ACTA CHEMICA SCANDINAVICA 24 (1970) 3129–3133

# *N*-Quaternary Compounds

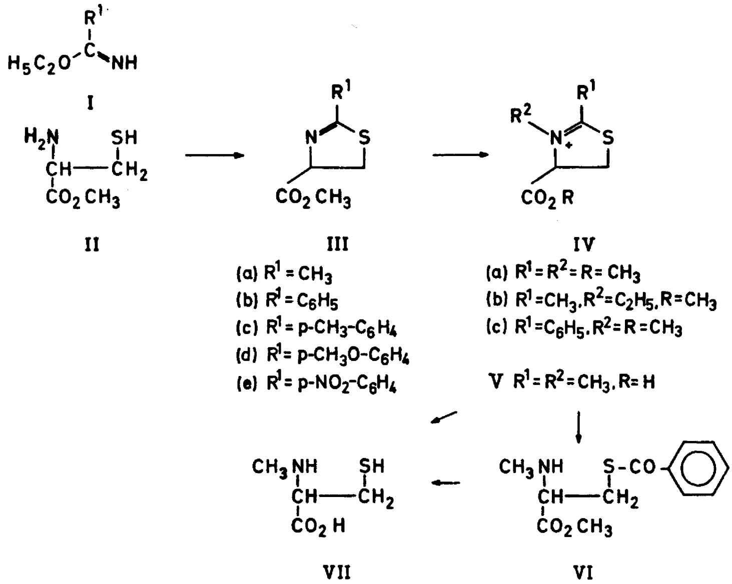
## Part XVI. 4-Carboxythiazolinium Derivatives

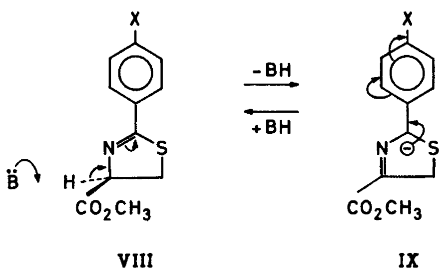
KJELL UNDHEIM and ÅSE EIDEM

*Chemical Institute, University of Oslo, Oslo 3, Norway*

Optical stability studies on 2-methyl and 2-phenyl derivatives of L-4-carboxymethyl-$\Delta^2$-thiazoline show the former to be more stable. Electron donating groups in the *p*-position in the phenyl ring increases the optical stability. The 2-methyl derivative could be *N*-methylated or -ethylated. Acid hydrolysis gives L-*N*-alkylcysteines. This is an improved method for their preparation. *N*-Methylation of the 2-phenyl derivative resulted in hydrolytic opening of the thiazolinium ring and complete racemisation.

Our studies on dihydrothiazolo[3,2-a]pyridinium derivatives [1] have led us to investigate the properties, especially the chemical and optical stabilities, of the thiazolinium ring detached from the pyrido system. The thiazolinium derivative should have a carboxy group in the 4-position and be optically active. L-Cysteine would be the natural starting material for the thiazoline which then would have to be *N*-alkylated. Of the various ways the C-2 carbon in thiazoline can be introduced into vicinal amino-thiol derivatives [2–4] treatment with imino-ethers [2] in methylene chloride seemed to offer the mildest conditions. Mild reaction conditions are important to avoid racemisation. The 4-carbomethoxy-2-methylthiazoline [2] thus prepared from cysteine methyl ester could be purified by distillation without loss of optical activity while the 2-phenyl [2] derivative was racemised on distillation. The decreased optical stability of the phenyl derivative as compared with the alkyl derivative is explained by the negative inductive effect of the phenyl group as well as resonance stabilisation of the carbanion (IX) which therefore makes the C-4 proton more acidic. This was verified by preparing derivatives with various *p*-substituents [2] in the phenyl ring. The *p*-nitro derivative (IIIe), was optically inactive. The other derivatives have electron donating groups in the *p*-position so as to increase the optical stability. These thiazolines (IIIb – d) are thought to be only weakly racemised during their syntheses and isolation. The 2-methyl derivative (IIIa) and its *N*-methyl thiazolinium analogue (IVa) presumably have a high degree of optical purity as discussed below. Making these assumptions a




qualitative guide to the respective optical stabilities was established by measuring the rate of racemisation at the sodium D-line in 0.1 N triethylamine in methanol at 23°. After 90 min the ratio $[\alpha_t]/[\alpha_0]$ was found to be: 0.87 (IIIa); 0.74 (IIId; *p*-$OCH_3$); 0.73 (IIIc; *p*-$CH_3$); 0.35 (IIIb; *p*-H). The same ratio for the *N*-quaternary derivative (IVa) was 0.25 after only 20 min. The negative inductive effect of the neighbouring quaternary nitrogen is here responsible for the acidity of the methine proton and thereby racemisation.

