ACTA CHEMICA SCANDINAVICA 17 (1963) 2479–2486

The Structure of Two Dimeric 2(3H)-Thiazolones

RICHARD DAHLBOM

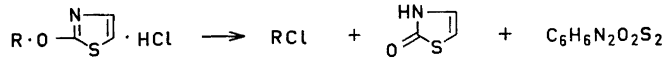
Department of Chemistry, Royal Institute of Pharmacy, Stockholm, Sweden

SALO GRONOWITZ and BIRGITTA MATHIASSON

Chemical Institute, University of Uppsala, Sweden

The structures of the dimers of 2(3H)-thiazolone (I) and 4-methyl-2(3H)-thiazolone (II) have been elucidated by means of nuclear magnetic resonance spectroscopy and found to be 5-(2-thiazolidon-4-yl)-2(3H)-thiazolone (IV) and 4-methyl-5-(4-methyl-2-thiazolidon-4-yl)-2(3H)-thiazolone (V), respectively. A mechanism for the formation of the dimers is proposed.

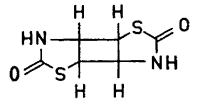
2(3H)-Thiazolone (I) was first prepared by Schwaneberg [1] by heating the hydrochlorides of 2-ethoxy- or 2-methoxythiazole above their melting points. As a by-product, Schwaneberg obtained a compound melting above 220°, which he showed to be a dimer of the 2(3H)-thiazolone.



I

The dimerisation was apparently brought about by the hydrogen chloride, as the dimer was obtained in quantitative yield by heating 2(3H)-thiazolone with hydrochloric acid on a water bath. It could also be prepared by boiling 2-methoxy- or 2-ethoxythiazole with dilute hydrochloric acid or from the reaction between ethyl thioncarbamate (ethyl xanthogenate) and α,β-dichloroethyl ether, in which reaction 2-ethoxythiazole and 2(3H)-thiazolone apparently are intermediates.

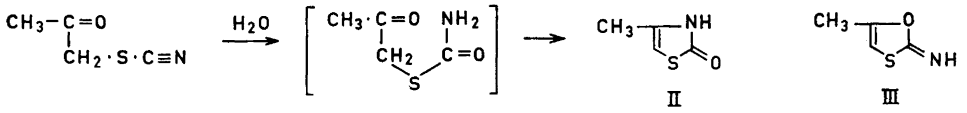
Schwaneberg found the molecular weight of the dimer to be about 215, and suggested the following structural formula:



This dimeric thiazolone together with 2(3H)-thiazolone has later been encountered by Klein and Prijs [2] when they treated 2-chlorothiazole-5-carboxylic acid with mineral acids. They report a melting point of 238° for the dimer.

A thiazole derivative melting at 183—184° related to the dimeric 2(3H)-thiazolone had been obtained as a by-product already in 1919 by Tscherniac [3] when he treated thiocyanoacetone with hydrogen chloride. The main product was 4-methyl-2(3H)-thiazolone, earlier obtained by Hantzsch and co-workers by treating thiocyanoacetone with sodium carbonate [4] or hydrochloric acid.[5]

Tscherniac contested the structure (II) of this compound proposed already in 1887 by Hantzsch and considered the compound to be an 1,3-oxathiole derivative (III) which he called "α-methylrhodim". The by-product, which he supposed to be a dimeric form of α-methylrhodim, he called "β-methylrhodim"



Tscherniac also prepared the dimer in about 25 % yield by treating "α-methylrhodim" with cold hydrochloric acid, and showed that the reaction was reversible: when the dimer was heated with concentrated hydrochloric acid for 2 h at 100°, the monomer was obtained in almost quantitative yield.

Tscherniac's "β-methylrhodim" was later encountered by Schwaneberg [1] as a by-product in the preparation of 4-methyl-2(3H)-thiazolone from ethyl thioncarbamate and chloroacetone. Schwaneberg found the molecular weight to be about 228 and assigned a structure containing a cyclobutane ring, analogous to that he had proposed for the dimeric 2(3H)-thiazolone. He noted a great dissimilarity in the tendency to dimerise between the 2(3H)-thiazolone, which easily forms a dimer stable to concentrated hydrochloric acid, and 4-methyl(3H)-thiazolone, which gives a dimer in very moderate yield, easily split by the acid to the monomeric thiazolone. His attempts to dimerise 4,5-dimethyl-2(3H)-thiazolone were unsuccessful.

