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Nuclear Magnetic Resonance Studies on 2-Phenyl-4-thiazolone and Some Related Compounds

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The structures of 2-phenyl-4-thiazolone (I), 2-phenyl-5-methyl-4-thiazolone (II), the dimer of I (III), the dehydrated dimer (IV), and a condensation product of the dimer with acetone (V) have been studied by means of nuclear magnetic resonance spectroscopy.

2-Phenyl-4-thiazolone (I) was first claimed to have been synthesized by Holmberg[1] by treating carboxymethyl thiobenzimidate hydrobromide with hydrochloric acid. Some years later, Chabrier *et al.*[2] reported the preparation of I by the reaction of chloroacetic acid with thiobenzamide. However, their product melted about 100° higher than the compound of Holmberg, whose work the French authors apparently did not know.

In 1951, Beyer and Lässig,[3] also apparently unaware of the works of Holmberg and of Chabrier *et al.*, claimed to have prepared I from thiobenzamide and ethyl chloroacetylcyanoacetate. This product seems to be identical with that of Holmberg. From thiobenzamide and chloroacetic acid, Beyer and Lässig also obtained the higher melting compound of Chabrier *et al.*, which they

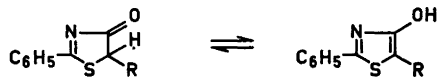
considered to be an ether formed from two molecules of the enol form of I. In addition, they obtained a third compound apparently closely related to that of Holmberg, when thiobenzamide was caused to react with chloroacetic acid at 100° and the product treated with acetone.

In a recent paper, Jensen and Crossland [4] made a thorough investigation of the structures of these compounds, mainly by means of infrared spectroscopy. The product first obtained by Holmberg, henceforth called "Holmberg's thiazolone" was found to be not 2-phenyl-4-thiazolone, but a dimer having the structure III. The product obtained by Chabrier *et al.*, "Chabrier's thiazolone", was found to be not an ether as suggested by Beyer and Lässig but a dehydration product of III with the suggested structure IV. The third product obtained by Beyer and Lässig, "Beyer's thiazolone", was shown to be a condensation product of III with acetone and given the structure V a. Jensen and Crossland were also able to prepare the true 2-phenyl-4-thiazolone (I). Their paper contains a thorough discussion of the chemistry of the different compounds and also gives an extensive account of earlier investigations in this field.

In connection with NMR-studies of dimeric 2-thiazolones [5] and 2-aminothiazole [6] and of tautomerism in heterocyclic compounds in general,[7,8] we considered it to be of interest to study the structures of the compounds mentioned above by means of this technique.

Due to the slight solubility of these compounds in other solvents, their spectra were studied in dimethyl sulphoxide (DMSO) and N,N-dimethylformamide, and in a few cases, when the solubility permitted, also in acetone or deuteriochloroform. Another convenient solvent is trifluoroacetic acid (TFA), although in this case possible protonation complicates the picture.

2-Phenyl-4-thiazolone. In solutions of dimethyl sulphoxide and dimethylformamide, three bands occur at about −0.7 τ, 2.3 τ, and 3.8 τ, with relative intensities of 0.8:5:0.8. The chemical shifts, width and intensities of the bands are those expected for the enol form I b. However, besides these bands, a weak band (relative intensity 0.1) occurs at 5.7 τ. It seems very probable that this band belongs to the CH_2 group of the carbonyl form I a, especially as in acetone solution the intensity of the 3.8 τ band is strongly diminished and the band at 5.7 τ increased, so that the relative intensities are reversed and no band is detected in the −0.7 τ region. It thus appears that in dimethyl



Ia, R = H
IIa, R = CH_3

Ib, R = H
IIb, R = CH_3

sulphoxide and dimethylformamide, the enol form I b predominates (*ca.* 80 %), while in acetone solution both forms appear in about equal amounts. In trifluoroacetic acid, the CH peak of I b occurs at 3.3 τ and the CH_2 peak of I a at 5.4 τ. The relative intensities of these two peaks are 1:2 indicating equal amounts of the two tautomeric forms or their protonated forms.

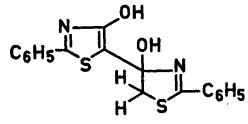
The IR-spectrum of the crystalline compound indicates that in the solid state it exists in the carbonyl form, since the strong absorption peak at 1715 cm^{-1} can only be attributed to a carbonyl group.[4]

2-Phenyl-5-methyl-4-hydroxythiazole, on the other hand, exists both in DMSO solution and in TFA in the enol form (II b) showing in DMSO the broad enolic OH in the 0 τ region, phenyl absorption at 2.5 τ and no absorption around 5.7 τ; the methyl group at 7.8 τ is sharp.

