

Synthesis of Oxazolidines, Thiazolidines, and 5,6,7,8-Tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole (or thiazole)-1,3-diones from β -Hydroxy- or β -Mercapto- α -amino Acid Esters†

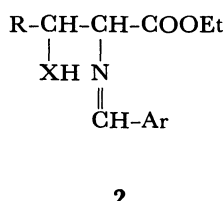
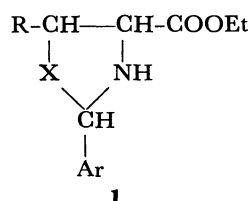
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2-Aryl-4-(ethoxycarbonyl)oxazolidines and thiazolidines (**1**) were prepared from the corresponding α -amino acid ethyl esters containing either hydroxyl or mercapto groups in the β -position by fusion with some aromatic aldehydes. Dehydrogenation of **1** with *N*-bromosuccinimide gave the corresponding oxazoles and thiazoles. The oxazolidines and thiazolidines gave Mannich bases on interaction with *p*-nitrobenzaldehyde and piperidine. Acetylation of **1** gave the corresponding *N*-acetyl derivatives, which on fusion in the presence of anhydrous ZnCl_2 undergo cyclization, giving the corresponding bicyclic compounds, 5,6,7,8-tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole (or thiazole)-1,3-diones.

Fusion of the β -hydroxy and/or β -mercapto- α -amino acid ethyl esters (*L*-serine, 3-phenyl-*DL*-serine, *L*-threonine, or *L*-cysteine) with aromatic aldehydes such as benzaldehyde, *p*-anisaldehyde, *p*-chlorobenzaldehyde, and/or *p*-nitrobenzaldehyde gave the corresponding oxazolidines or thiazolidines **1** rather than azomethine derivatives (**2**).



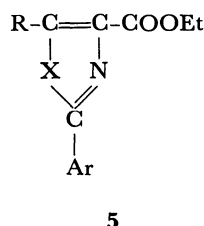
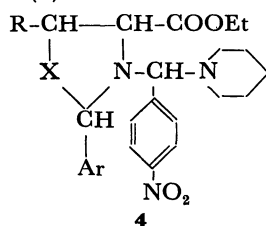
X=O or S;

R=H, CH_3 or C_6H_5 ;

Ar= C_6H_5 , *p*- $\text{CH}_3\text{OC}_6\text{H}_4$, *p*- ClC_6H_4 , *p*- $\text{NO}_2\text{C}_6\text{H}_4$, or *p*- BrC_6H_4 .

Structure **1** is apparent by elemental analysis data, UV, and IR spectral data, the latter two reasonably agreeing with those of the comparable compounds.^{1,2} The alternative structure **2** for the products is excluded by the absence of the NMR signal near δ 7.5 ascribable to azomethine.

The oxazolidines and/or thiazolidines (**1**) on treatment with acetyl bromide in glacial acetic acid afforded *N*-acetyl derivative (**3**) whose IR spectra showed an absorption band at 1570 cm^{-1} due to the amide group ($>\text{NCOCH}_3$) but no NH stretching vibration band. On treatment with piperidine and *p*-nitrobenzaldehyde (**1**) gave the corresponding Mannich base (**4**).



The oxazolidines and thiazolidines (**1**) were con-

verted into the corresponding oxazoles and thiazoles (**5**) on dehydrogenation using *N*-bromosuccinimide in boiling carbon tetrachloride. The IR spectra of the oxazoles and thiazoles (**5**) showed no NH band but an apparent shift in the ester group was observed at $1735\text{--}1750\text{ cm}^{-1}$ due to conjugation with the double bond at $\text{C}_4\text{--C}_5$.³ The C=N absorption band at $1590\text{--}1550\text{ cm}^{-1}$ is affected by substituents on aryl moiety at C_2 ; *p*-nitro group causes a decrease in wave number down to 30 cm^{-1} , whereas *p*-methoxyl group causes an increase up to *ca.* 10 cm^{-1} . In addition, characteristic absorptions of oxazole ring⁴ were observed in the range $1190\text{--}1250\text{ cm}^{-1}$.

