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Reaction of Oxalyl Chloride and Alkyloxalyl Chlorides with Isocyanates and Isothiocyanates

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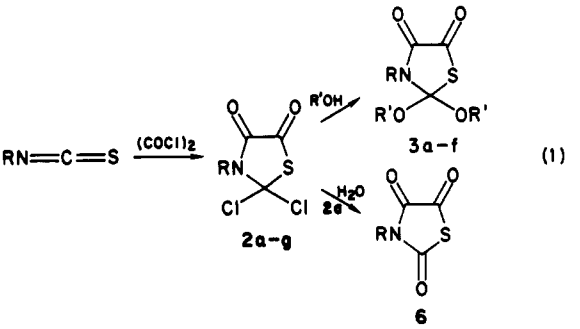
Alkyl and aryl isothiocyanates react with oxalyl chloride (1) on both double bonds of the heterocumulene to yield 3-alkyl- or 3-aryl-2,2-dichlorothiazolidine-4,5-diones **2**. The two chlorines in these novel orthocarbonic acid derivatives are readily exchanged by alkoxy groups to yield 2,2-dialkoxythiazolidine-4,5-diones **3**; hydrolysis of **2a** (R = CH_3) gave 3-methylthiazolidine-2,4,5-trione. 3-Substituted 5,5-dichlorooxazolidine-2,4-diones **8** and 5-chloro-5-alkoxyoxazolidine-2,4-diones **13** are obtained on reacting alkyl, aryl, and benzyl isocyanates with 1 and alkyloxalyl chloride, respectively. Structure assignment to these novel cycloadducts is based on IR, ^1H NMR, and ^{13}C NMR spectroscopic as well as X-ray crystallographic analysis. Formation of **8** and **13** is a stepwise process involving labile acyclic intermediates **7** and **12**. The cyclizations to **8** and **13** take place only on the C=N bond of the isocyanate group.

Isocyanates have been reported to react as acylating agents by insertion into CH bonds of activated alkyl groups, olefins (enol ethers, enamines), or aromatic compounds to produce N-substituted carboxamides.[1] On the other hand, acylating agents have also been found to attack isocyanates.[2-4] Thus, phosgene was found to add to the NCO bond of alkyl isocyanates in the presence of carbon as a catalyst to afford the synthetically useful *N*-bis(chlorocarbonyl)amines[5,6] and carboxylic acid halides added in the presence of Lewis acid catalysts to give *N*-chlorocarbonyl carboxamides. On the other hand, reactions of alkyl and aryl isothiocyanates with acylating agents of the type RCOCl have, to our knowledge, not been described in the literature.[7]

As an extension of our work on the reactivity of oxalyl chloride (1) toward heterocumulenes, we studied the behavior of 1 and alkyloxalyl chlorides toward isocyanates and isothiocyanates.

1. Isothiocyanate–Oxalyl Chloride Adducts. On mixing equivalent amounts of methyl isothiocyanate and oxalyl chloride (1) at room temperature, an exothermic reaction ensues within minutes which leads to formation of 3-methyl-2,2-dichlorothiazolidine-4,5-dione (**2a**) in virtually quantitative yield (eq 1). Other aliphatic isothiocyanates as well as benzyl isothiocyanate require longer reaction times (up to 120 h) at room temperature to produce quantitatively the structurally equivalent adducts in solid or liquid form. Reactions between phenyl isothiocyanate or *p*-methoxyphenyl isothiocyanate and 1 under similar conditions were found to require extremely long reaction times (25 and 40 days) for the conversion to reach 25% and 23%, respectively. Progress of the reactions was monitored by IR spectroscopy in following the disappearance of the N=C=S bands (between 2100–2200 cm^{-1}) and the carbonyl bands of 1 (at 1750–1800 cm^{-1}); the new



(1)

