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†

Mahmoud Zarif Amin BADR,* Morsy Mohamed ALY, Atiat Mohamed FAHMY, and Mansour Esmael Younis MANSOUR

Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt

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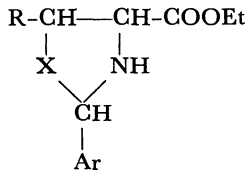
2-Aryl-4-(ethoxycarbonyl)oxazolidines and thiazolidines (**1**) were prepared from the corresponding α-amino acid ethyl esters containing either hydroxyl or mercapto groups in the β-position by fusion with some aromatic aldehydes. Dehydrogenation of **1** with *N*-bromosuccinimide gave the corresponding oxazoles and thiazoles. The oxazolidines and thiazolidines gave Mannich bases on interaction with *p*-nitrobenzaldehyde and piperidine. Acetylation of **1** gave the corresponding *N*-acetylderivatives, 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**).



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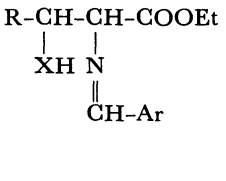

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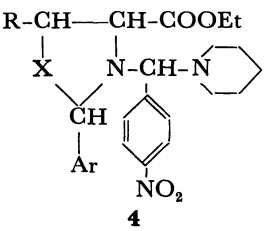
X=O or S;
R=H, CH_3 or C_6H_5;
Ar=C_6H_5, *p*-$CH_3OC_6H_4$, *p*-ClC_6H_4, *p*-$NO_2C_6H_4$, or *p*-BrC_6H_4.

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 (>$NCOCH_3$) but no NH stretching vibration band. On treatment with piperidine and *p*-nitrobenzaldehyde (**1**) gave the corresponding Mannich base (**4**).



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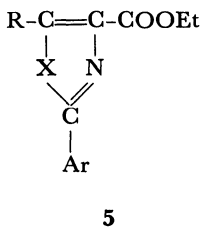

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The oxazolidines and thiazolidines (**1**) were converted into the corresponding oxazoles and thiazoles (**5**) on dehydrogenation using *N*-bromosuccinimide in boiling carbon tetrachloride. The IR spectra of the oxazoles and thiazoles (**5**) showed no NH band but an apparent shift in the ester group was observed at 1735—1750 cm^{-1} due to conjugation with the double bond at C_4–C_5.[3] The C=N absorption band at 1590—1550 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 ring[4] were observed in the range 1190—1250 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 deuterochloroform with tetramethylsilane as an internal standard.

Amino Acids Ethyl Esters. Prepared in more than 80% yield by the general method described by Fischer[5] 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—90 °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 1×50 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-

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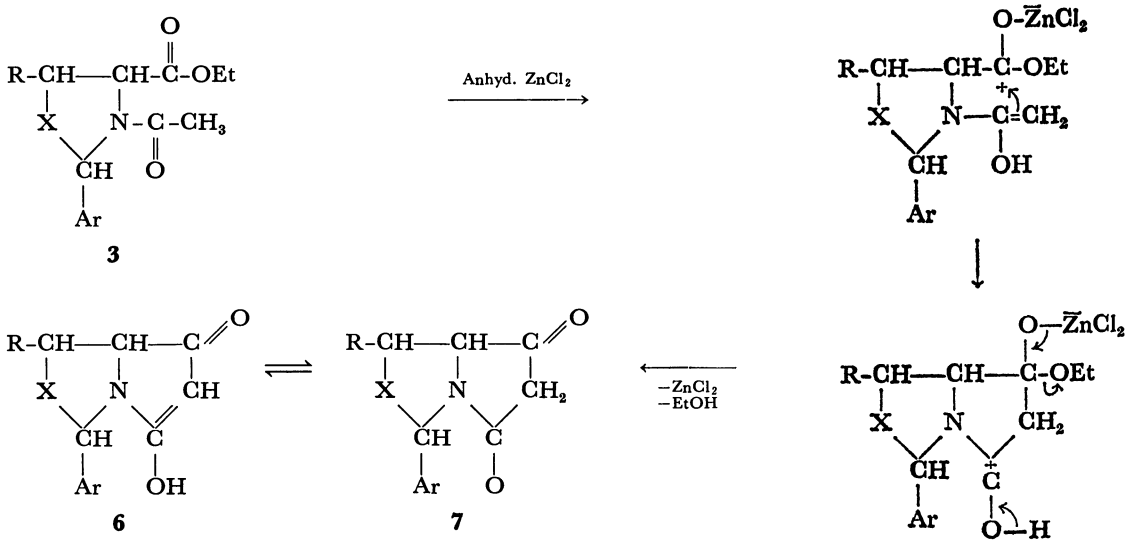

