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Heterocycles from Substituted Amides III. (1) 1,2,3-Oxathiazolidin-4-one 2-Oxides from Thionyl Chloride and α-Hydroxyacylanilides

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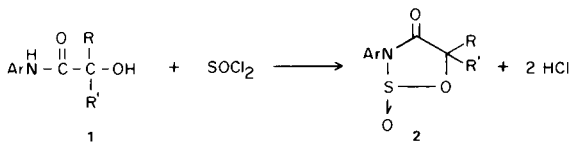
A new heterocyclic series was synthesized for the first time, from reaction of thionyl chloride with α-hydroxyacylanilides (**1**). Structural features of the resulting 1,2,3-oxathiazolidin-4-one 2-oxides (**2**) are discussed with particular reference to their spectral properties, and are compared with the previously reported 1,2,3-oxathiazolidine 2-oxides (**3**).

In the course of investigating the synthesis and properties of α-haloacetanilides (2), a number of α-hydroxyacylanilides (**1**), were reacted in excess refluxing thionyl chloride. Contrary to expectations, the classical replacement of the hydroxy group by chlorine with evolution of sulfur dioxide did not occur. Rather, after vacuum removal of excess thionyl chloride, along with hydrogen chloride, the residues were found to be readily purified by crystallization to give material belonging to a new heterocyclic ring system; namely, 1,2,3-oxathiazolidin-4-one 2-oxides (**2**) (Scheme I).

Scheme I



The reaction appears to be quite general, with **2** resulting in good yield from a wide variety of α-hydroxyacylanilides. The materials, with certain physical properties, are listed in Table I.

Although the 1,2,3-oxathiazolidin-4-one 2-oxides (**2**) represent a new heterocyclic series, near relatives to it have made their appearance from time to time, some only very recently. The parent ring system was first reported at an early date (3), wherein 3*H*-1,2,3-oxathiazole 2-oxides were obtained from the action of thionyl chloride on the enol forms of α-amino ketones. The saturated ring system was first reported from the reaction of epoxides with sulfinyl amines (4), and related substances (5). Shortly thereafter, Deyrup (6,7), devised a general synthesis of 1,2,3-oxathiazolidine 2-oxides (**3**) involving reaction of α-amino alcohols with thionyl chloride in the presence of base. Reported also for the first time were some ir and nmr spectral data peculiar to the stereochemistry of this system. Later, other investigators (8-11) extended these studies, including ms degradation pathways.

It is, therefore, surprising that the corresponding 1,2,3-oxathiazolidin-4-one 2-oxides (**2**) have not been reported. The preparation is quite facile, and merely involves dissolving the α-hydroxyamide in excess thionyl chloride. If the remaining acid portion is substituted with an α-isopropyl group, complete cyclization takes place to form **2**, as can be easily ascertained from the nmr in thionyl chloride solution. On the other hand, regardless of the hindrance on the *N*-aryl group, if the acid moiety is substituted with lesser groups than α-isopropyl, cyclization does not immediately occur. Rather, thionyl chloride reacts with the α-hydroxy group, but the presence of the N-H is still clearly evident from the nmr spectra. Simple refluxing then for 15-60 minutes is sufficient to effect ring closure to the heterocycle. The thionyl chloride is removed by vacuum stripping and the residue recrystallized to give fair to good yields of product. There is no necessity for a hydrogen chloride scavenger, as there is in the reaction between amino alcohols and thionyl chloride.