In connection with work on the nuclear magnetic resonance of thiazole derivatives, the present authors decided to investigate the two dimeric thia-

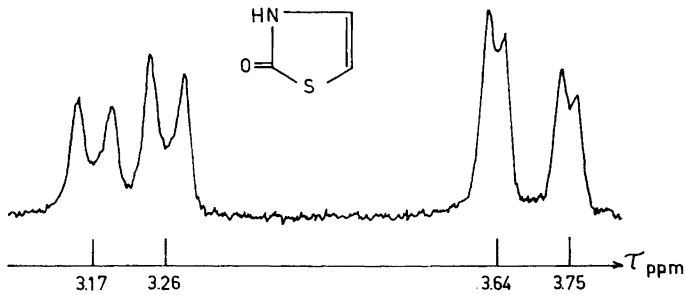


Fig. 1. NMR-Spectrum of 2(3H)-thiazolone (I) in dimethyl sulphoxide.

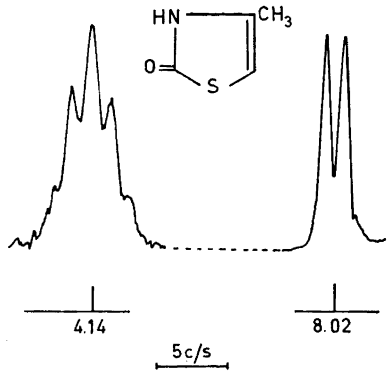
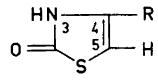


Fig. 2. NMR-Spectrum of 4-methyl-2(3H)-thiazolone (II) in dimethyl sulphoxide.

zolones obtained by Schwaneberg and Tscherniac in order to see if their structures could be established by this technique. We had a considerable amount of the dimeric 2(3H)-thiazolone at our disposal, obtained some years ago by one of the authors (R.D.) as a by-product in the Schwaneberg preparation of 2(3H)-thiazolone required as starting material in the synthesis of 5-(*p*-aminobenzenesulphonyl)-2(3H)-thiazolone.[6]

The NMR-spectra of the monomeric 2(3H)-thiazolone (I, Fig. 1 and Table 1) and 4-methyl-2(3H)-thiazolone (II, Fig. 2 and Table 1) were first studied in trifluoroacetic acid (TFA) and dimethyl sulphoxide (DMSO). The compounds show broad NH resonances at $\tau = -0.38$ and -0.33, respectively, in TFA and at -1.14 and -1.05 in DMSO. The 4-hydrogen band of I in DMSO appears as a quartet centred at $\tau = 3.22$, with splittings of 2.50 c/s and 5.30 c/s. The 5-hydrogen band appears as a quartet centred at $\tau = 3.70$, with splittings of 1.10 c/s and 5.30 c/s. The larger splitting is due to the coupling J_{45}, while the two smaller splittings are due to coupling with the NH, although these couplings are not resolved in the broad NH resonance. That the band at

Table 1. Chemical shift data and coupling constants for 2(3H)-thiazolones.

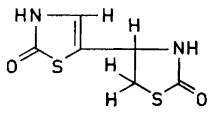


Compounds	R	Solvent	Concentration weight %	τ_3	τ_4	τ_{CH_3}	τ_5	J_{34}	J_{35}	J_{45}	$J_{CH_3\text{-}5}$
I	H	TFA	4.7	−0.38	3.08		3.48			5.20	
II	CH_3	TFA	10.7	−0.33		7.75	3.87				1.30
I	H	DMSO	14.3	−1.14	3.22		3.70	2.50	1.10	5.30	
II	CH_3	DMSO	15.4	−1.05		8.02	4.14		1.40		1.40