This, as well as the chemical shift, excludes the possibility of a $CH_3 \cdot \overset{/}{\underset{\backslash}{CH}}$ group.

According to Jensen and Crossland,[4] the IR-spectrum of II in the solid state showed both OH stretching and C=O stretching frequencies, indicating the crystalline product to be a mixture of both tautomeric forms (II a and II b). However, we were not able to discover any absorption band at 1725 cm^{-1} which could be attributed to a carbonyl group in the spectrum of a newly-synthesized product, the physical properties of which were otherwise identical with those described by Jensen and Crossland. A reinvestigation of the IR-spectrum of the original sample of Jensen and Crossland revealed that its spectrum was now identical with that of a newly-prepared product. Apparently, the carbonyl form in the original product had rearranged to the enol form during storage. The two different preparations had the same melting point, which might be due to rearrangement of the carbonyl form, obviously contained in Jensen and Crossland's sample, to the enol form during the heating.

"*Holmberg's thiazolone*". Regarding the structure of the dimer of I, known as "Holmberg's thiazolone", its NMR-spectrum in DMSO solution is in accordance with the enolic structure III suggested by Jensen and Crossland. It shows a peak with relative intensity 1 at 0.4 τ assigned to the enolic OH as in compound I. A broad band around 2.4 τ with relative intensity of about 10 is assigned to the 10 phenyl hydrogens. Finally, a hard coupled AB-spectrum with a coupling constant of 15.3 cps appears at 6.3 τ with $|\nu_A - \nu_B| = 0.13$ ppm, which is due to the non-equivalence of the two hydrogens of the CH_2 group. This non-equivalence has also been observed in dimeric 2-thiazolones[5] and



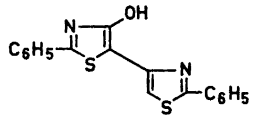
III

in dimeric 2-aminothiazole;[6] the geminal coupling constant in these cases was somewhat smaller. Finally, it remains to find the resonance of the alcoholic hydroxyl group. Though it is possible that due to the rapid proton exchange it coincides with the enolic hydroxyl group; the relative intensity of this band speaks against it. On the other hand, the relative intensity of the central lines of the AB-spectrum is almost 3 and somewhat unsymmetrical, hence it is quite probable that a broad alcoholic hydrogen resonance falls under this band.

In TFA solution, the CH_2 group resonance occurs as an unresolved band at 5.4 τ with a half width of 2 cps.

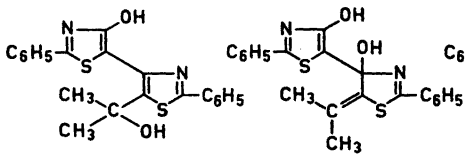
In the NMR-spectrum of the acetyl derivative of "Holmberg's thiazolone" the enol OH band at 0.4 τ of the original compound has disappeared, indicating it to be the enol acetate as suggested by Jensen and Crossland.

"*Chabrier's thiazolone*". Due to its slight solubility, "Chabrier's thiazolone" could only be studied in 3 % TFA solution, and its spectrum is not very informative. However, it is not in disagreement with the structure IV suggested by Jensen and Crossland. A peak at 2.1 τ, which rises above the complex phenyl absorption region, might belong to the thiazolic hydrogen. This is even clearer in the spectrum of the acetate of Chabrier's thiazolone in deuteriochloroform, where the thiazolic resonance occurs at 2.7 τ.

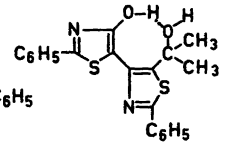


IV

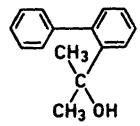
"*Beyer's thiazolone*". The question of the structure of "Beyer's thiazolone" which is a much less sharply defined compound (*cf.* Jensen and Crossland [4]), is more difficult. In TFA solution, besides the unresolved phenyl absorption at 2.1 τ containing ten hydrogens and a peak containing one hydrogen at 5.2 τ, two distinct methyl absorptions at 7.2 τ and 7.4 τ are observed. This is hardly expected for the structure originally suggested (V a). There is, however, a possibility that due to steric effects, the free rotation of the $(CH_3)_2C(OH)$- group is hindered, making the two methyl groups non-equivalent. Molecular models indicate, however, that this group can rotate quite freely, hence in



Va Vb



Vc



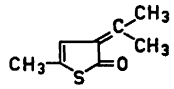
VI

order to get more definite evidence, we studied the NMR spectra of dimethylphenylcarbinol and especially of *o*-biphenylyldimethylcarbinol (VI) as model compounds. These compounds show only one sharp methyl resonance at 8.5 τ and 8.6 τ, respectively, in carbon tetrachloride. In DMSO solution, the methyl peak occurs at 8.7 τ in the phenyl derivative and at 8.8 τ in the biphenyl compound. Regarding the spectra in TFA, which is not a very suitable solvent for compounds containing the $(CH_3)_2C(OH)$- group, *o*-biphenylyldimethylcarbinol gives an easily identified methyl absorption at 8.5 τ, but the dimethylphenylcarbinol is rapidly dehydrated to dimethylstyrene, as evidenced by its complex NMR-spectrum.