It is immediately obvious that there are similarities between the oxathiazolidine (**3**) and the oxathiazolidin-4-one (**2**). Like the former, the ring system is asymmetric due to the pyramidal nature of the sulfoxide linkage. Previous studies of the oxathiazolidines (6-11) indicated that both *cis* and *trans* isomers were formed, and moreover, the groups *cis* to the sulfoxide oxygen were deshielded and downfield from groupings *trans* to the sulfinyl oxygen (Scheme II). Similarly, in materials such as **2b**, **f**, classical AB quartets are observed, with the

TABLE I

1,2,3-Oxathiazolidin-4-one 2-Oxides

Material	Ar	R	R′	Yield	M.P., °C	C=O	S→O	Nmr (Deuteriochloroform)
2								
a	3,4-$Cl_2C_6H_3$-	CH_3	H	50	95-96	5.8	9.65	CH_3CH δ 5.21 (quartet, J = 6 Hz, one proton)
b	2,6-$(C_2H_5)_2C_6H_3$-	H	H	60	102-103	5.8	10.00 (broad) 8.6 (multiple	-CH_2O- δ 4.80, 5.20 (AB quartet, J = 14 Hz, two protons)
c	2,6-$(C_2H_5)_2C_6H_3$-	$(CH_3)_2CH$-	H	62	96-97	5.8	9.8 (broad)	$(CH_3)_2CHCH$ δ 5.20 (doublet, J = 3 Hz) δ 4.80 (doublet, J = 5 Hz) (total one proton)
d	2,6-$(C_2H_5)_2C_6H_3$-	CCl_3	H	45	93-94.5	5.8	10.1 or 9.4	-$CHCCl_3$ δ 5.60 (s) δ 5.27 (s) total one proton ratio isomers 60:40
e	2,6-$(C_2H_5)_2C_6H_3$-	CH_3	CH_3	73	57-58	5.8	10.05	C-$(CH_3)_2$ δ 1.65 (s) (3 protons) δ 1.94 (s) (3 protons)
f	2-(t-C_4H_9)-6-$(CH_3)C_6H_3$-	H	H	48	118-119	5.8	10.00 (doublet) 8.6 (multiple)	-CH_2O- δ 4.80, 5.20 (AB quartet, J = 14 hz, two protons)
g	2-(t-C_4H_9)-6-$(CH_3)C_6H_3$-	$(CH_3)_2CH$-	H	—	oil	5.8		$(CH_3)_2CH$-CH δ 4.60, doublet J = 4 Hz, 0.42 proton, δ 5.00, (doublet J = 5 Hz, 0.58 proton

chemical shifts of both methylene protons at δ 4.8 and 5.2, respectively. There is a considerably larger geminal coupling constant (*ca.* 14 Hz) than observed (6,8) in 1,2,3-oxathiazolidines. Mixtures of *cis* and *trans* isomers (diastereomers) are evident in the nmr spectra of either **2c** or **2g**. In these as well as others in Table I, the *trans*

Scheme II

3 *(trans)* (ref. 6)
δa 5.08, J_{ac} = 7 Hz
δb 4.13, J_{ab} = 8 Hz
δc 4.67, J_{bc} = 1.5 Hz

2b, f
J_{ab} = 14 Hz
δa = 5.20
δb = 4.80

J_{ab} = 3 Hz
δa = *ca.* 5.0-5.2

J_{ab} = 5 Hz
δa = 4.6-4.8

isomer is present in greater amounts. Actually, the crystalline *trans* isomer could be nearly completely purified from the oily *cis* isomer in **2c**. The *cis* material also appears to slowly revert to the more thermodynamically stable *trans* on standing. These findings parallel those found for the 1,2,3-oxathiazolidine 2-oxides. In **3** the *trans* isomer predominates, with investigators (6,8) able to purify one, but not both of the diastereomers. An exception to the usual *cis-trans* distribution in **3** was found when a chloromethylene group was a ring substituent (10). From Table I it is obvious, however, that the trichloromethyl group in **2d** does not alter the usual *trans* predominance. Material **2a** is interesting in that only one isomer (presumably the *trans* isomer) can be isolated.