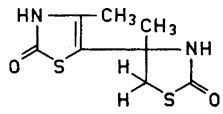
τ = 3.22 with the larger NH coupling must be due to the 4-hydrogen is evident from the spectrum of 4-methyl-2(3H)-thiazolone (II, Fig. 2); the smaller splitting only is observed here which must be due to the 5-hydrogen. The 5-hydrogen band of II at τ = 4.14 appears as an 1:4:6:4:1 quintet (Fig. 2) due to couplings of the same magnitude (1.4 c/s) to the NH and the methyl group. It is natural that the larger J_{CH-NH} coupling in I is that over the smaller number of bonds. In TFA solution, the couplings to the NH disappear, probably due to rapid prototropy, and the 4- and 5-hydrogen resonances of I occur as doublets with a coupling of 5.2 c/s. Also on heating the DMSO solutions these couplings disappear. It is interesting to note that J_{45} in 2(3H)-thiazolone is much larger than in "true" non-tautomerizable thiazoles.[7]

Chemical shift evidence is also in accordance with these assignments, as it is very improbable that methyl substitution in the 4-position could cause an upfield shift of 0.92 ppm of the 5-hydrogen. An upfield shift of 0.44 ppm is more in accordance with what is known for other methyl substituted heterocycles.[8–10]

The NMR-spectra of the dimeric 2(3H)-thiazolone and 4-methyl-2(3H)-thiazolone were then investigated. On the basis of the spectra obtained the structures IV and V are suggested for the two compounds.



IV



V

The NMR-spectra (Figs. 3—5 and Table 2) of the dimers are in complete agreement with the suggested structures. The broad band at −0.23 τ in TFA and at −1.05 τ in DMSO of the dimer IV is assigned to the NH of the thiazolone ring. The somewhat sharper band at 2.25 τ in TFA and at 1.46 τ in DMSO, also corresponding to one hydrogen atom is assigned to the NH of the saturated thiazolidone ring. The somewhat broadened resonance at 2.94 τ in TFA occurs as a quartet centred at 3.13 τ, with splittings of 0.6 c/s and 2.8 c/s in DMSO. The latter splitting due to coupling with the NH proves that this resonance is due to a 4-hydrogen in a 2-thiazolone system and that the 5-position is blocked by a substituent. The smaller coupling is most probably to hydrogen C (see Table 2) and causes broadening of its band.

The bands at 4.71 τ, 6.05 τ and 6.48 τ of IV in TFA solution constitute an ABX spectrum (Fig. 4) characteristic for a $CH-CH_2$ grouping. The band at 4.71 τ shows splittings of 5.45 c/s and 7.85 c/s, the band at 6.05 τ splittings of 7.85 c/s and 11.8 c/s and the band at 6.48 τ splittings of 5.45 c/s and 11.8 c/s.

The connection between the dihedral angles and the magnitude of coupling constants has not been studied in five-membered ringsystems to the same extent as in the six-membered cyclohexane derivatives or in the pyranosidic sugars. Especially five-membered saturated heterocyclic compounds have not been investigated extensively and it might be possible that the Karplus relation [11] cannot be applied accurately to the thiazolidone ring system. It is, however, obvious from comparison with other data [12] that the coupling of about

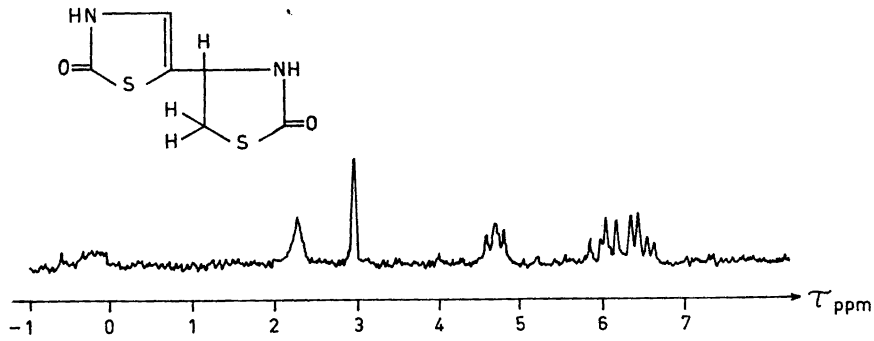


Fig. 3. NMR-Spectrum of dimer of 2(3H)-thiazolone (IV) in trifluoroacetic acid.