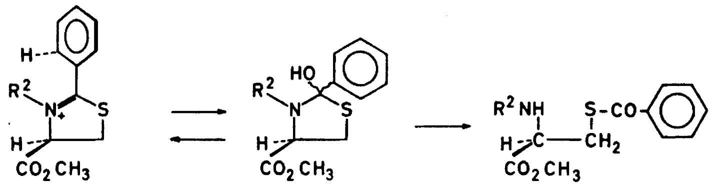
The 2-methyl derivative (IIIa) was methylated in methyl iodide by heating for 1 h or standing in the cold overnight, or by heating with methyl tosylate in acetonitrile overnight. *N*-Alkylation and not *S*-alkylation was confirmed by hydrolysis in boiling 2 N HCl when *N*-methyl cysteine was obtained. For comparison *S*-methyl cysteine was synthesized by treatment of cysteine in barium hydroxide with dimethyl sulphate.[5] In the NMR spectra in TFA the methyl groups of these isomeric compounds were found at 6.83 and 7.80 $\tau$, respectively. The specific rotation for *N*-methylcysteine from the hydrolysis of the 2,3-dimethylthiazolinium derivative (IVa) was $[\alpha]_D^{23} = +15.5°$ (HCl) and $[\alpha]^{25}_D = +12.0°$ (HCl) depending on whether the thiazoline was methylated with methyl iodide or methyl tosylate, respectively. Previously, *N*-methyl cysteine has been prepared by sodium in liquid ammonia reduction of 4-carboxythiazolidine.[6,7] In our hands the sodium in liquid ammonia reduction yielded largely the *N*-methyl derivative as shown by chromatography and NMR, but the heavily contaminated product was difficult to purify. Thiazoline formation, *N*-methylation, and acid hydrolysis therefore constitute an improved method for *N*-methylation of cysteine.

With ethyl iodide as alkylating agent the reaction was much slower, requiring 8–10 days in the cold or heating in ethyl iodide overnight. Other active alkylating agents such as benzyl bromide or alkyl bromide failed to react under normal reaction conditions. This must be due to steric reasons. It was also found that the 2-phenyl derivative failed to react with methyl iodide, diazomethane or triethyloxonium borofluoride. With methyl tosylate in not dried acetonitrile an optically inactive product was obtained. In dry acetonitrile no reaction took place. The NMR signals from the methylene and methine protons in the cysteine moiety in the optically inactive product were at higher fields (6.2 and 5.4 $\tau$) than in the thiazolinium derivative (IVa) (5.6 and 4.1 $\tau$). The new methyl group was at 6.8 as compared to 6.1 $\tau$ in the quaternary derivative (IVa). In TFA the new methyl group appeared as a triplet which collapsed to a singlet in deuterated TFA. This parallels the behaviour of *N*-methylcysteine. The *N*-quaternary compound formed (IVc) therefore has suffered opening of the ring with formation of *N*-methyl-*S*-benzoylcysteine (VI) confirmed by hydrolysis to racemic *N*-methylcysteine.

The apparent resistance towards *N*-alkylation is caused by the *ortho* substituents, that is in the 2- and 4-position, which hinder the access of the alkylating agent to the annular nitrogen. Without the bulky 4-carbomethoxy group, 2-methyl-$\Delta^2$-thiazoline can be quaternized with higher alkyl groups[8] while in the above work only the methyl and ethyl derivatives could be prepared. Similarly 2-phenyl-$\Delta^2$-thiazoline can be methylated with methyl tosylate while the reaction with the 4-carbomethoxy derivative failed.

In the case of the 2-phenyl derivative one would expect that the two ring systems would tend to be coplanar because of resonance. The phenyl group will thus hinder the approach of the alkylating agent to the nitrogen. Also in the alkylated product, the *N*-alkyl group will cause non-bonded interaction with the *ortho* protons in the phenyl ring (X). The rings then become non-coplanar whereby the *N*-quaternary ylid group loses much of its resonance stabilisation from the phenyl ring. However, the electronegative effect of the phenyl ring remains, so that electronically the C-2 carbon should be more readily attacked by a nucleophile such as water. Relevant stability studies in acid solution of thiazolines have been reported.[2,9,10] In acid solution the thiazolines are protonated (*e.g.* X, $R^2 = H$).