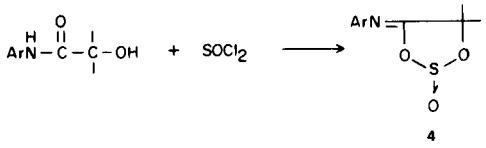
Considerable simplication of spin-spin splitting occurs in **2**, making it possible to measure the difference in vicinal coupling between a *cis* and *trans* ring proton and the adjacent proton in the ring substituent. As shown in Scheme II for **2c, g**, such coupling with the isopropyl methine proton is greater in the *trans* (*ca.* 5 Hz) than in the *cis* isomer.

The ir spectra of these materials are quite similar. As shown in Table I, the ring carbonyl group absorbs at 5.8 μ, the region expected for this moiety in a 5-membered ring. The sulfoxide absorption is open to some doubt. Previous authors (6,8) report a consistent S=O

absorption at *ca.* 8.3-8.7 μ. The 1,2,3-oxathiazolidin-4-one 2-oxides (**2**) exhibit strong absorption in this region (8.3-8.8 μ), often with multiple bands. At least some of this absorption, however, is present in the starting α-hydroxyamides. There is consistent strong absorption for all compounds in Table I at 9.4-10.0 μ. This region is usually assigned to sulfoxide only, with sulfinamides and sulfides at higher frequencies. Certain intense bands at 11-12 μ could conceivably be assigned to S-O-C band stretching.

Unlike the products from thionyl chloride and β-amino alcohols, the materials from thionyl chloride and α-hydroxyamides could alternatively give an isomeric product; namely, 1,3,2-dioxathian (Scheme III).

Scheme III



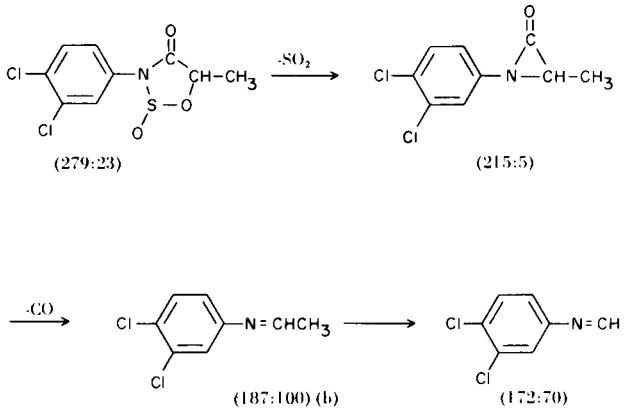
4

Consideration of the spectral properties of the products in question would argue against the assignment of the structure as the cyclic sulfite **4** (14). The strong ir absorption at 5.8 μ would much more likely arise from a cyclic amidic carbonyl rather than imino frequency. The latter are known to be less intense and occur at longer wavelength. In fact, a heterocycle related to **4**, containing a -S-O-C=N-Ar moiety, has recently been reported (12), with the imidate absorption recorded at 5.97 μ.

Uv spectra between **1f** (λ max 251, ϵ = 6,000; λ max 266, ϵ = 465) and **2f** (λ max 217, ϵ = 8,500; λ max 267, ϵ = 1,200) are quite similar. The only absorption in both cases stems from the aromatic E and B bands. It might be expected that **4** would display a K band (λ max 200-250, ϵ max > 10,000) because of the formal conjugation of the imino group with the aromatic ring. Its absence is added evidence in favor of **2** over **4**.

The mass spectra of **2** shows a strong propensity to expell sulfur dioxide, a result similar to that found for the previously studied 3-aryl-1,2,3-oxathiazolidin 2-oxides (**3**) (9,11). Material **2** necessarily differs from **3**, however, in that aziridinones are probably formed from **2** *via* such expulsion (Scheme IV). Following loss of carbon monoxide, imine is formed as the base peak, followed by azomethine formation, again resembling the degradation pathway observed for **3**.