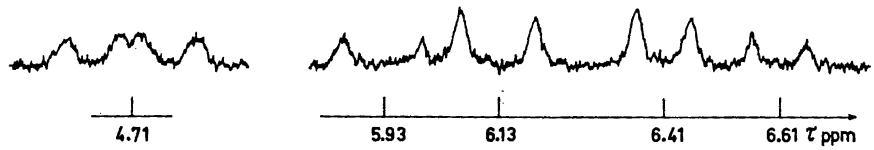


Fig. 4. NMR-Spectrum of the $CH-CH_2$ part of dimer of 2(3H)-thiazolone (IV) in trifluoroacetic acid.

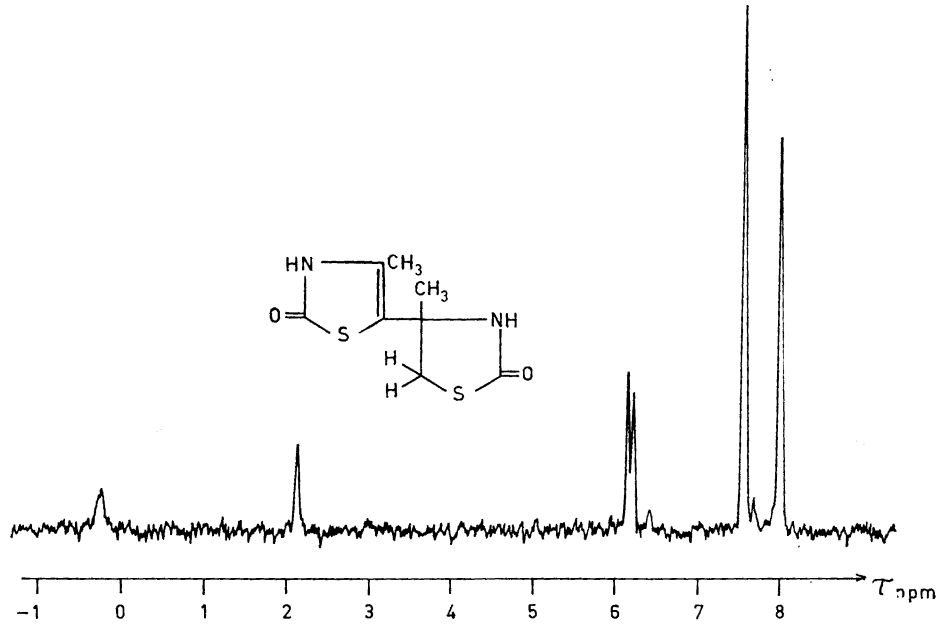
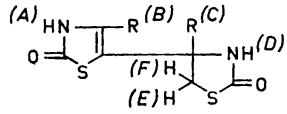


Fig. 5. NMR-Spectrum of dimer of 4-methyl-2(3H)-thiazolone (V) in trifluoroacetic acid.

Table 2. Chemical shift data and coupling constants for dimeric 2(3H)-thiazolones.



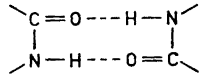
Compound	R	Solvent	Concentration weight %	τ_A	τ_B	τ_C	τ_D	τ_E	τ_F	J_{AB}	J_{BC}	J_{CE}	J_{CF}	J_{EF}
IV	H	TFA	5.3	−0.23	2.94	4.71	2.25	6.05	6.48			7.85	5.45	11.8
V	CH_3	TFA	7.4	−0.15	7.63	8.06	2.21	6.19	6.35					11.8
IV	H	DMSO	5.7	−1.05	3.13	5.09	1.46	6.30	6.76	2.80	0.60	7.50	5.90	11.4

11.8 c/s is between the geminal hydrogens of the CH_2 group whose resonances thus fall at 6.05 τ and 6.48 τ.

The NMR-spectrum of IV does not distinguish between structures in which the two rings are connected through the 5—5-positions and through the 5-position of the thiazolone ring and the 4-position of the thiazolidone ring. However, this structural detail could be solved by studying the NMR-spectrum of the dimer derived from 4-methyl-2(3H)-thiazolone (V). The spectrum in TFA shows two sharp methyl resonances, one at 7.63 τ, which by comparison with the methyl resonance of the monomer (7.75 τ) is assigned to the methyl group of the thiazolone ring, while the sharp methyl resonance of the thiazolidone ring occurs at 8.06 τ. The two aliphatic hydrogens give an AB-spectrum at 6.19 τ and 6.35 τ with a large coupling constant of 11.8 c/s showing that the hydrogens are geminal. These features prove that the thiazolidone ring is connected through its 4-position with the other ring.