N-Acetyloxazolidines and/or thiazolidines (**3**) undergo cyclization by fusion with anhydrous zinc chloride affording 5,6,7,8-tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole (or thiazole)-1,3-dione (**6**) whose IR spectra showed no absorption of (COCH_3) group, but a broad band at 3300 cm^{-1} due to associated OH group, confirming the assumption that the bicyclic structure **6** exists in the enolic form rather than its diketonic tautomer (**7**). The cyclization reaction seems to proceed according to the following mechanism.

Experimental

All melting points are uncorrected. IR spectroscopic analysis was carried out on a Pye-Unicam IR spectrophotometer, Model SP 200 G, UV absorptions were measured on a Pye-Unicam UV spectrophotometer, Model SP 8000, using 95% ethanol as a solvent. NMR spectra were taken with a Varian T-60 instrument in deuteriochloroform with tetramethylsilane as an internal standard.

Amino Acids Ethyl Esters. Prepared in more than 80% yield by the general method described by Fischer⁵ and used without further purification in the preparation of the oxazolidines and/or thiazolidines.

Preparation of Oxazolidine and/or Thiazolidine Derivatives (1**).** The amino acid ethyl ester (0.01 mol) was heated with the appropriate aldehyde (0.011 mol) in an oil bath at $80\text{--}90^\circ\text{C}$ for 2 h. Extraction with ethyl acetate gave the corresponding 2-aryl-4-(ethoxycarbonyl)oxazolidines and/or thiazolidines (**1**) which was purified by column chromatography using $1 \times 50\text{ cm}$ column of Davison 950 silica-gel, slurry packed with hexane and eluted with benzene-hexane (3:1 v/v). The results are given in Table 1.

Acetylation of Oxazolidines and Thiazolidines (3**).** Acetyl bromide (0.01 mol) was added to the oxazolidine or thia-

† Presented in part at the 7th International Congress of Heterocyclic Chemistry, University of South Florida, Tampa, Florida, U.S.A., August 1979.

