

2-Aminothiazoline-4-one and 2-Iminothiazolidine-4-one Derivatives

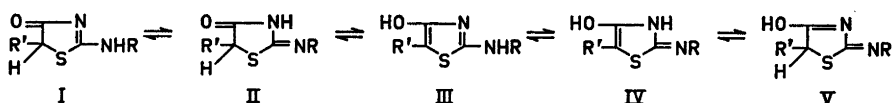
Part II.* Tautomerism

EVA AKERBLOM

Research Division, Pharmacia AB, Uppsala, Sweden

Tautomerism in 2-amino- and 2-alkylaminothiazoline-4-ones has been studied using infrared, ultraviolet, and NMR spectroscopy and polarography. It was found that these compounds existed in their amino forms.

2-Alkylaminothiazoline-4-ones can theoretically exist in five tautomeric forms. The presence of carbonyl frequencies and the absence of hydroxyl

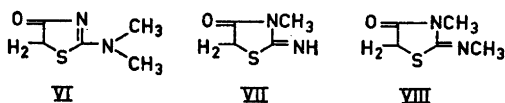


frequencies in the IR-spectra eliminated the structures III, IV, and V. Similar deductions had previously been made for some analogous compounds^{1,2} after more detailed studies. Najer *et al.*¹ have examined the tautomerism of 2-amino-5-arylthiazoline-4-one derivatives by studying their UV-spectra. They claimed that their studies favoured the amino form I. However, Comrie³ concluded from a similar examination that 2-aminothiazoline-4-one and 2-amino-5-alkyl(aryl)thiazoline-4-ones existed both in the amino (I) and imino (II) form.

In view of these contradictory results it was of interest to carry out some further studies on the tautomerism of 2-aminothiazoline-4-ones.

Some model compounds were synthesized, which were incapable of tautomerism, namely 2-dimethylaminothiazoline-4-one (VI), 2-imino-3-methylthiazolidine-4-one (VII), and 3-methyl-2-methyliminothiazolidine-4-one (VIII).

* Part I. *Acta Chem. Scand.* 21 (1967) 843.



To study the tautomerism of 2-amino- and 2-alkylaminothiazoline-4-ones their UV-, IR-, and NMR-spectra and polarographic behaviour were studied and compared with the corresponding data for the model compounds (VI–VIII).

Ultraviolet spectra. The UV-spectra were recorded in ether and in aqueous solution. 2-Alkylaminothiazoline-4-ones exhibit two absorption maxima in ether solution at 222–223 nm and at 248–250 nm (Fig. 1 and Table 1). 2-Dimethylaminothiazoline-4-one (VI) also exhibits two absorption maxima at 228 nm and at 251 nm, whereas 2-imino-3-methylthiazolidine-4-one (VII) and 3-methyl-2-methyliminothiazolidine-4-one (VIII) have only one maximum, at 213 nm and at 216 nm, respectively. The similarity between the UV-spectrum in ether solution of the 2-dimethylamino compound VI and those of the 2-alkylaminothiazoline-4-ones favours the amino structure I for the latter compounds.

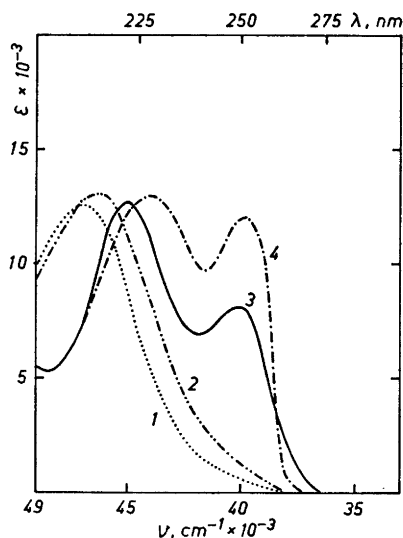


Fig. 1. UV absorption in ether solution.

- 1) 2-Imino-3-methylthiazolidine-4-one (VII).
- 2) 3-Methyl-2-methyliminothiazolidine-4-one (VIII).
- 3) 2-Methylaminothiazoline-4-one.
- 4) 2-Dimethylaminothiazoline-4-one (VI).

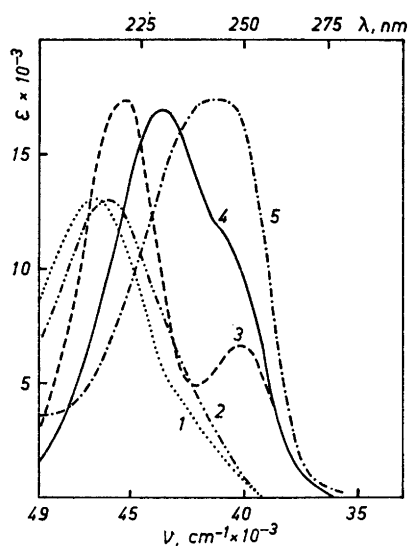
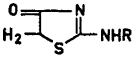


Fig. 2. UV absorption in water solution.