The NMR-spectrum thus speaks in favour of structure V, where the two rings are unsymmetrically attached to each other. It seems resonable to assume that the two dimers are formed by similar mechanisms and have similar structures. We therefore propose structure IV for the dimer of 2(3H)-thiazolone.

That the two dimers must be very closely related is evident also from the infra-red spectra, which are shown in Figs. 6 and 7. Another interesting feature in these spectra is that both compounds in the solid phase show strong bonded NH stretching absorption near 3175 cm^{-1}, which is attributed to the following arrangement in cyclic lactams:[13]



Concerning the mechanism of the dimerisation, nothing can be said with certainty: as it is well known, however, that 2(3H)-thiazolones are easily attacked in the 5-position by electrophilic agents,[14] it seems reasonable to

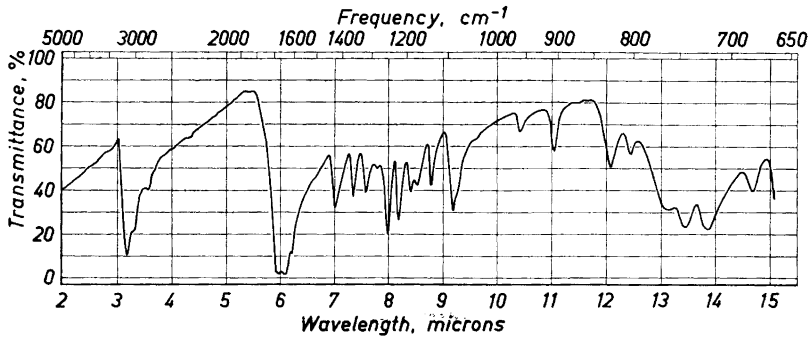


Fig. 6. IR-Spectrum of dimer of 2(3H)-thiazolone (IV) in KBr.

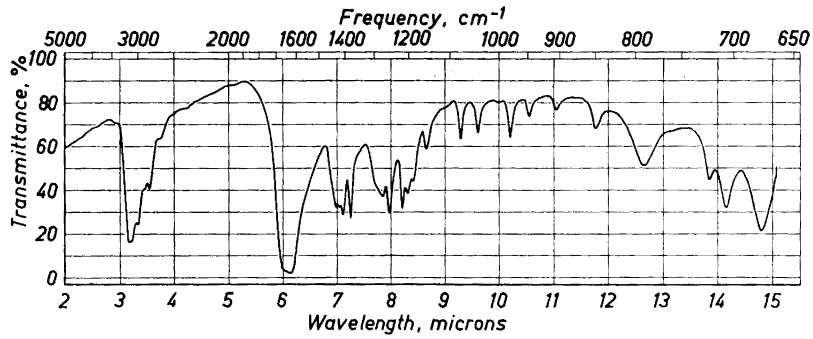
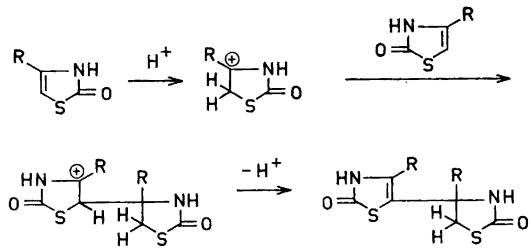


Fig. 7. IR-Spectrum of dimer of 4-methyl-2(3H)-thiazolone (V) in KBr.

assume that the first step in the reaction is an addition of a proton to the 5-position followed by an attack of the resulting carbonium ion on the 5-position of the second molecule of the 2(3H)-thiazolone:



The great difference in dimerisation tendency between 2-(3H)-thiazolone and the 4-methyl derivative may be attributed to steric factors.

EXPERIMENTAL

The nuclear magnetic resonance spectra were obtained on a Varian A-60 high resolution instrument at 60 Mc/s. The chemical shifts are given in τ-units [15] using tetramethylsilane as internal standard. The infra-red spectra were recorded on a Perkin-Elmer No. 21 instrument with NaCl prism.

