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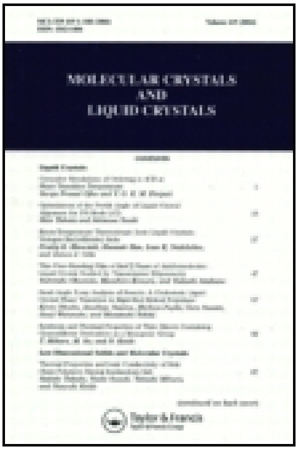

Molecular Crystals and Liquid Crystals Incorporating Nonlinear Optics
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Solid-Gas Hydrolysis and Aminolysis of Crystalline 2,4,5-Substituted-6H-1,3-Thiazin-6-Ones

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SOLID-GAS HYDROLYSIS AND AMINOLYSIS OF CRYSTALLINE 2,4,5-SUBSTITUTED-6H-1,3-THIAZIN-6-ONES.

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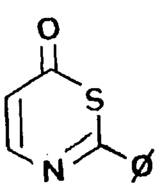
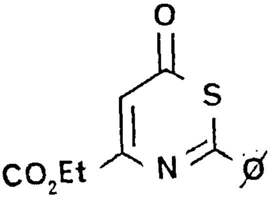
Abstract. This communication reports our studies on the reactivity of two thiazinones in the solid state. Gaseous hydrolysis of crystalline 2-phenyl-1,3-thiazin-6-one,1a,(monoclinic, $\underline{a}$ = 7.61Å, $\underline{b}$ = 9.91Å, $\underline{c}$ = 11.89Å, β = 93.55°, Z = 4, $P2_1/c$) occurs autocatalytically. This effect is explained by the short distance between the nitrogen atom of 1a and the nearest sulfur atom of a neighbouring 1a in the crystal . Assistance by H-bonding between one starting molecule and one produced molecule is assumed. Gaseous aminolysis by N,N-dimethylamine of single crystals of 4-ethoxy-2-phenyl-1,3-thiazin-6-one, 1b,(monoclinic, $\underline{a}$ = 8.86Å, $\underline{b}$ = 19.63Å, $\underline{c}$ = 7.21Å, β = 97.37°, Z = 4, $P2_1$) is anisotropic. The process is rationalized based on the molecular packing.

The work reported here is directly related to preceding studies on the reactivity of organic molecules bearing in their framework both competitive carbonyl (>C=O) and imine (>C=N-) functions [1]. In this communication we report our recent results on the reactivity of thiazinones, 1, involved in solid-gas reactions.



1a

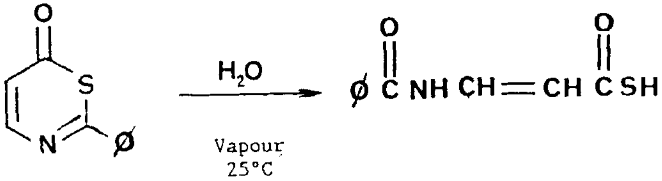


1b

Reactions of thiazinones, 1, in solution with nucleophiles have been reported by us elsewhere[2].

Hydrolysis of 2-phenyl-1,3-thiazin-6-one 1a

According to described procedures[1], we exposed yellow microcyrstals of 1a (168 mg; mp 70-71°C) in a well-closed flask to air saturated with 17% $HCl-H_2O$ vapor at 25°C for 11 days. It produced a yellow pale powder (175 mg; mp 113-114°C). The residue was identified, without further purification, as *cis* isomer 2a by proton NMR, IR, mass spectra, and elemental analysis.



1a 2a

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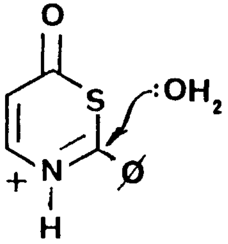
From the presence of 2a only in the reacting mixture , it was concluded that the nucleophilic attack of water molecules takes place exclusively on the imine function. This was accounted for by proposing that hydrolysis of thiazinone 1a in the solid state in acidic conditions involves at one step of the reaction, H-bond arrays of water and acid which protonate the basic nitrogen atom leading to a preferential attack on the imine center[1]. An intermediate 1a-H is therefore assumed :