(1) For a review, see: Richter, R.; Ulrich, H. In "The Chemistry of Cyanates and Their Thio Derivatives"; Patai, S., Ed.; Wiley-Interscience: Chichester, England, 1977; p 756.
(2) Hagemann, H.; Ley, K. (Farbenfabriken Bayer A.-G.) Ger. Pat. 1 932 830, 1971.
(3) Farbenfabriken Bayer A.-G. French Dem. 2 016 469, 1970; *Chem. Abstr.* **1971**, *75*, 35397.
(4) Ottmann, G. F.; Hooks, H., Jr. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 672.
(5) Richter, R.; Ulrich, H. *Tetrahedron Lett.* **1974**, 1875.
(6) Maurer, R.; Heywang, G.; Hammann, I.; Homeyer, B. (Farbenfabriken Bayer A.-G.) Ger. Offen. DE 3 111 139, 1982; *Chem. Abstr.* **1983**, *98*, 16847.
(7) For a recent review on reactions of isothiocyanates, see: Drobnica, L.; Kristian, P.; Augustin, G. In "The Chemistry of Cyanates and Their Thio Derivatives", Patai, S., Ed.; Wiley-Interscience: Chichester, New York, 1977; p 1003.

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Table I. 2,2-Dichlorothiazolidine-4,5-diones 2 and 2,2-Dialkoxythiazolidine-4,5-diones 3[a]

2	R	mp (bp), °C	yield, %	^{13}C chemical shift[b] C-2	C-4	C-5	3	R′	mp, °C	yield, %	^{13}C chemical shift[b] C-2	C-4	C-5
a	CH_3	134–135	quant	94.08	154.41	178.75	a	CH_3	99–100	73	118.15	157.32	183.59
							b	C_2H_5	56–57	70	116.68	157.35	183.90
b	C_2H_5	(69–70/0.1 mm)	quant	93.82	154.32	178.93							
c	C_4H_9	(90/0.1 mm)	quant	93.93	154.52	178.78							
d	C_6H_{11}	86–87	quant	94.50	153.74	179.00	c	CH_3	93	95	118.92	156.73	183.83
e	$C_6H_5CH_2$	79–80	quant	93.85	155.02	178.56							
f	C_6H_5	145–146	25	93.25	154.61	178.79	d	CH_3	90–92	81	118.93	156.90	183.38
							e	C_2H_5	101–102	80	117.45	156.94	183.79
g	4-$CH_3OC_6H_4$	126–127 dec	23	93.61	154.71	178.99	f	CH_3	135–136	(low)	118.84	156.90	183.53

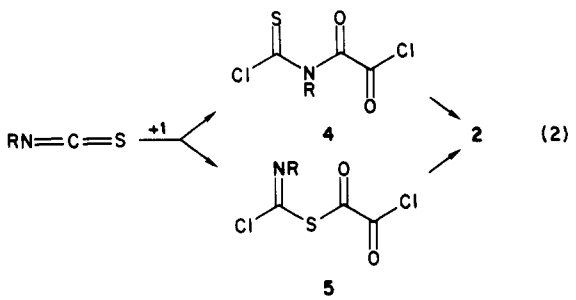
[a] Satisfactory combustion analytical data for C, H, N, and Cl (±0.3) were reported for compounds **2a-f** and **3a-f**, **2g** was partially hydrolyzed: calcd for $C_{10}H_7Cl_2NO_3S$: C, 41.12; H, 2.41; N, 4.79; Cl, 24.28. Found: C, 42.12; H, 2.60; N, 4.86; Cl, 22.10. [b] Samples dissolved in $CDCl_3$ with Me_4Si as internal standard.

adducts **2** show one characteristic intense carbonyl band at 1745–1750 cm^{-1} in the double-bond region.

All novel 2,2-dichlorothiazolidine-4,5-diones were obtained virtually free of byproducts; however, samples were purified by recrystallization or, as in the case of **2b** and **c**, distillation at reduced pressure. Overheating during distillation has to be avoided as it was found in the case of **2d** (R = C_6H_{11}) that heating to 120 °C led to partial dissociation into the starting materials (cyclohexyl isothiocyanate identified spectroscopically).

