SCHEME 1



structure analogous to **7**, but now known to be a dimer probably formed according to the mechanism in Scheme 1.[24a, b] It should be noted, however, that with other benzthiazolium salts, monomeric products of proton abstraction have been isolated.[24a, 25] Dimerization of 2,3-dialkylbenzoxazolium salts terminates with ring-opening, as in the formation of **1**.[24c]

The chemistry of the more extensively studied ketene-O,O-acetals and the corresponding acetoxonium salts offers interesting parallels to the acylthiazolinium system. Cyclohexene acetoxonium salts undergo proton abstraction to ketene-O,O-acetals, followed by dimerization as above.[26] In the presence of water, however, hydrolytic ring opening supervenes. Appropriately, acid treatment of ketene diethyl acetal produces not only dimers and linear polymers, but also 1,1,3,3,5,5-hexaethoxycyclohexane (*cf* **9**) and 1,3,5-triethoxybenzene.[27] Trimerization, culminating in aromatization to 1,3,5-trisubstituted benzene derivatives also has been found with an enamine[28] and with cyclohexanone dimethyl ketal[29] (the latter presumably *via* 1-methoxycyclohexene).

To account for the products obtained on reaction of acylating agents with Δ^2-oxazolines, the intermediacy of N-acyloxazolinium ions has been suggested in several cases. Thus, acylation in water-containing solvents gave N,O-diacylethanolamine derivatives,[30] while N,N-diacyl-β-chloroethylamines were isolated from reactions performed under anhydrous conditions.[30c, 31] The latter compounds presumably arose as a result of nucleophilic attack at C-5 of the N-acyloxazolinium cation, a reaction type not yet seen in the thiazoline series but of which many examples have been recorded with other ambident cations.[32] The synthesis and isolation of N-acyloxazolinium salts has been described in a preliminary report;[33] a few related cyclic N-acyliminoester salts have been known for some time.[32, 34]

EXPERIMENTAL*

All m.ps are uncorrected. IR spectra were obtained with a Perkin–Elmer Model 137B Infracord Spectrophotometer and UV spectra with a Perkin–Elmer Model 350 recording spectrophotometer. Mass spectra were determined with an A.E.I. MS-9 Mass Spectrometer operating at an ionizing current of 100 μamp, ionizing potential of 70 ev, and ion source temp 225–250°. NMR spectra were obtained with Varian Models HR-60 and A-60 spectrometers operating at 60 Mc, using TMS as internal standard. Acetonitrile was purified according to method D of Coetzee *et al.*,[35] and stored in sealed glass ampoules in the absence of light.

2-(β-(2′-*Acetamidoethylthio*)-β-*methyl*) vinyl-Δ^2-*thiazoline* (**1**). A soln of 3·9 g (50 mmole) of redistilled acetyl chloride in 75 ml anhyd acetonitrile was added dropwise to a soln of 5·11 g (50·4 mmole) 2-methylthiazoline (distilled from powdered BaO) in 125 ml acetonitrile with exclusion of moisture. After keeping the reaction mixture for 4 hr at room temp with magnetic stirring, the soln was concentrated *in vacuo* to an oily residue, to which was added 100 ml water followed by *ca* 15 g $NaHCO_3$. The resulting suspension was either filtered to remove the trimer-containing solid (see below) or directly extracted with 10×60 ml portions of ether. The combined ethereal extracts were washed with $NaHCO_3$ aq saturated with NaCl, and dried with $MgSO_4$. Removal of the solvent under reduced pressure left an oil which was triturated with 5 × 10 ml cold cyclohexane, dissolved in 5 ml abs EtOH and rapidly added to a soln of 1·0 g (5·25 mmole) 2-nitroindane-1,3-dione in 30 ml acetone. The yellow crystalline solid which precipitated immediately was collected after storage for 1 hr in the cold and dried *in vacuo* over P_2O_5, yield 1·80 g (16%) m.p. 160–165° d. Recrystallization from hot abs EtOH gave yellow needles, m.p. 169·5–170·5 d. (Found: C, 51·30; H, 5·45; N, 9·51; S, 13·57. $C_{19}H_{21}N_3O_5S_2$ requires: C, 52·30; H, 4·87; N, 9·64; S, 14·70%).

Alternatively, the dimer was isolated as the picrate which was prepared by adding an ethanolic soln of the crude oily product to a 6% soln of picric acid in abs EtOH, yield 17%, m.p. 133–138°, which increased to

* Elemental microanalyses were performed by Schwarzkopf Microanalytical Laboratory, New York, N.Y., and S. M. Nagy, Massachusetts Institute of Technology, Cambridge, Massachusetts.

143·5–144° after recrystallization from abs EtOH. (Found: C, 40·90; H, 3·91; N, 14·87; S, 13·24, 13·57. $C_{16}H_{19}N_3O_8S_2$ requires: C, 40·57; H, 4·04; N, 14·79; S, 13·54%).

The finely powdered indanedionate salt (930 mg, 2·14 mmole) was shaken with a mixture of 50 ml ether and 100 ml water containing *ca* 12 g $NaHCO_3$. After addition of 10 g NaCl, the dimer-free base was extracted from the aqueous phase with 10 × 15 ml portions ether. The combined extracts were washed with 200 ml water saturated with NaCl and $NaHCO_3$, dried with $MgSO_4$ and concentrated *in vacuo* to a colorless solid (343 mg, 11% overall yield) which had m.p. 77–77·4° after recrystallization from cyclohexane.