Scheme IV



(279:23) (215:5)

(187:100) (b) (172:70)

(a) (m/e: relative intensity), high resolution ms

(b) (187 peak not 3,4-$Cl_2C_6H_3NCO$)

EXPERIMENTAL

The spectra obtained were recorded from a Perkin-Elmer Infracord (ir), Varian T-60 nmr spectrometer, Bausch and Lamb Spectronic 505 (uv), and CEC 110C (high resolution mass spectrometer). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

The preparation of the 1,2,3-oxathiazolidin-4-one 2-oxides, (**2**) necessitated prior preparation of α-hydroxyacylanilides, either *via* hydrolysis of the corresponding α-chloracylanilides or a Passerini reaction involving an arylisocyanide and the appropriate carboxylic acid (13). Since the starting α-hydroxyacylanilides have not been previously reported, their preparation and properties are described under the respective synthesis procedure describing the 1,2,3-oxathiazolidin-4-one 2-oxides. The yields and pertinent physical properties of **2** are enumerated in Table I.

3-(3,4-Dichlorophenyl)-1,2,3-oxathiazolidin-4-one 2-Oxides (**2a**).

Lactic acid (20.0 g., 0.2 mole) and 35.6 g. of 3,4-dichloroaniline were placed in refluxing toluene and water removed by azeotrope over 12 hours. The hot toluene was then treated with charcoal and filtered. The crystals obtained upon cooling the filtrate and filtering were recrystallized again from toluene to give 3',4'-dichlorolactanilide, m.p. 93-95°.

Anal. Calcd. for $C_9H_9Cl_2NO_2$: C, 46.18; H, 3.87; N, 5.99. Found: C, 45.76; H, 4.16; N, 5.61.

3',4'-Dichlorolactanilide (2.2 g., 0.094 mole) was placed in 15 ml. of thionyl chloride and the mixture refluxed for 1 hour. The material was vacuum treated to remove excess thionyl chloride and the residue recrystallized from a mixture of methylcyclohexane/ethyl acetate or ethanol to give 1.2 g. of colorless crystals.

Anal. Calcd. for $C_9H_7Cl_2NO_3S$: C, 38.59; H, 2.52; N, 5.00. Found: C, 38.70; H, 2.46; N, 4.95.

3-(2,6-Diethylphenyl)-1,2,3-oxathiazolidin-4-one 2-Oxide (**2b**).

A solution of 10 g. of sodium hydroxide in 375 moles of water was added to a solution of 11.3 g. of 2-chloro-2',6'-diethylacetanilide in 250 ml. of 2-propanol. The resulting solution was refluxed 8 hours, then diluted with 500 ml. of water and extracted with 2 x 500 ml. portions of chloroform. The chloroform

extracts were combined, washed with 2 x 500 ml. portions of water, then dried over sodium sulfate. After filtering and vacuum removal of the solvent from the filtrate, 8.9 g. of the light yellow solid was recrystallized from 50 ml. of carbon tetrachloride to give 4.8 g. white crystals, 2′,6′-diethylglycolanilide, m.p. 81-85°.

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.51; H, 8.17; N, 6.65.

2′,6′-Diethylglycolanilide (3.5 g., 0.017 mole) was mixed with 10 ml. of thionyl chloride, and the material refluxed for 45 minutes to cause cyclization. The thionyl chloride was removed under vacuum (with ether/pentane treatments) and 2.5 g. of solid was obtained, which upon recrystallization from methylcyclohexane or ethanol, gave **2b**.

Anal. Calcd. for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 57.07; H, 6.23; N, 5.33.

3-(2,6-Diethylphenyl)-5-isopropyl-1,2,3-oxathiazolidin-4-one 2-Oxide (**2c**).

2,6-Diethylphenyl isocyanide (13) [b.p. 85-89° (0.05 mm)] (4.77 g., 0.03 mole) was added to a mixture of 2.8 g. of isobutyraldehyde and 2.7 g. of oxalic acid in 50 ml. of methanol. The mixture was stirred overnight, then methanol evaporated and ether added to cause crystallization. The material was recrystallized to give 3.6 g. of 2′,6′-diethyl-2-hydroxyisovaleranilide, m.p. 112-113°.

