

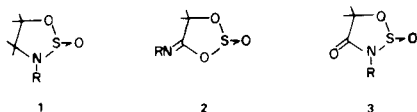
Heterocycles From Substituted Amides. IV (1). Structural Confirmation of 1,2,3-Oxathiazolidin-4-one 2-Oxides

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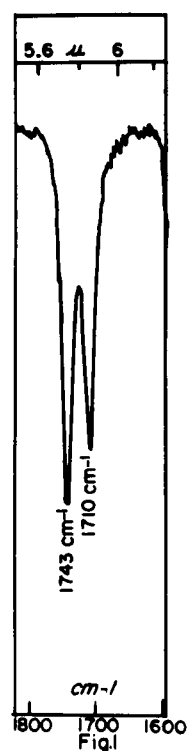
The synthesis and properties of oxathiazolidines (1) from the reaction of thionyl chloride and β -aminoalcohols has been described by Deyrup (2). Recently the reaction of α -hydroxyacylanilides with thionyl chloride was shown likewise to give a new group of heterocycles (1). Unlike formation of the parent material (1), the latter products could arise from attack of the remaining sulfur ligand on either the amidic oxygen or nitrogen. Depending on this consequence, either imino-1,3,2-oxathiole (2) or the isomeric 1,2,3-oxathiazolidin-4-one 2-oxides (3) would be formed. On the basis of certain ir and uv spectral data, the more likely assignment was concluded to be the oxo-isomer (3).



It was therefore interesting to note that the related α -aminoacylamide (anilides) could be reacted with thionyl chloride to likewise produce a new group of heterocycles (3). In this recent report, however, the imino structure 4, rather than the oxo structure 5, was chosen as the most likely product. In choosing 4, the predominate 5.83 μ band was assigned to the imino group, because a previously reported compound, a 5-iminooxazoline (6) (4), absorbed at the same wavelength. The ready hydrolysis of the heterocycle to starting amide (observed also for the α -hydroxyamide-thionyl chloride products) was interpreted as supportive evidence for 4.



Unfortunately, these two criteria do not of themselves confirm the structure as 4. Thus homologous oxo isomers of the model compound 6, namely the imidazolinones, absorb strongly at 5.8 ($C=O$), demonstrating that this absorption wavelength is just as characteristic of the oxo isomer (5,6,7). By the same token, it could be argued that either of the isomeric arrangements in the pairs 2, and 3, or 4, and 5 would be susceptible to hydrolysis to



C^{16} and C^{18}
ir Absorptions for 3a.

starting amide.

Clearly, more precise means must be used to confirm the correct alternatives in 2-3, and 4-5. Two such methods utilized to confirm 3, were O^{18} labeling and X-ray crystallography. The use of O^{18} to verify a carbonyl absorption was first carried out by Baumgarten (8), identifying the α -lactam from cyclization of an α -chloroacetamide, rather than the alternative isomeric iminolactone. In like manner, lactic acid was labeled using H_2O^{18} , and as shown in Scheme 1, converted to 3a. The labeling was carried out so that nearly equal amounts of O^{16} and O^{18} appeared in the carbonyl. Figure 1 shows the carbonyl region for ca 45 percent labeled 3a. The observed differential in frequency (33 cm^{-1}) is greater than the maximum calculated isotope mass effect for (O-C=N), but well