IR spectrum ($CHCl_3$): —NH— 2·92 μ; —CONH— 6·0, 6·63 μ; —C=N— 6·23 μ; UV spectrum (95% EtOH): λ_{max} 283 mμ. ε_{max} 18,500; with 0·01 N HCl added, λ_{max} 333 mμ. ε_{max} 28,600; NMR spectrum (7% in $CDCl_3$): singlet at 8·01 τ 3H, —CO<u>CH</u>$_3$; singlet at 7·70 τ, 3H, —CH=C(—<u>CH</u>$_3$)—; triplet at 5·72 τ, 2H, —<u>CH</u>$_2$— (C_4 of thiazoline nucleus); multiplet at 6·2–7·2 τ, 6H; singlet at 4·00 τ, 1H, —<u>CH</u>=; broad signal at 3·58 τ, 1H, —CONH—. Molecular weight: molecular ion at *m/e* 244; osometry 232; neutralization equivalent 252. pK_a: from titration with HCl in 10% EtOH–water, 25°, μ 0·10–0·11 M (KCl), 5·94 ±0·01; from spectrophotometric titration under the same conditions but with the addition of 0·01 M histidine buffer, 5·98 ±0·02. (Found: C, 49·43; H, 6·16; N, 11·09; S, 26·31; $C_{10}H_{16}N_2OS_2$ (244·38) requires: C, 49·14; H, 6·60; N, 11·45; S, 26·24%).

1,3,5-*Tris* (*2'-acetamidoethylthio*)*benzene* (**3**). The trimer-containing fraction (see isolation of **1**) was crystallized from hot abs alcohol, with filtration to remove contaminating salt, yielding the crude trimer (250 mg, 7% m.p. 158–161°). Two recrystallizations from the same solvent (charcoal) gave colorless crystals, m.p. 181–182°.

IR spectrum (Nujol): —NH— 3·1 μ; —CONH— 6·1 and 6·45 μ; NMR spectrum (8% in CF_3COOH): singlet at 7·54 τ, 3H, —CO<u>CH</u>$_3$; triplet centered at 6·79 τ, 2H, —<u>CH</u>$_2$—, triplet centered at 6·28 τ, 2H, —<u>CH</u>$_2$—; singlet at 2·70 τ, 1H, aromatic; broad signal at 1·35 τ, 1H, —<u>NH</u>—. Molecular ion at *m/e* 429; prominent ions at *m/e* 370, 311 and 252; metastable ions at 319·6 (*m/e* 429→*m/e* 370 requires 319·8), 261·3 (*m/e* 370→*m/e* 311 requires: 261·4) and 204·2 (*m/e* 311→*m/e* 252 requires: 204·2). (Found: C, 50·45; H, 6·37; N, 10·11; S, 22·23. $C_{18}H_{27}N_3O_3S_3$ (429·62) requires: C, 50·32; H, 6·33; N, 9·78; S, 22·39%).

N,S-*Diacetylcysteamine* (**6**) was prepared from cysteamine hydrochloride according to the procedure of Hawkins and Tarbell[36] but without prior conversion to cysteamine-free base. The product had b.p. 155° at 3·5 mm, m.p. 28–30°; UV spectrum in 2% EtOH–0·05 N HCl: λ_{max} 231 mμ, ε_{max} 4550 (reported:[36] b.p. 131–133° at 1 mm, m.p. 28–30°; UV spectrum in 0·01 N HCl, λ_{max} 233 mμ, ε_{max} 4510); IR spectrum (thin film): —NH— 3·1 μ; —S—C(=O)— 5·95 μ; —CONH— 6·1, 6·4 μ; NMR spectrum (30% in $CDCl_3$): singlet at 7·99 τ, 3H, <u>CH</u>$_3$—CONH; singlet 7·62 τ, 3H, <u>CH</u>$_3$COS—; triplets at 6·90 and 6·59 τ, 4H, *J* 6 c/s, —CH_2CH_2—; broad signal at 2·78 τ, 1H, —CO<u>NH</u>—.

Hydrolysis of dimer. The kinetics of the disappearance of **1** in 10% EtOH–water, μ = 1·0 M, 100°, were followed spectrophotometrically by measuring the rates of decrease in absorption at 333 mμ. At pH >4, the rate of hydrolysis obeys Eq (1), which describes the pH dependence of the rate of hydrolysis of a base susceptible to hydrolysis in its conjugate acid form only, k_{obs} = apparent first-order rate constant: k = rate

$$k_{obs} = k[H^+]/([H^+] + K_a) \quad (1)$$

constant for hydrolysis of fully protonated substrate; K_a = acid dissociation constant of protonated substrate. The constants selected to fit the observed rates were: $k = 5{\cdot}3 \times 10^{-3}$ min^{-1}; pK_a = 5·80.

Product analysis by gas chromatography. The yields of N,S-diacetylcysteamine produced under various reaction conditions were determined by direct gas chromatography of reaction mixtures at selected times. Reactions were generally carried out in vials stoppered with a rubber cap, through which 1 μl aliquots were removed with a 10 μl Hamilton syringe. Reactions were followed until no further increase in product yield was seen. A Perkin–Elmer Model 810 Gas Chromatograph equipped with a Honeywell–Brown recorder and a differential flame ionization detector was used. Six foot, ¼ inch o.d. stainless steel columns were packed with silicone gum rubber (Perkin–Elmer SE-30), 17% by weight on Anakrom ABS (90/100 mesh), and N_2 was the carrier gas. With a column temp of 150° and a flow rate for N_2 of 76 ml/min, retention time for **6** was 4·2 min. At a column temp of 90° and a flow rate of 50 ml/min, 2-methylthiazoline was eluted in 2·5 min.

Product yields were calculated by comparison of peak areas to those of solutions of known concentration (*ca* 10 mg/ml); the response of the detector was found to be linear over at least the concentration range of 7–30 mg/ml. For sample collection, the effluent gas stream was split by means of a T-joint, one arm leading to

the detector and the other to a vent in the oven wall, into which was inserted a snugly-fitting capillary glass tube.

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