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.22; H, 9.40; N, 5.74.

The 2′,6′-diethyl-2-hydroxyisovaleranilide (2.0 g., 0.08 mole) was dissolved in 20 ml. of thionyl chloride. Nmr examination indicated complete reaction at room temperature to give *ca.* 3:2 ratio of isomeric oxathiazolidin-4-one 2-oxides. Excess thionyl chloride was removed under vacuum, and successive amounts of pentane were added and removed under vacuum. The solid in pentane was filtered off to give 1.0 g. of product **2c** which was recrystallized from ether to give 0.5 g. of white solid (pure major *trans* isomer, m.p. 96-97°). Pentane was evaporated to give an oil which proved to be mainly the *cis* isomer (see Discussion). On standing, it crystallized and partially reverted to the *trans* isomer. No further attempt was made to isolate the minor isomer.

Anal. Calcd. for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N, 4.74. Found: C, 61.14; H, 7.17; N, 4.62.

3-(2,6-Diethylphenyl)-5-trichloromethyl-1,2,3-oxathiazolidin-4-one 2-Oxide (**2d**).

2,6-Diethylphenyl isocyanide (8.0 g., 0.05 mole) and 7.6 g. chloral were added to 75 ml. of wet ether. Several small drops of concentrated sulfuric acid was added, whereupon the mixture darkened somewhat and a mild exotherm was noted. After stirring for ½ hour, the material was vacuum treated to remove ether, and the residue recrystallized from acetonitrile to give 5.0 g. of 2′,6′-diethyl-3,3,3-trichloroacetanilide, m.p. 175.5-177.0°.

Anal. Calcd. for $C_{13}H_{16}Cl_3NO_2$: C, 48.10; H, 4.97; N, 4.31. Found: C, 47.99; H, 5.04; N, 4.25.

2′,6′-Diethyl-3,3,3-trichlorolactanilide (4.0 g., 0.012 mole) was added to 20 ml. of thionyl chloride. After refluxing 40 minutes, nmr examination indicated complete reaction with *ca.* 60:40 isomer distribution. After vacuum removal of thionyl chloride (using both pentane and ether in successive amounts to aid in its removal), the solid was recrystallized from methylcyclohexane (charcoal) to give 2 g. of a sharp melting solid, **2d**, with however, the same isomer distribution in deuterated chloroform as found in the thionyl chloride solution.

Anal. Calcd. for $C_{13}H_{14}Cl_3NO_3S$: C, 42.12; H, 3.81; N, 3.78. Found: C, 41.99; H, 3.72; N, 3.66.

3-(2,6-Diethylphenyl)-5,5-dimethyl-1,2,3-oxathiazolidin-4-one 2-Oxide (**2e**).

2,6-Diethylphenyl isocyanide was mixed with an acetone water solution (v/v ~ 90:10) containing a few drops of concentrated sulfuric acid. Upon vacuum removal of solvent and recrystallization from cold ether, white crystalline 2′,6′-diethyl-2-hydroxyisobutyranilide (m.p. 124-125°) was isolated.

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.95. Found: C, 71.69; H, 9.03; N, 5.83.

2′,6′-Diethyl-2-hydroxyisobutyranilide (1.7 g., 0.07 mole) was dissolved in 7 ml. of thionyl chloride. The mixture was refluxed for 30 minutes. Examination of the solution by nmr revealed complete reaction. The thionyl chloride was removed under vacuum, the last traces of sulfuric dioxide and hydrogen chloride removed by repeated vacuum treatment of successive portions of ether added to the residue. The residue was then recrystallized from cold pentane or ethanol to give 1.5 g. of white crystals.

Anal. Calcd. for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98; S, 11.40. Found: C, 59.67; H, 6.68; N, 4.72; S, 11.40.