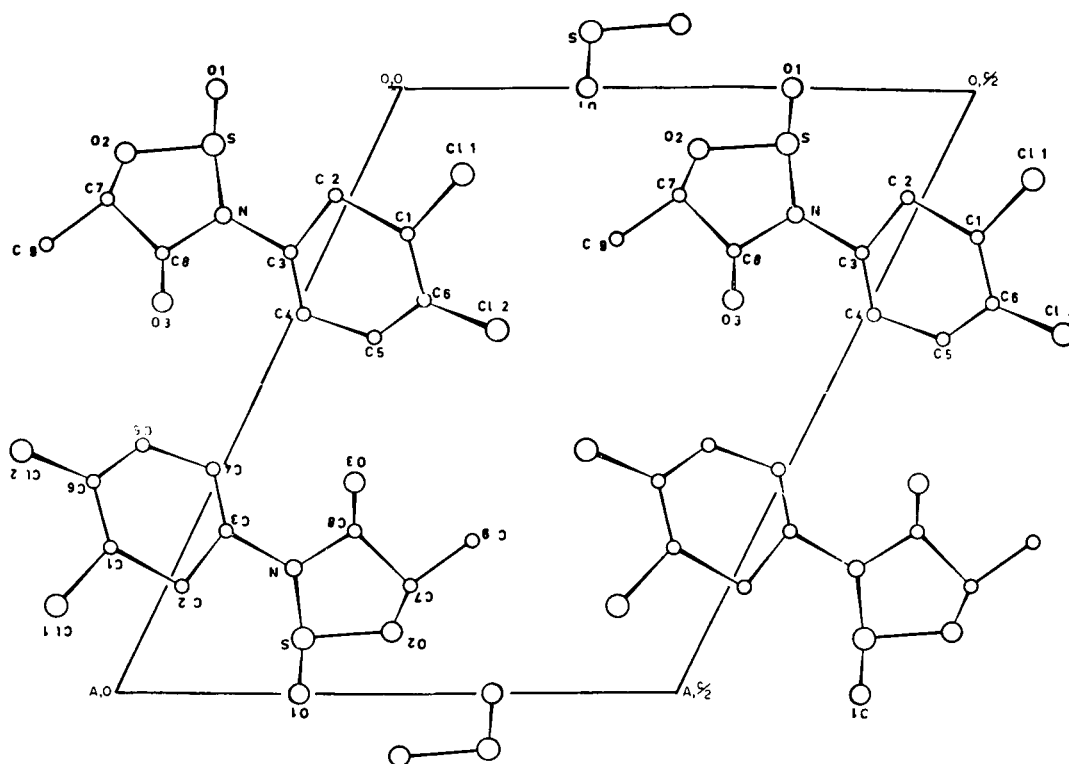
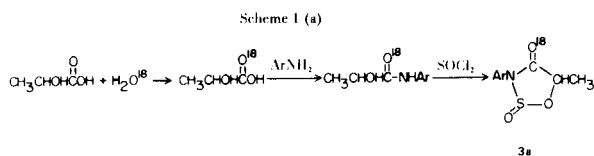


Figure 2.

within the range for (N-C=O) (9), thus confirming the oxo assignment **3**.



(a) Ar = 3,4-Cl₂C₆H₃

Unlabeled **3a** was also chosen as the candidate for X-ray crystallographic study. As isolated in the crystalline state this material was known to represent only one diastereomer even though both isomers are visible from nmr in solution of crude product with thionyl chloride. The pure crystalline isomer had been assigned the configuration wherein the 5-methyl group is *trans* to the sulfinyl oxygen. The basis for this assignment, namely the differential anisotropic shielding effect of the sulfinyl oxygen on *cis* and *trans* groups has been used to advantage in assigning configuration to diastereomeric mixtures of **1** (2,10). More recently use of this method was suspended for conformational assignments due to certain admitted uncertainties (3). The X-ray confirmation of **3a** as *trans*, in accordance with the predicted shielding, therefore maintains credence of this method.

Figure 2 shows the molecular structure and packing in the unit cell's *h0k* projection. Thus, X-ray crystal structure determination shows clearly that the molecule has structure **3** and not **2**. Further analysis (see Experimental) also permits assignment of the *trans* configuration to pure **3a**.

EXPERIMENTAL

Spectral data were recorded as follows: Nmr determined by a Varian T-60, ir by a Beckman IR-12, and X-ray by a General Electric XRD-6 equipped with goniostat and scintillation counter. O¹⁸ Labeled 3-(3,4-Dichlorophenyl)-5-methyl-1,2,3-oxathiazolidin-4-one 2-Oxide (**3a**).