The hydrolysis has been shown to proceed *via* a thiazolidine analogue (*e.g.* XI, $R^2 = H$) arisen by water attack on the C-2 carbon. The hydrolysis rate is pH dependent in such a way that it has a maximum at a certain pH below which it falls off again. Thus 2-methyl-$\Delta^2$-thiazoline becomes increasingly



X XI XII

more resistant towards acid hydrolysis from about pH 2 and downwards. The results seem best explained by a marked decrease in the concentration of the intermediate, uncharged tetrahedral thiazolidine with increase in acid concentration.[2]

Since the hydrolysis rate of thiazolines decreases with pH below a certain critical value,[2,9] ester hydrolysis in strong acid solution is possible. Thus the ester group in 2-methyl-4-carbomethoxy-$\Delta^2$-thiazoline is selectively hydrolysed in 7 N HCl in the cold in the course of 10 min.[14] In the same way we could hydrolyse the thiazolinium ester IVa to the corresponding acid (V). The aqueous acid was removed in vacuum in the cold since heating led to hydrolysis of the ring. Attempts to isolate the zwitterion by neutralisation or by passage through a weak anion exchanger led to partial hydrolysis of the thiazolinium ring as one would expect from the above quoted studies of thiazolines. In IV and V the nitrogen is already charged and therefore water should readily attack the C-2 carbon giving a high concentration of the neutral thiazolidine. Since the proton concentration is low, it therefore exists favourable conditions for opening of the ring as observed.

## EXPERIMENTAL

The following chromatographic systems were found useful: BuOH:EtOH:$NH_3$:$H_2O$, (4:1:2:1), BuOH:HOAc:$H_2O$ (100:22:50) and BuOH:EtOH (4:1) saturated with $H_2O$. NMR spectra were recorded on a 60 Mc/s instrument.

*4-Carboxymethyl-2,3-dimethyl-$\Delta^2$-thiazolinium iodide* (*IVa*). A solution of 4-carboxymethyl-2-methyl-$\Delta^2$-thiazoline [5] (15.9 g, 0.1 mol) in methyl iodide (30 ml) was heated under reflux for 1 h, the reaction mixture evaporated and the residue crystallized from ethanol; white crystalline material, m.p. 119–120°, yield 24.0 g (84 %). At room temperature the reaction time was 24 h. (Found: C 28.04; H 4.32; N 4.81; S 10.68. Calc. for $C_7H_{12}NO_2SI$: C 27.91; H 4.02; N 4.65; S 10.65.) $[\alpha]_D^{23} = -14.1°$ ($c$=3.0 in MeOH).

*4-Carboxymethyl-2,3-dimethyl-$\Delta^2$-thiazolinium tosylate* (*IVa*). A solution of 4-carboxymethyl-2-methyl-$\Delta^2$-thiazoline [5] (5.3 g, 0.03 mol) and methyl tosylate (8.0 g, 0.05 mol) in acetonitrile (100 ml) was heated at 70° overnight, the solvent distilled off, the residue triturated with ether and crystallized from acetone-ethyl acetate; white crystalline material, m.p. 89–90°, yield 5.4 g (52 %). (Found: C 48.44; H 5.33; N 4.11. Calc. for $C_{14}H_{19}NO_5S_2$: C 48.68; H 5.54; N 4.06.) $[\alpha]_D^{23} = -10.6$ ($c$=3.0 in MeOH).

*4-Carboxymethyl-3-ethyl-2-methyl-$\Delta^2$-thiazolinium iodide* (*IVb*). A solution of 4-carboxymethyl-2-methyl-$\Delta^2$-thiazoline [5] (8.0 g, 0.05 mol) in ethyl iodide (25 ml) was heated under reflux for 24 h, excess ethyl iodide distilled off, the residue triturated with ether and crystallized from acetone-ethyl acetate; white crystalline material, m.p. 215–216°, yield 10.0 g (63 %). In the cold the reaction requires 8–10 days. (Found: C 30.02; H 4.75; N 4.56. Calc. for $C_8H_{14}NO_2SI$: C 30.49; H 4.48; N 4.44.) $[\alpha]_D^{23} = -39.4°$($c$=3.0 in MeOH).