3-(6-*t*-Butyl-*o*-tolyl)-1,2,3-oxathiazolidin-4-one 2-Oxide (**2f**).

6′-*t*-Butyl-2-chloro-*o*-acetotoluidide, (2), (240 g., 1 mole) and 150 g. of potassium carbonate were mixed with 1.5 l. of water and placed in a 3 l. rocking autoclave and heated 4 hours at 175°. On cooling, the taffy-like product was stirred for 2 hours in 500 ml. of benzene and both layers discharged. The benzene portion was subjected to vacuum distillation and 143 g. of pale yellow distillate collected between 165-175° (0.1 mm). A redistillation gave 130 g. which upon solidification, recrystallized from 50% methanol to give 116 g. of pale yellow crystals, m.p. 102.5-103.5° of 6′-*t*-butyl-*o*-glycolotoluidide (**1f**).

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65. Found: C, 70.48; H, 8.82.

6′-*t*-Butyl-*o*-glycolotoluidide (**1f**) was placed in excess thionyl chloride. Immediate inspection of the ir spectra revealed a carbonyl band at *ca.* 6.0 μ and an N-H band at *ca.* 3.3 μ. Isolation of a solid after vacuum removal of thionyl chloride showed by ir and nmr monitoring, that at room temperature, reaction at the $HOCH_2$ had taken place (downfield shift of OCH_2). No heterocycle had been formed however, because the carbonyl still absorbed at 6.0 μ. The reaction was then repeated using 5.1 g. of **1f** and 25 ml. of thionyl chloride. After 45 mintues reflux, no N-H bond remained as observed in the ir and nmr, and the reaction was essentially complete. The thionyl chloride, as well as traces of sulfur dioxide and hydrogen chloride were removed under vacuum, aided by successive addition and vacuum elimination of pentane. The residue was crystallized from cold ether/pentane or ethanol to give 2.0 g. of white crystals while an additional amount (0.75 g.) was obtained from the filtrate.

Anal. Calcd. for $C_{13}H_{17}NO_3S$: C, 58.40; H, 6.41; N, 5.24. Found: C, 58.66; H, 5.96; N, 5.20.

3-(6-*t*-Butyl-*o*-tolyl)-5-isopropyl-1,2,3-oxathiazolidin-4-one 2-Oxide (**2g**).

6-*t*-Butyl-*o*-tolyl isocyanide (m.p. 63-65°), (0.058 mole, 7.3 g.) was added to a wet ether solution containing 5.1 g. of isobutyraldehyde. After stirring for ½ hour, several drops of concentrated sulfuric acid were added and the material stirred overnight. Solid sodium carbonate was then added to neutralize the acid, and the ether layer was filtered, then evaporated to give a solid residue which was recrystallized from cold methylcyclohexane to give 10.2 g. of 6′-*t*-butyl-2-hydroxy-*o*-isovalerotoluidide, m.p. 124-125°.

Anal. Calcd. for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32. Found: C, 72.67; H, 9.57; N, 5.04.

6′-*t*-Butyl-2-hydroxy-*o*-isovalerotoluidide (5.7 g., 0.03 mole) was dissolved in 20 ml. of thionyl chloride and after ½ hour at room temperature, monitoring of the solution by its nmr spectra indicated complete reaction (compare this behavior with formation of **2c**, and contrast with the preparation of **2b** and **2f**). After vacuum treatment to remove thionyl chloride and traces of hydrogen chloride and sulfuric dioxide, an oil remained which failed to crystallize.

Anal. Calcd. for $C_{16}H_{23}NO_3S$: C, 62.11; H, 7.4; N, 4.53. Found: C, 62.68; H, 7.80; N, 4.56.

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(14) Note added in proof: the structural assignment as **2** rather than **4** was confirmed by x-ray crystallographic examination of **2a**. Detailed results of this study, as well as related chemistry will be the subject of a forthcoming publication.