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Table 1. 2-Aryl-4-(ethoxycarbonyl)oxazolidines or thiazolidines

Compound No.	X	R	Ar	Yield %	n_D^{27}	ν(NH) cm⁻¹	ν(COOEt) cm⁻¹	Molecular formula	Analysis (Calcd/Found) % C	H	N
1a	O	H	C_6H_5	85.9	1.5522	3370	1720	$C_{12}H_{15}O_3N$	65.14	6.83	6.33
									65.08	6.80	6.35
1b	O	H	*p*-$CH_3OC_6H_4$	87	1.5522	3350	1730	$C_{13}H_{17}O_4N$	62.15	6.82	5.57
									62.12	6.78	5.58
1c	O	H	*p*-ClC_6H_4	86.2	1.5440	3360	1700	$C_{12}H_{14}O_3NCl$	56.36	5.48	5.48
									56.32	5.49	5.51
1d	O	H	*p*-$NO_2C_6H_4$	88.7	1.5605	3380	1730	$C_{12}H_{14}O_5N_2$	54.13	5.30	10.52
									54.08	5.28	10.56
1e	O	CH_3	C_6H_5	85	1.5210	3370	1740	$C_{13}H_{17}O_3N$	66.36	7.28	5.95
									66.36	7.26	5.95
1f	O	CH_3	*p*-$CH_3OC_6H_4$	86.7	1.5592	3300	1730	$C_{14}H_{19}O_4N$	63.38	7.22	5.28
									63.50	6.98	5.30
1g	O	CH_3	*p*-ClC_6H_4	89.27	1.5500	3320	1700	$C_{13}H_{16}O_3NCl$	57.88	5.94	5.19
									57.86	5.96	5.21
1h	O	CH_3	*p*-$NO_2C_6H_4$	94	1.5435	3300	1730	$C_{13}H_{16}O_5N_2$	55.71	5.75	10.00
									55.70	5.73	10.02
1i	O	C_6H_5	*p*-ClC_6H_4	98.1	1.5530	3320	1730	$C_{18}H_{19}O_3NCl$	64.96	5.71	4.21
									65.02	5.42	4.22
1j	S	H	C_6H_5	80.1	1.5532	3400	1740	$C_{12}H_{15}O_2NS$	60.76	6.37	5.90
									60.74	6.34	5.90
1k	S	H	*p*-$CH_3OC_6H_4$	82.3	1.5718	3400	1730	$C_{13}H_{17}O_3NS$	58.42	6.41	5.24
									58.40	6.38	5.26
1l	S	H	*p*-ClC_6H_4	81.5	1.5855	3420	1730	$C_{12}H_{14}O_2NClS$	53.04	5.16	5.16
									53.01	5.18	5.16
1m	S	H	*p*-BrC_6H_4	83.3	1.5528	3400	1730	$C_{12}H_{14}O_2NBrS$	45.57	4.43	4.43
									45.55	4.46	4.45
1n	S	H	*p*-$NO_2C_6H_4$	82.6	1.5608	3410	1735	$C_{12}H_{14}O_4N_2S$	51.06	5.00	9.93
									51.08	4.98	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-1*H,*3*H-*pyrrolo*[*1,2*-c]*oxazole-1,3-diones and Their Thiazole Analoges (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	ν(NCOCH$_3$) cm^{-1}	ν(COOEt) cm^{-1}	Molecular formula	N% Calcd	N% Found
3a	O	H	C_6H_5	72.2	170—172	1670	1747	$C_{14}H_{17}O_4N$	5.32	5.30
3b	O	H	*p*-$CH_3OC_6H_4$	75	167—169	1670	1750	$C_{15}H_{19}O_5N$	4.78	4.73