*S-Benzoyl-N-methylcysteine methyl ester tosylate (VI).* A solution of 4-carboxymethyl-2-phenyl-$\Delta^2$-thiazoline [2] (11.0 g, 0.05 mol) and methyl tosylate (19.0 g, 0.1 mol) in acetonitrile (150 ml) was heated at 70° overnight, the solvent evaporated, the residue triturated with ether and the residue crystallized from acetone-ethyl acetate. Alternatively, the residue after ether trituration can be crystallized from water (charcoal); white needles in 69 % yield (14.5 g), m.p. 144–145°. (Found: C 54.01; H 5.49; N 3.43. Calc. for $C_{19}H_{24}NO_6S_2$: C 53.76; H 5.22; N 3.30.)

*3-Methyl-2-phenyl-$\Delta^2$-thiazolinium tosylate.* A solution of 2-phenyl-$\Delta^2$-thiazoline [4] (4.1 g, 0.025 ml) and methyl tosylate (8.3 g, 0.05 mol) in acetonitrile (50 ml) was heated at 70° overnight, the solvent evaporated, the residue triturated with ether and crystallized from acetone-ethyl acetate; white needles, m.p. 130–132°, yield 6.7 g (76 %). (Found: C 58.40; H 5.62; N 3.96. Calc. for $C_{17}H_{19}NO_3S_2$: C 58.42; H 5.48; N 4.01.)

*4-Carboxy-2,3-dimethyl-$\Delta^2$-thiazolinium chloride (V).* 4-Carboxymethyl-2,3-dimethyl-$\Delta^2$-thiazolinium tosylate (3.5 g, 0.01 mol) was dissolved in cold 7 N HCl (50 ml) and the solution left in the cold for 10 min. The solution was then evaporated to dryness at reduced pressure without heating, the *p*-toluene sulphonic acid extracted into acetone and the solid residue crystallized from methanol; m.p. 190–192°, yield 1.75 g (90 %). (Found: C 37.17; H 5.16; N 7.02. Calc. for $C_6H_9NO_2S \cdot HCl$: C 36.82; H 5.15; N 7.06.) $[\alpha]_D^{23} = -15°$ ($c = 2.1$ in MeOH).

L-N-*Methylcysteine (VII).* The *N*-methylthiazolinium derivatives were dissolved in 2 N HCl, the solution heated under reflux for 15 h, the solution evaporated, the residue dissolved in water and the solution passed through a column of Amberlite IR45. *N*-Methylcysteine was eluted with water. The title compound was isolated by evaporation of the water eluates; m.p. 222–223°. $[\alpha]_D = +15.5°$ ($c = 2.5$ in 0.1 N HCl) (from the iodide); $[\alpha]_D = +12.0°$ ($c = 2.5$ in 0.1 N HCl) (from the tosylate).

*S*-Benzoyl-*N*-methylcysteine methyl ester was hydrolyzed and worked up in the same way. $[\alpha]_D = 0$.

## REFERENCES


1. Undheim, K. *et al. Acta Chem. Scand.* **23** (1969) 1704, 1715, 1966, 1975, 2505.
2. Schmir, G. L. *J. Am. Chem. Soc.* **87** (1965) 2743.
3. Cook, H. H. and Heilbron, I. M. In Clarke, H. T., Johnson, I. R. and Robinson, R. *The Chemistry of Penicillins*, Princetown University Press 1949, p. 938.
4. Kuhn, R. and Drawert, F. *Ann.* **590** (1954) 55.
5. du Vigneaud, V., Loring, H. S. and Craft, H. A. *J. Biol. Chem.* **105** (1934) 481.
6. Ref. 3, p. 945.
7. Joullie, M., Laurre, M., Maillard, G. and Muller, P. *Fr. 1.167,617* (1958); *Chem. Abstr.* **55** (1961) 1469 f.
8. Ferris, A. F., Salermi, O. L. and Schutz, B. A. *J. Med. Chem.* **9** (1966) 391.
9. Martin, R. B., Hedrick, R. I. and Parcell, A. *J. Org. Chem.* **29** (1964) 3197.
10. Smith, H. A. and Gorin, G. *J. Org. Chem.* **26** (1961) 820.


Received March 13, 1970.