- 1) 2-Imino-3-methylthiazolidine-4-one (VII).
- 2) 3-Methyl-2-methyliminothiazolidine-4-one (VIII).
- 3) 2-Aminothiazoline-4-one.
- 4) 2-Methylaminothiazoline-4-one.
- 5) 2-Dimethylaminothiazoline-4-one (VI).

Table 1. The UV absorption of 2-alkylaminothiazoline-4-ones in ether and water solution.

 R =	λ_{\max} (nm) (in ether)	$\epsilon \times 10^{-3}$	λ_{\max} (nm) (in water)	$\epsilon \times 10^{-3}$
CH ₃	222 250	12.7 8.1	229 shoulder about 247	16.9
C ₂ H ₅	223 248	15.1 8.0	232 shoulder about 247	18.6
n-C ₃ H ₇	223 248	14.3 7.6	232 shoulder about 247	18.3
iso-C ₃ H ₇	223 248	15.5 8.9	234 shoulder about 247	19.7

Methylation of the methylamino group causes a bathochromic shift of the peak at 222 nm to 228 nm in accordance with observations on other compounds after similar treatment.^{4,5} Unfortunately, 2-aminothiazoline-4-one is not soluble enough in ether to give a satisfactory spectrum and therefore cannot be compared with the other compounds.

In aqueous solution, 2-alkylaminothiazoline-4-ones exhibits a single absorption maximum at 229–234 nm with a shoulder about 247 nm (Fig. 2 and Table 1). The spectra of 2-imino-3-methylthiazolidine-4-one (VII) and 3-methyl-2-methyliminothiadiazolidine-4-one (VIII) in water and ether are very similar. In water a single maximum is observed at 215 nm and 217 nm, respectively. 2-Dimethylaminothiazoline-4-one (VI) which exhibits two maxima in ether, gives only a single broad peak in water at 242 nm presumably owing to overlapping of the two maxima. The asymmetrical absorption maximum of the 2-alkylamino compounds may also be explained similarly. Thus, the similarity of the UV-absorptions of the 2-dimethylamino compound (VI) and the 2-alkylamino compounds indicates that the latter compounds also exist in their amino form I in water.

2-Aminothiazoline-4-one exhibits two absorption maxima in aqueous solution at 221 nm and 249 nm (Fig. 2). The position of the former peak is close to the absorption maxima of the imino compounds VII and VIII. Comrie³ accordingly assigned this peak to the imino tautomer II and the peak at 249 nm to the amino tautomer I. However, the UV-spectrum of 2-aminothiazoline-4-one is very similar to those of 2-alkylamino- and 2-dimethylaminothiazoline-4-one (I and VI). A bathochromic shift of the shorter wavelength band by 7 nm on methylation of the amino group is in accordance with previous experience for other compounds.^{4,5} Further, the bands are of equal intensity to those of the amino compounds. Therefore it is concluded that 2-aminothiazoline-4-one exists as the amino tautomer I (R = R' = H).

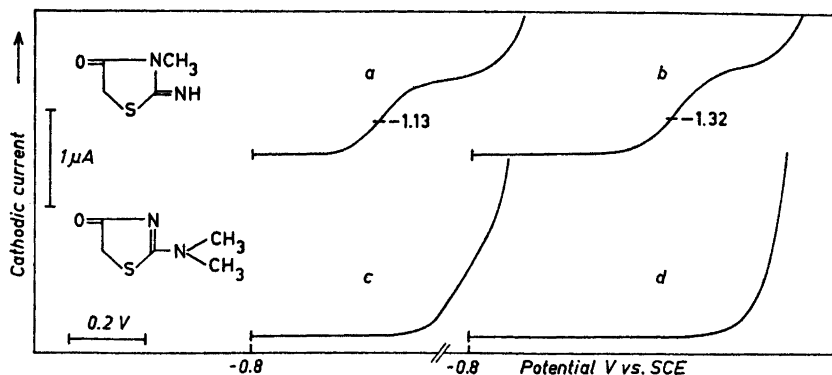


Fig. 3. Schematic polarograms related to given structures. Conc. 1×10^{-4} M. (a) and (c) acetate buffer pH 4.8; (b) and (d) phosphate buffer pH 7.2. All polarograms are started at -0.8 V vs. SCE.

Infrared spectra. The IR-spectra of 2-amino- and 2-alkylaminothiazoline-4-ones were recorded in chloroform solution and in the solid state. The position of the carbonyl frequencies of the model compounds (VI–VIII) were studied and compared with those of the 2-amino- and 2-alkylamino compounds. However, the differences were too small to supply any information concerning the tautomerism of these compounds.

NMR-spectra. The NMR-spectra were recorded in D_2O -solution. The shifts of the protons of the model compounds were too similar to give any information about the tautomerism of the 2-alkylamino compounds.