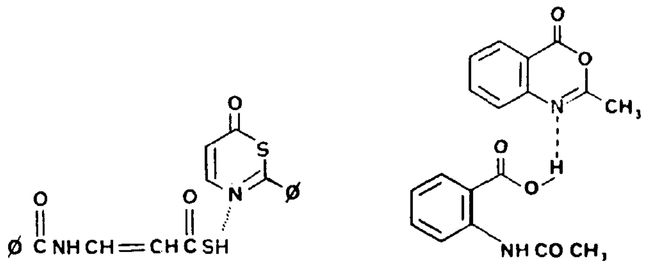
1a-H

Solid or microcrystals of 1a were observed to react in these conditions in an autocatalytic manner (Figure 1)
As in the case of a related example, it is assumed that the induction period in the reaction of 1a with gaseous acidic water is due to the formation of cracks and defects during the hydrolysis process and/or to the formation of H-bonds between the starting molecule 1a and the formed produced 2a, which activated the reaction in the reacting solid[1].

In order to clarify this effect, the X-ray structure of 1a has been determined (monoclinic, a = 7.16 Å, b = 9.91 Å, c = 11.89 Å, β = 93.55°, Z = 4, $P2_1/c$). Figure 2 presents the molecular packing of 1a.

In this packing the two nearer neighboring molecules 1a are related by an inversion center of symmetry along the b direction. This arrangement of molecules is similar to the arrangement of acetylanthranyl which was already studied by us[1]. It is assumed that the catalytic effect is due to the formation of H-bonds between starting molecule 1a and produced molecule 2a as depicted in Figure 3a. A similar supermolecule was assumed during the autocatallytic hydrolysis of related acetylanthranyl (Figure 3b)[1].

It is noticed that the distance[3] between one sulfur atom of 1a to the nearest nitrogen atom of neighbouring 1a, from which to which hydrogen bond is formed, is 4.01 Å. This value is approximate to the value found for related systems which are known to present an induction period due to the presence of such H-bond (4.21 Å for acetylanthranyl[1].)



(a) (b)

FIGURE 3a. Supermolecule between 1a and 2a.

b. Supermolecule during gaseous hydrolysis of acetylanthranyl[1].

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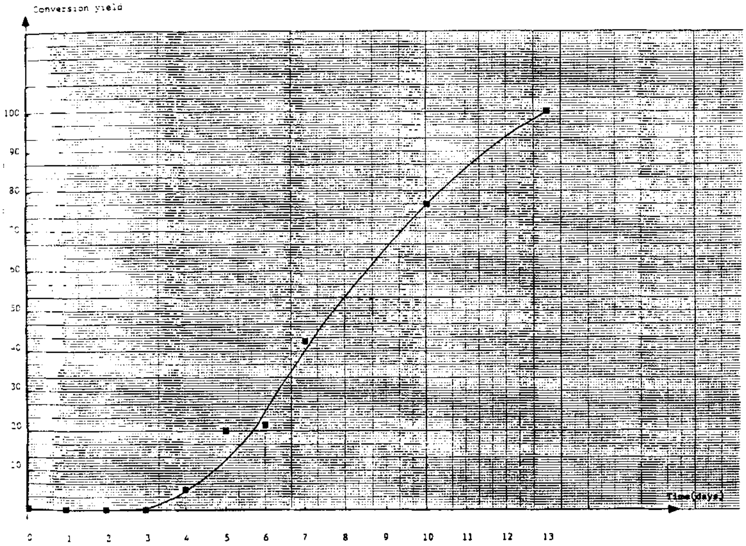


FIGURE 1. Gaseous hydrolysis of solid thiazinone <u>1a</u>. The S-shaped curve is suggestive of an autocatallytic effect[1].