3c	O	H	*p*-ClC_6H_4	74.4	168—169	1670	1745	$C_{14}H_{16}O_4NCl$	4.71	4.53
3d	O	H	*p*-$NO_2C_6H_4$	75.6	165	1660	1750	$C_{14}H_{16}O_6N_2$	9.09	8.88
3e	S	H	*p*-ClC_6H_4	67.3	195	1650	1720	$C_{14}H_{16}O_3NClS$	4.47	4.50
3f	S	H	*p*-BrC_6H_4	64.2	120—122	1600	1750	$C_{14}H_{16}O_3NBrS$	3.91	3.87
3g	S	H	*p*-$NO_2C_6H_4$	67.9	205	1670	1740	$C_{14}H_{16}O_5N_2S$	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	ν(C=O) cm^{-1}	ν(C=C) cm^{-1}	ν(OH) cm^{-1}	Molecular formula	Analysis (Calcd/Found) % C	H	N
7a	O	H	C_6H_5	78.3	320	1680	3010	3300	$C_{12}H_{11}O_3N$	66.35	5.10	6.45
										66.34	5.08	6.45
7b	O	H	*p*-$CH_3OC_6H_4$	80.3	245	1700	3020	3300	$C_{13}H_{13}O_4N$	63.15	5.30	5.67
										63.12	5.28	5.68
7c	O	CH_3	*p*-$CH_3OC_6H_4$	76	242	1700	3020	3300	$C_{14}H_{15}O_4N$	64.36	5.79	5.36
										64.34	5.76	5.35
7d	S	H	*p*-ClC_6H_4	78.2	220	1700	3020	3320	$C_{12}H_{10}O_2NClS$	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	ν(C=C) cm^{-1}	ν(C=N) cm^{-1}	Molecular formula	Analysis (Calcd/Found) % C	H	N
5a	O	H	C_6H_6	70.7	75	3030	1580	$C_{12}H_{11}O_3N$	66.35	5.10	6.45
									66.33	5.08	6.46
5b	O	H	*p*-$CH_3OC_6H_4$	73.5	105	3050	1590	$C_{13}H_{13}O_4N$	63.15	5.30	5.67
									63.14	5.28	5.67
5c	O	H	*p*-ClC_6H_4	74.7	98	3050	1590	$C_{12}H_{10}O_3NCl$	57.25	3.97	5.56
									57.22	3.98	5.55
5d	O	H	*p*-$NO_2C_6H_4$	76.4	125	3050	1550	$C_{12}H_{10}O_5N_2$	54.96	3.84	10.68
									54.92	3.84	10.66
5e	S	H	C_6H_5	72.9	116	3050	1580	$C_{12}H_{11}O_2NS$	61.80	4.75	6.01
									61.76	4.75	6.00
5f	S	H	*p*-$CH_3OC_6H_4$	72.2	95	3050	1595	$C_{13}H_{13}O_3NS$	59.31	4.94	5.32
									59.25	4.97	5.34
5g	S	H	*p*-$NO_2C_6H_4$	75.5	98—99	3040	1550	$C_{12}H_{10}O_4N_2S$	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	ν(NO$_2$) cm^{-1}	ν(COOEt) cm^{-1}	Molecular formula	N% Calcd	N% Found
4a	O	CH_3	*p*-$CH_3OC_6H_4$	72	142	1350, 1560	1750	$C_{26}H_{33}O_6H_3$	0.69	8.68
4b	O	H	*p*-ClC_6H_4	67	128	1370, 1570	1700	$C_{24}H_{28}O_5N_3Cl$	8.87	8.87
4c	S	H	C_6H_5	55.5	135	1300, 1500	1700	$C_{24}H_{29}O_4N_3S$	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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