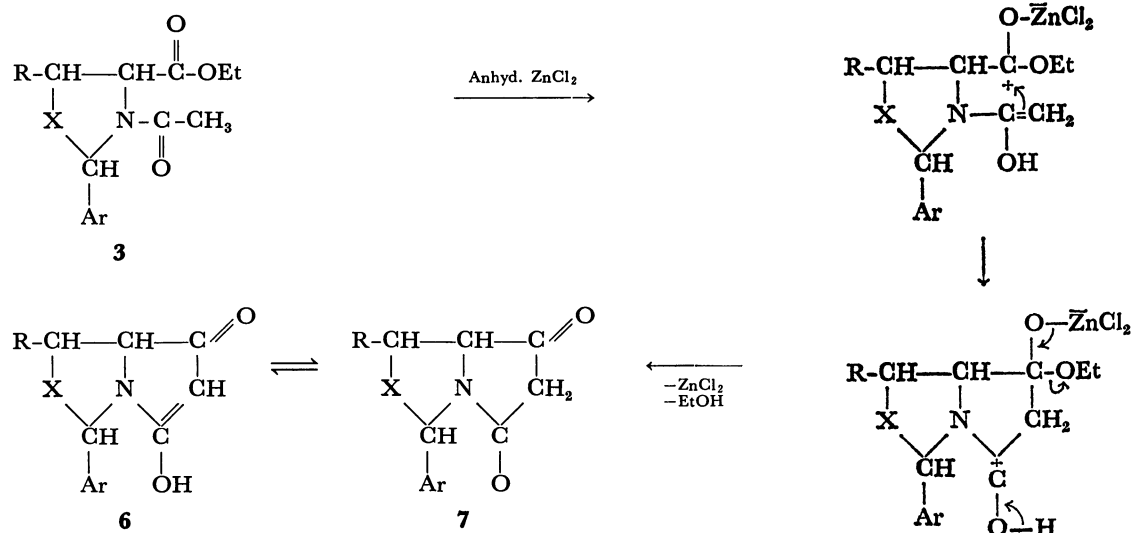


TABLE 1. 2-ARYL-4-(ETHOXYCARBONYL)OXAZOLIDINES OR THIAZOLIDINES

Compound No.	X	R	Ar	Yield %	n_D^{27}	$\nu(\text{NH})$ cm ⁻¹	$\nu(\text{COOEt})$ cm ⁻¹	Molecular formula	Analysis (Calcd/Found) %		
									C	H	N
1a	O	H	C ₆ H ₅	85.9	1.5522	3370	1720	C ₁₂ H ₁₅ O ₃ N	65.14 65.08	6.83 6.80	6.33 6.35
1b	O	H	<i>p</i> -CH ₃ OC ₆ H ₄	87	1.5522	3350	1730	C ₁₃ H ₁₇ O ₄ N	62.15 62.12	6.82 6.78	5.57 5.58
1c	O	H	<i>p</i> -ClC ₆ H ₄	86.2	1.5440	3360	1700	C ₁₂ H ₁₄ O ₃ NCl	56.36 56.32	5.48 5.49	5.48 5.51
1d	O	H	<i>p</i> -NO ₂ C ₆ H ₄	88.7	1.5605	3380	1730	C ₁₂ H ₁₄ O ₅ N ₂	54.13 54.08	5.30 5.28	10.52 10.56
1e	O	CH ₃	C ₆ H ₅	85	1.5210	3370	1740	C ₁₃ H ₁₇ O ₃ N	66.36 66.36	7.28 7.26	5.95 5.95
1f	O	CH ₃	<i>p</i> -CH ₃ OC ₆ H ₄	86.7	1.5592	3300	1730	C ₁₄ H ₁₉ O ₄ N	63.38 63.50	7.22 6.98	5.28 5.30
1g	O	CH ₃	<i>p</i> -ClC ₆ H ₄	89.27	1.5500	3320	1700	C ₁₃ H ₁₆ O ₃ NCl	57.88 57.86	5.94 5.96	5.19 5.21
1h	O	CH ₃	<i>p</i> -NO ₂ C ₆ H ₄	94	1.5435	3300	1730	C ₁₃ H ₁₆ O ₅ N ₂	55.71 55.70	5.75 5.73	10.00 10.02
1i	O	C ₆ H ₅	<i>p</i> -ClC ₆ H ₄	98.1	1.5530	3320	1730	C ₁₈ H ₁₉ O ₃ NCl	64.96 65.02	5.71 5.42	4.21 4.22
1j	S	H	C ₆ H ₅	80.1	1.5532	3400	1740	C ₁₂ H ₁₅ O ₂ NS	60.76 60.74	6.37 6.34	5.90 5.90
1k	S	H	<i>p</i> -CH ₃ OC ₆ H ₄	82.3	1.5718	3400	1730	C ₁₃ H ₁₇ O ₃ NS	58.42 58.40	6.41 6.38	5.24 5.26
1l	S	H	<i>p</i> -ClC ₆ H ₄	81.5	1.5855	3420	1730	C ₁₂ H ₁₄ O ₂ NCIS	53.04 53.01	5.16 5.18	5.16 5.16
1m	S	H	<i>p</i> -BrC ₆ H ₄	83.3	1.5528	3400	1730	C ₁₂ H ₁₄ O ₂ NBrS	45.57 45.55	4.43 4.46	4.43 4.45
1n	S	H	<i>p</i> -NO ₂ C ₆ H ₄	82.6	1.5608	3410	1735	C ₁₂ H ₁₄ O ₄ N ₂ S	51.06 51.08	5.00 4.98	9.93 9.94

zolidine derivative (1) (0.01 mol) in glacial acetic acid (30 ml) and the solution was refluxed for 3 h. The reaction product was poured in cold dilute sodium hydrogencarbonate solution; the solid deposited were collected, washed with water and crystallized from ethanol to give the corresponding *N*-acetyl oxazolidines or thiazolidines (3). The results

are given in Table 2.