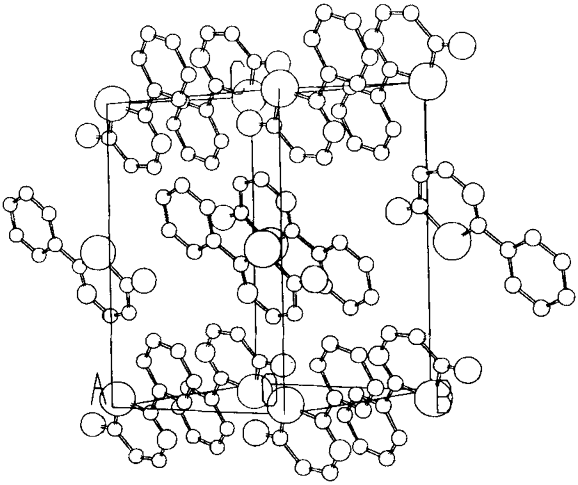
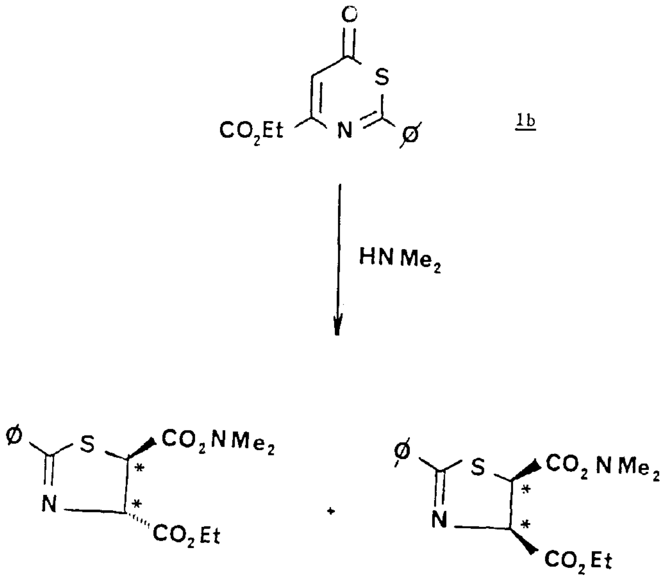


FIGURE 2. Molecular packing of <u>1a</u>.

Aminolysis of 4-ethoxycarbonyl-2-phenyl-1,3-thiazin-6-one 1b

We previously reported that thiazinone 1b reacts with N,N dimethylamine ($HNMe_2$) in solution and in the solid state to yield a mixture of diastereoisomers 2b[2].



1b

2b''

yellow oil [2]

2b'

mp 124-125°C [2]

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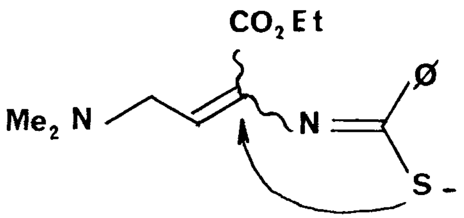
The reaction pathway to produce 2b involves a preliminary attack of the amine on the carbonyl function. Then the linear intermediate A cyclises into five - membered ring products[2]. As part of preceding studies on the anisotropic behaviour of single crystals of the parent molecules[1], we decided to investigate the reaction of single crystals 1b with $HNMe_2$ vapor.

Crystallization of 1b from hexane-ethylacetate (80 : 20) at room temperature gives thin yellow needle-like crystals. The needles were deposited on microscopic slides and exposed to 5 % $HNMe_2$ - H_2O vapor in a dessicator at 25°C in the presence of air. Microscopic observation of the needles during the reaction showed that they are perferentially attacked at the ends of the crystals to produce a liquid phase. After 18 hours, the reaction was completed, as shown by the presence of a liquid phase only. Analysis of the liquid by thin layer chromatography (Merk Kieselgel $60F_{254}$) with a mixture of hexane - methanol -



linear intermediate A

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ethylacetate (40 : 20 : 40) as eluent showed that diastereoisomers 2b are formed as sole products.