In view of the above facts, the NMR-spectrum of "Beyer's thiazolone" in TFA is therefore more in accordance with structure V b, for which two methyl resonances are expected in the observed region.

The only other solvent in which we obtained a NMR-spectrum of "Beyer's thiazolone" was deuterated dimethyl sulphoxide. We observed there a broad peak at -0.6 τ, which we ascribe to an enolic hydrogen, and also the uncharacteristic phenyl absorption centered at 2.4 τ. We also observed a broad band at 6.3 τ, which could be the alcoholic hydrogen. However, only one peak containing three hydrogens was observed at 8.2 τ. The other methyl group apparently coincides with the resonance of dimethyl sulphoxide at 7.5 τ.

The large difference in absolute and internal shifts of the methyl groups in TFA and DMSO is somewhat disconcerting. However, the protonating effect of the strong acidic solvent could in part be responsible for this effect. It is interesting to note that in 3-isopropylidene-5-methyl-4-thiolene-2-one



VII

(VII), a compound of somewhat similar structure, an internal shift of the methyl groups of the same magnitude is observed,[9] the resonances of the two non-equivalent methyl groups occurring at 7.9 τ and 8.4 τ.

Though the NMR-spectrum speaks for structure V b, this is hardly compatible with the infrared data. The IR-spectra of compounds containing a 2-thiazoline moiety (I a, III, and acetyl derivative of III) have a very strong band at 1670—1690 cm^{-1}, which may be attributed to C=N stretching. This band is also found in oxazolones, as pointed out by Jensen and Crossland,[4] but is absent in compounds having only aromatic thiazole rings (II b, IV, and acetyl derivatives of I b and IV). Since "Beyer's thiazolone" has neither a band in this region nor a C=C stretching band around 1600 cm^{-1}, it apparently does not possess the structure V b, but has instead two aromatic thiazole rings. The non-equivalence of the two methyl groups as indicated by the NMR-spectrum could quite possibly have it's origin in steric factors. An intramolecular hydrogen bond of the type shown in formula V c would fix the positions of the rings, and if the new ring thus formed is not entirely planar, the methyl groups will be non-equivalent, accounting for the pattern given by the NMR-spectrum.

EXPERIMENTAL

2-Phenyl-4-thiazolone (I), 2-phenyl-5-methyl-4-hydroxythiazole (II), "Holmberg's thiazolone" (III), the *acetyl derivative* of *III, "Chabrier's thiazolone" (IV)* and *"Beyer's thiazolone" (V)* were all prepared according to the methods described by Jensen and Crossland.[4] Melting points and infrared spectra were in agreement with the data published by these authors with the exception of the infrared spectrum of II, the reason for which has been discussed in the introduction.

o-Biphenylyldimethylcarbinol (VI) was prepared from the Grignard reagent derived from *o*-bromobiphenyl and acetone, m.p. 72° after recrystallization from petroleum ether. (Found: C 84.4; H 7.34. Calc. for $C_{15}H_{16}O$: C 84.9; H 7.60).

The nuclear magnetic resonance spectra were obtained on a Varian A-60 and a Varian HR-60 high resolution intrument. The chemical shifts are given in τ-units using tetramethylsilane as internal standard.

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REFERENCES

1. Holmberg, B. *Arkiv Kemi, Mineral. Geol.* **20 A** (1945) No. 1.
2. Chabrier, P., Renard, S. H. and Smarzewska, K. *Bull. Soc. Chim. France* **1949** 237.
3. Beyer, H. and Lässig, W. *Chem. Ber.* **84** (1951) 467.
4. Jensen, K. A. and Crossland, I. *Acta Chem. Scand.* **17** (1963) 144.
5. Dahlbom, R., Gronowitz, S. and Mathiasson, B. *Acta Chem. Scand.* **17** (1963) 2479.
6. Dahlbom, R., Ekstrand, T., Gronowitz, S. and Mathiasson, B. *Acta Chem. Scand.* **17** (1963) 2518.
7. Hörnfeldt, A. B. and Gronowitz, S. *Arkiv Kemi* **21** (1963) 239.
8. Gronowitz, S., Norrman, B., Gestblom, B., Mathiasson, B. and Hoffman, R. A. *Arkiv Kemi* **22** (1964) 65.
9. Hörnfeldt, A. B. *Arkiv Kemi* **22** (1964) 211.

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