Cyclization of N-Acetyloxazolidines and Thiazolidines: Formation of 5,6,7,8-Tetrahydro-1H,3H-pyrrolo[1,2-c]oxazole-1,3-diones and Their Thiazole Analogues (7). *N*-Acetyloxazolidine or thiazolidine (3) (0.01 mol) was fused with anhydrous zinc chloride (0.0125 mol) in an oil bath at 180 °C for 20 min.

TABLE 2. *N*-ACETYLOXAZOLIDINES AND THIAZOLIDINES

Compound No.	X	R	Ar	Yield %	Mp °C	$\nu(\text{NCOCH}_3)$ cm^{-1}	$\nu(\text{COOEt})$ cm^{-1}	Molecular formula	N %	
									Calcd	Found
3a	O	H	C ₆ H ₅	72.2	170—172	1670	1747	C ₁₄ H ₁₇ O ₄ N	5.32	5.30
3b	O	H	<i>p</i> -CH ₃ OC ₆ H ₄	75	167—169	1670	1750	C ₁₅ H ₁₉ O ₅ N	4.78	4.73
3c	O	H	<i>p</i> -ClC ₆ H ₄	74.4	168—169	1670	1745	C ₁₄ H ₁₆ O ₄ NCl	4.71	4.53
3d	O	H	<i>p</i> -NO ₂ C ₆ H ₄	75.6	165	1660	1750	C ₁₄ H ₁₆ O ₆ N ₂	9.09	8.88
3e	S	H	<i>p</i> -ClC ₆ H ₄	67.3	195	1650	1720	C ₁₄ H ₁₆ O ₃ NCIS	4.47	4.50
3f	S	H	<i>p</i> -BrC ₆ H ₄	64.2	120—122	1600	1750	C ₁₄ H ₁₆ O ₃ NBrS	3.91	3.87
3g	S	H	<i>p</i> -NO ₂ C ₆ H ₄	67.9	205	1670	1740	C ₁₄ H ₁₆ O ₅ N ₂ S	8.64	8.62

TABLE 3. 5,6,7,8-Tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole or thiazole-1,3-diones

Compound No.	X	R	Ar	Yield %	Mp °C	$\nu(\text{C=O})$ cm^{-1}	$\nu(\text{C=C})$ cm^{-1}	$\nu(\text{OH})$ cm^{-1}	Molecular formula	Analysis (Calcd/Found) %		
										C	H	N
7a	O	H	C ₆ H ₅	78.3	320	1680	3010	3300	C ₁₂ H ₁₁ O ₃ N	66.35	5.10	6.45
										66.34	5.08	6.45
7b	O	H	<i>p</i> -CH ₃ OC ₆ H ₄	80.3	245	1700	3020	3300	C ₁₃ H ₁₃ O ₄ N	63.15	5.30	5.67
										63.12	5.28	5.68
7c	O	CH ₃	<i>p</i> -CH ₃ OC ₆ H ₄	76	242	1700	3020	3300	C ₁₄ H ₁₅ O ₄ N	64.36	5.79	5.36
										64.34	5.76	5.35
7d	S	H	<i>p</i> -ClC ₆ H ₄	78.2	220	1700	3020	3320	C ₁₂ H ₁₀ O ₂ NCIS	53.83	3.79	5.23
										53.80	3.81	5.24