The X-ray structure of 1b has been determined (monoclinic a = 8.86 Å, b = 19.63 Å, c = 7.21 Å, β = 97.37°, Z = 4, $P2_1$). Figure 4 shows the arrangement of four molecules 1b in the unit cell two of which are independent. These two independent molecules are almost related by a centre of symmetry. The molecules are almost planar (Figure 5). Their mean planes are parallel to the ab plane of the unit cell. As β (97.37°) is close to 90°, the c-axis is perpendicular to the bonds of the molecules and, more particulary, to the carbonyl function belonging to the ring containing the sulfur atom. The c-axis corresponds to the long axis of the needle-like crystals, 1b. Therefore, in the molecular packing, carbonyl functions in the crystal are perpendicular to the long axis of the needles 1b. It has been shown by Dunitz et al.[4], that the easiest pathway for the nucleophilic addition of an amine on a carbonyl function corresponds to a perpendicular trajectory of the nitrogen atom in direction to carbonyl center (Figure 6). In our case, we assume that carbonyl functions in crystal 1b are attacked by N,N-dimethylamine molecules via a perpendicular trajectory. This trajectory corresponds to the direction of the observed reactivity and which is the long axis of the needle. The formation of a liquid phase during the reaction is probably due to the production of a mixture of diastereoisomers 2b. From previous work[2] diastereoisomers are known to be a mixture of a solid 2b' and liquid 2b". The crystalline structure and the molecular shape of 2b' are rather different from those of 1b[2]. It may be advanced that during the reaction process, the crystalline network of 1b is unable to accomodate the

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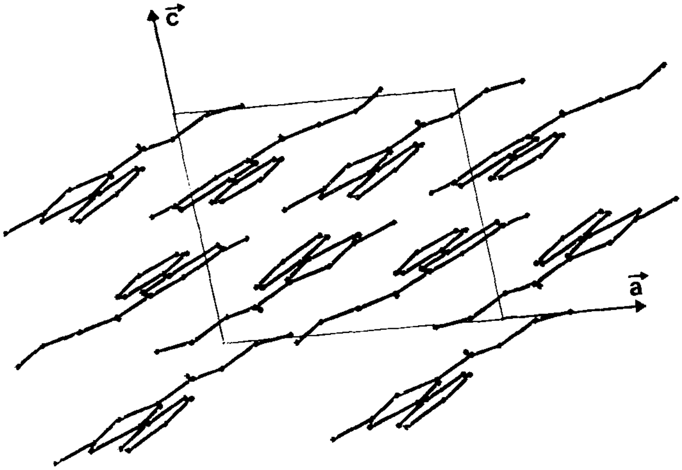

FIGURE 4. Arrangement of molecules <u>1b</u> in the unit cell.

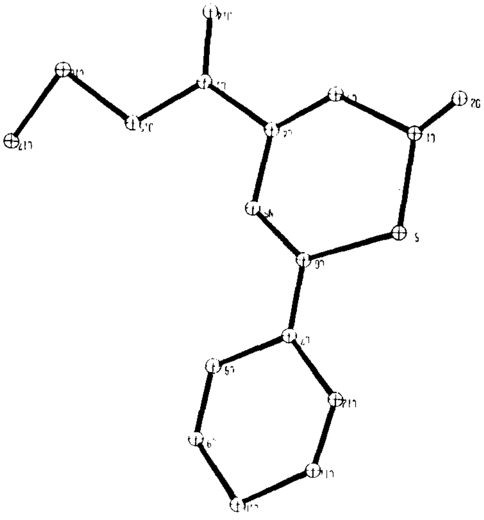

FIGURE 5. Isolated molecule <u>1b</u>.

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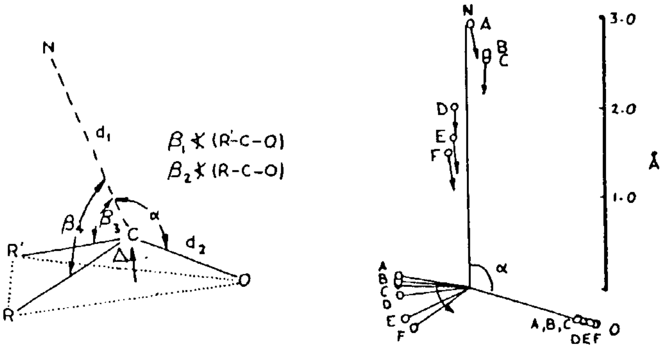

FIGURE 6. Reaction pathway for the nucleophilic attack of an amine on carbonyl function.[4]

linear intermediate A and/or produced molecules, leading to a liquid mixture. In addition 2b", which is also formed, may behave as a solvent for both starting-material and reaction products.

Synthetic applications of this reaction for preparing penicillic derivatives have been presented[2]. The observation that compound 1a crystallizes in a chiral space group $P2_1$ should offer convenient routes, through topochemical solid state reactions, to chiral products from achiral precursors.

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