2(3H)-Thiazolone (I). 2-Ethoxythiazole, prepared as described by Schwaneberg [1] from α,β-dichloroethyl ether and ethyl thioncarbamate in the presence of sodium acetate, was transformed to the hydrochloride by treating it with dry hydrogen chloride in ether. The hydrochloride (16.6 g, 0.1 mole) was heated on a steam bath for 25 min; the salt melted and there was evolution of gas, which subsided after about 15 min. After cooling, the crystalline mass was extracted with hot chloroform (50 ml) leaving an insoluble residue (1.4 g) of dimeric 2(3H)-thiazolone (IV). From the chloroform was obtained practically pure 2(3H)-thiazolone (9.2 g). Recrystallisation from light petroleum gave long light white needles melting at 61–62°.

Dimeric 2(3H)-thiazolone (IV). This compound could be obtained in a pure state by recrystallisation from ethanol of the chloroform insoluble residue obtained in the previous experiment. It could also be prepared by heating 2-ethoxythiazole with concentrated hydrochloric acid on a steam bath for 20 min. The crystalline mass was recrystallised from ethanol, giving white rods of m.p. 232–234°. (Found: C 35.7; H 3.11; N 13.9; S 31.7. Calc. for $C_6H_6N_2O_2S_2$: C 35.6; H 2.99; N 13.85; S 31.7).

4-Methyl-2(3H)-thiazolone (II) was prepared from chloroacetone and potassium thiocyanate as described by Tscherniac.[3]

Dimeric 4-methyl-2(3H)-thiazolone (V). This compound was prepared essentially as described by Tscherniac:[3] 4-Methyl-2(3H)-thiazolone (1.7 g) was dissolved in a mixture of concentrated hydrochloric acid (10 ml) and ethanol (5 ml), heated on a steam bath for 3 h and then kept in an open dish at room temperature. After about two weeks the solvent had evaporated and the residual crystalline mass was extracted with boiling ligroin to remove the monomeric thiazolone. The insoluble residue was recrystallised from ethanol giving crystals (0.55 g) of m.p. 187–188°. Further recrystallisation from water raised the m.p. to 189–190°. (Found: C 41.5; H 4.35; N 12.3. Calc. for $C_8H_{10}N_2O_2S_2$: C 41.7; H 4.37; N 12.2).

REFERENCES

1. Schwaneberg, H. *Über Oxy- und Amino-thiazole und ihre Umwandlungs-Produkte* (Diss.) Leipzig 1930.
2. Klein, G. and Prijs, B. *Helv. Chim. Acta* **37** (1954).
3. Tscherniac, J. *J. Chem. Soc.* **115** (1919) 1071.
4. Hantzsch, A. and Weber, J. H. *Ber.* **20** (1887) 3127.
5. Hantzsch, A. and Arapides, L. *Ann.* **249** (1888) 20.
6. Dahlbom, R., Ekstrand, T. and Frisk, A. R. *Acta Pharmacol. Toxicol.* **2** (1946) 371.
7. Taurins, A. and Schneider, W. G. *Can. J. Chem.* **38** (1960) 1237.
8. Gronowitz, S. and Hoffman, R. A. *Arkiv Kemi* **16** (1960) 539.
9. Gronowitz, S., Sörlin, G., Gestblom, B. and Hoffman, R. A. *Arkiv Kemi* **19** (1962) 483.
10. Reddy, G. S., Hobgood, Jr., R. T. and Goldstein, J. H. *J. Am. Chem. Soc.* **84** (1962) 336.
11. Karplus, M. *J. Chem. Phys.* **30** (1959) 11.
12. Gutowsky, H. S., Karplus, M. and Grant, D. M. *J. Chem. Phys.* **31** (1959) 1278.
13. Bellamy, L. J. *The infra-red spectra of complex molecules*, 2nd Ed., Methuen & Co. London 1958, p. 208.
14. Ochiai, E. and Nagasawa, F. *Ber.* **72** (1939) 1470.
15. Tiers, G. V. D. *J. Phys. Chem.* **62** (1958) 1151.

Received June 20, 1963.