TABLE 4. OXAZOLE OR THIAZOLE DERIVATIVES

Compound No.	X	R	Ar	Yield %	Mp °C	$\nu(\text{C=C})$ cm^{-1}	$\nu(\text{C=N})$ cm^{-1}	Molecular formula	Analysis (Calcd/Found) %		
									C	H	N
5a	O	H	C ₆ H ₆	70.7	75	3030	1580	C ₁₂ H ₁₁ O ₃ N	66.35	5.10	6.45
									66.33	5.08	6.46
5b	O	H	<i>p</i> -CH ₃ OC ₆ H ₄	73.5	105	3050	1590	C ₁₃ H ₁₃ O ₄ N	63.15	5.30	5.67
									63.14	5.28	5.67
5c	O	H	<i>p</i> -ClC ₆ H ₄	74.7	98	3050	1590	C ₁₂ H ₁₀ O ₃ NCl	57.25	3.97	5.56
									57.22	3.98	5.55
5d	O	H	<i>p</i> -NO ₂ C ₆ H ₄	76.4	125	3050	1550	C ₁₂ H ₁₀ O ₅ N ₂	54.96	3.84	10.68
									54.92	3.84	10.66
5e	S	H	C ₆ H ₅	72.9	116	3050	1580	C ₁₂ H ₁₁ O ₂ NS	61.80	4.75	6.01
									61.76	4.75	6.00
5f	S	H	<i>p</i> -CH ₃ OC ₆ H ₄	72.2	95	3050	1595	C ₁₃ H ₁₃ O ₃ NS	59.31	4.94	5.32
									59.25	4.97	5.34
5g	S	H	<i>p</i> -NO ₂ C ₆ H ₄	75.5	98—99	3040	1550	C ₁₂ H ₁₀ O ₄ N ₂ S	51.80	3.62	10.07
									51.74	3.61	10.06

TABLE 5. MANNICH BASES CONTAINING OXAZOLIDINE OR THIAZOLIDINE MOIETY

Compound No.	X	R	Ar	Yield %	Mp °C	$\nu(\text{NO}_2)$ cm^{-1}	$\nu(\text{COOEt})$ cm^{-1}	Molecular formula	N %	
									Calcd	Found
4a	O	CH ₃	<i>p</i> -CH ₃ OC ₆ H ₄	72	142	1350, 1560	1750	C ₂₆ H ₃₃ O ₆ H ₃	0.69	8.68
4b	O	H	<i>p</i> -ClC ₆ H ₄	67	128	1370, 1570	1700	C ₂₄ H ₂₈ O ₅ N ₃ Cl	8.87	8.87
4c	S	H	C ₆ H ₅	55.5	135	1300, 1500	1700	C ₂₄ H ₂₉ O ₄ N ₃ S	9.23	9.26

The mixture was treated with cold dilute hydrochloric acid, the solid formed being collected by filtration. Crystallization of the solid from dilute acetic acid gave 5,6,7,8-tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-1,3-diones or their thiazole analoges (**7**). The results are given in Table 3.

Dehydrogenation of Oxazolidine and Thiazolidine Derivatives by N-Bromosuccinimide: Formation of Oxazole and Thiazole Derivatives (5). *N*-Bromosuccinimide (0.02 mol) and benzoyl peroxide were added to the oxazolidine or thiazolidine derivative (0.01 mol) dissolved in carbon tetrachloride (100 ml) and the solution was refluxed for 6 h. The reaction product was filtered off in order to separate the succinimide and the filtrate was concentrated. The oxazole or thiazole derivatives (**5**) obtained were crystallized from petroleum ether (40–60 °C). The results are given in Table 4.

Preparation of Mannich Bases (4). A mixture of 2-aryl-4(ethoxycarbonyl)oxazolidine or thiazolidine (0.01 mol)

p-nitrobenzaldehyde (0.01 mol) and piperidine (0.02 mol) in ethanol (50 ml) was refluxed for 6 h. The reaction product was poured onto ice, washed with petroleum ether (40–60 °C) several times and extracted with ether. The Mannich bases (**4**) were crystallized from dilute acetic acid. The results are given in Table 5.

References

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