Polarography. The polarographic behaviour of 2-dimethylaminothiazoline-4-one (VI) and of 2-imino-3-methylthiazolidine-4-one (VII) and 3-methyl-2-methyliminothiazolidine-4-one (VIII) was examined. The imino compounds VII and VIII were reducible at the dropping mercury electrode. At pH 4.8 the half-wave potential vs. the saturated calomel electrode (SCE) was -1.13 V and at pH 7.2 it was -1.32 V (Fig. 3). The polarographic diagram for the amino compound VI showed no cathodic steps within this potential region. Thus the different polarographic properties of the model compounds could be used to study the tautomerism of 2-amino- and 2-alkylaminothiazoline-4-ones. The assignment of the amino structure to the latter compounds was corroborated by the observation that they did not give a reduction wave (Fig. 4). 2-Phenyliminothiazolidine-4-one (IX), which is known to exist in the imino form,^{1,6} gave the expected reduction wave similar to that of 2-imino-3-methylthiazolidine-4-one (VII) (Fig. 4).

DISCUSSION

Different methods have been used to determine the structure of compounds capable of tautomerism. Although UV-spectroscopic examinations are very often used, the interpretation of UV-spectra may be difficult. Disagreement

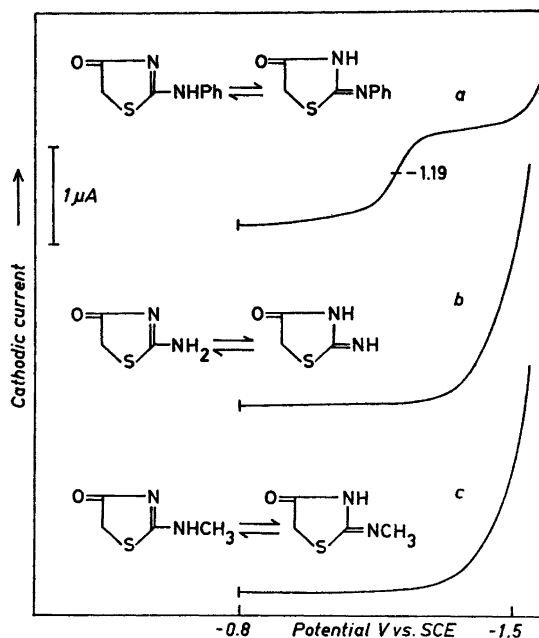


Fig. 4. Schematic polarograms related to alternative structures. Conc. 1×10^{-4} M. All polarograms are started at -0.8 V vs. SCE and run in acetate buffer pH 4.8.

between Comrie³ and Najer *et al.*¹ over the interpretation of the UV-spectra of 2-aminothiazoline-4-ones led to contradictory conclusions about the tautomerism of these compounds.

The UV-spectra of 2-aminothiazoline-4-ones and 2-iminothiazolidine-4-ones are very different (see Figs. 1 and 2). In the author's view the UV-spectra of 2-amino- and 2-alkylaminothiazoline-4-ones are very similar to the UV-spectra of the 2-dialkylaminothiazoline-4-ones. The shifts obtained between the free amino and the alkylated amino derivatives are quite in accordance with established data. This interpretation is at variance with that of Comrie.³

In order to verify the conclusions from the UV-spectroscopic examination the IR- and NMR-spectra and the polarographic behaviour of 2-aminothiazoline-4-ones were examined. Examination of the IR- and NMR-spectra was inconclusive. However, the polarographic method convincingly showed that 2-amino- and 2-alkylaminothiazoline-4-ones existed in their amino form I in accordance with the UV-spectroscopic interpretation.

However, some shift in the tautomeric equilibrium $I \rightleftharpoons II$ may occur during the polarographic registration. This would result in the formation of the most easily reducible compound, in this case the imino compound (II). Since no reduction wave was obtained such a possibility can be disregarded.

EXPERIMENTAL

The ultraviolet spectra were measured with a Unicam SP 700 recording spectrophotometer using 1 cm quartz cells and concentrations of 5×10^{-5} M. The polarographic measurements were performed with a Radiometer Polariter P04.

Acknowledgements. The author is deeply indebted to Professor Arne Fredga for his kind interest in this work and to Dr. Bengt Nygård for his contribution to the interpretation of the polarographical data. My thanks are also due to Messrs. R. Andersson and M. Sandberg for the spectral measurements.

REFERENCES

1. Najer, H., Giuducelli, R., Morel, C. and Menin, J. *Bull. Soc. Chim. France* **1963** 1022.
2. Peresleni, E. M., Tscheinker, J. N. and Zosimora, N. P. *Zh. Fiz. Khim.* **39** (1965) 926.
3. Comrie, A. M. *J. Chem. Soc.* **1964** 3478.
4. Brown, D. J. and Short, L. N. *J. Chem. Soc.* **1953** 331.
5. Najer, H., Menin, J. and Giudicelli, J.-F. *Compt. Rend.* **258** (1964) 4579.
6. Najer, H., Armand, J., Menin, J. and Voronine, N. *Compt. Rend.* **260** (1965) 16.

Received March 6, 1967.