Lactic acid (85%) was slowly heated to *ca* 100-120° under oil-pump vacuum. Essentially anhydrous lactic acid (>97%) (11) was distilled through a six inch vigreux column and collected, b.p. 85-90° (1 mm). In a 10 ml. (16 mm) tube fitted with a ground glass joint, 1.2 g. of anhydrous lactic acid and 0.4 g. > 95% H₂O¹⁸ (12) were thoroughly mixed using a magnetic stirrer. The sealed homogeneous mixture was then allowed to stand for 48 hours. The amount of exchange could be monitored by making a two percent solution of an aliquot in dry tetrahydrofuran, and measuring the relative C=O¹⁶ and C=O¹⁸ absorption intensities (at 1746 cm⁻¹ and 1714 cm⁻¹ respectively). The material was then vacuum treated (0.7 mm) for two to four hours on a rotary evaporator. To this mixture another 0.35 g. of H₂O¹⁸ was added and the above procedure again repeated. In this way, lactic acid with approximately 50% carbonyl label could be prepared.

Labeled lactic acid (0.7 g., 7.8 mmoles) was mixed with 3,4-dichloroaniline (1.6 g., 10 mmoles) in 10 ml. toluene. The mixture was azeotroped for ten hours. After cooling, and removal of the stirrer-bar, the tube was scratched to induce crystallization of the lactanilide. The material (0.9 g.) was filtered off, and possessed m.p. (1) and nmr identical to unlabeled material. The ir displayed two carbonyl absorptions at ca 1690 cm^{-1} , separated by 20 cm^{-1} ; Ms [m/e, identity, (relative intensity)]: 235, M^+ , both $O^{18}-Cl^{35}$ and $O^{16}-Cl^{37}$ (17.5); 233, M^+ $O^{16}-Cl^{35}$ (12.4); 45, CH_3CHOH (100).

The above labeled lactanilide (0.7 g.) was mixed in 5 ml. of thionyl chloride and refluxed for 35 minutes. The thionyl chloride, along with hydrogen chloride and sulfur dioxide were removed under vacuum on the rotary evaporator to give a residue which was treated with ether, and again subjected to vacuum treatment. The residue was recrystallized from ethanol to give **3a**, identical in m.p. and nmr (1) to that of unlabeled material. See Figure 1 for ir: ms [m/e, identity, (relative intensity)]: 281, M^+ , both $O^{18}-Cl^{35}$ and $O^{16}-Cl^{37}$ (21); 279, M^+ , $O^{16}-Cl^{35}$ (13.3); 187, $3,4Cl_2C_6H_3N=CHCH_3$ (100).

X-Ray crystallography (13).

Material **3a** crystallizes in monoclinic space group $P2_1/C$ with $a = 13.21 \text{ \AA} \pm 0.03$, $b = 4.07 \text{ \AA} \pm 0.01$, $c = 22.43 \text{ \AA} \pm 0.05$ and $\beta = 64.0^\circ \pm 0.5$. For $z = 4$ the calculated density is 1.71 compared to a density of 1.65 measured by flotation.

In view of the short b axis, an initial attempt was made to solve the structure using only $h0l$ data. The largest member of each centrosymmetric pair of the 162 $h0l$ reflections collected was selected to minimize the effect of crystal alignment errors. When peak overlap prevented easy interpretation of the two dimensional Patterson, data with $K = 1$ and $K = 2$ were collected and a three dimensional Patterson function was deciphered to give the co-ordinates of the sulfur and chlorine atoms.

A two dimensional Fourier map, phased using these positions, was calculated and clearly showed the carbon, nitrogen and oxygen atoms. The x and z co-ordinates of all atoms were refined by least squares with individual isotropic temperature factors. After convergence to a weighted R of .073, a different Fourier showed noise but no features which indicated an incorrect or incomplete structure. The final x and z coordinates of all atoms other than hydrogen are displayed in Figure 2.

Further, a full three dimensional analysis is not necessary to prove the *trans* configuration of pure **3a**. Rather, the relative position of the sulfinyl oxygen (O1) and methyl group (C9) can be deduced (13), using molecular models in conjunction with the projection (Figure 2) and the known three dimensional coordinates of the heavier chlorine and sulfur atoms.

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- (13) Additional data and procedures regarding the X-ray determination furnished upon request.