The cyclization of isothiocyanates with **1** is reminiscent of the formation of 1,3-disubstituted 2,2-dichloroimidazolidine-4,5-diones from *N,N′*-dialkyl- or diarylcarbodiimides and oxalyl chloride.[8,9]

Carbon 13 NMR spectra of all adducts of type **2** show signals at approximately 93 to 94.5 ppm downfield from Me_4Si for the carbons at position 2 of the heterocycle. This chemical shift value is well in agreement with the orthocarbonic acid structure of **2** but not with the open-chain forms **4** or **5** which have only C=O or C=N carbons (eq 2). As expected, the geminal chlorines of **2** are hydrolytically labile and are slowly hydrolyzed on exposure to moist air. Treatment of **2a** with water at room temperature leads readily to formation of 3-methylthiazolidine-2,4,5-trione (**6**)[10] in 50% yield.



Several of the cycloadducts **2** were treated with excess methanol or ethanol at room temperature, resulting in a rapid exchange of both chlorines by alkoxy groups to produce the novel 2,2-dialkoxythiazolidine-4,5-diones **3a–f** in moderate to good yield (see Table I). Immediate workup of the reaction mixture is necessary since prolonged contact of **3** with alcohol/HCl evidently leads to degradation of the heterocycle and thus lowering of the yield. The ^{13}C NMR shifts for the alkoxy group bearing carbons in position 2 of the thiazolidine ring are all found around 118 ppm. This downfield shift of about 24 ppm (from δ = 94 ppm) associated with the Cl/OR exchange in **2** is about equal in size in comparison with the chemical shift differences between CCl_4 (at 96.5 ppm) and $C(OCH_3)_4$ (at 120.9 ppm). ^{1}H NMR as well as ^{13}C NMR spectra of **3a,c,d** and **f** show each only one signal for the methoxy group.

The sensitivity of **2** toward water and alcohols is very much like the lability of the chlorines in 1,3-disubstituted 2,2-dichloroimidazolidine-4,5-dione (carbodiimide–oxalyl chloride adducts).[9] On the other hand, cycloadducts derived from isocyanates and oxalyl chlorides, identified to be 5,5-dichlorooxazolidine-2,4-diones (see Section 2 below), are relatively inert toward water and are also not altered by methanol (in absence of any base) on heating for several hours, showing a clear difference of reactivity of the chlorines in the 2 and 5 position on these heterocycles.

2. Isocyanate–Oxalyl Chloride Adducts. Mixtures of alkyl as well as aryl isocyanates and **1** were found to form molecular adducts on heating for a prolonged period of time. Absence of the characteristic NCO band in the IR spectra of the products shows clearly that addition of **1** takes place on the heterocumulene group. The solid product formed in quantitative yield from isopropyl isocyanate and **1** on heating an equimolar mixture for 20 h at 90–95 °C was identified as 3-isopropyl-5,5-dichloro-oxazolidine-2,4-dione (**8d**). Cyclohexyl isocyanate and **1** reacted similarly to give the corresponding cycloadduct **8g** in quantitative yield within 16 h at 95 °C, while *tert*-butyl isocyanate required 120 h of heating at 110 °C to produce 38% of adduct **8f** (see Table II). In each case progress of the reaction was followed by IR spectroscopy: disappearance of the C=O bands of **1** and the NCO band of the isocyanate coincides with the appearance of new characteristic bands for adducts of type **8** in the double-bond region at approximately 1845 and 1770 cm^{-1}.

Primary alkyl isocyanates and benzyl and aryl isocyanates react also with **1** yielding in each case a mixture of two adducts. Thus, heating *n*-propyl isocyanate and **1** (18 h, 90 °C) produces **8c** and **7c**. The intermediate **7c** has characteristic IR bands at 1720 and 1750 cm^{-1} and the ^{13}C NMR spectrum of the crude reaction mixture shows signals for three carbonyl carbons at 159.32, 159.10 and 152.29 ppm aside from signals for **8c**. Several attempts to separate the isomeric liquid adducts by fractional distillation failed. Extending the heating period during adduct formation leads to a gradual conversion of **7c** into **8c**, thus indicating that type **7** adducts are precursors of **8**. In all other cases where the presence of *N*-(chlorocarbonyl)-*N*-(chlorooxalyl)amines **7** was detected by IR spectroscopy (see Table II), the amounts formed were very small as judged by the intensity of the C=O bands. In no case were we able to isolate pure samples of the precursors **7** owing in part to their hydrolytic instability and

(8) Stachel, H. D. *Angew. Chem.* **1959**, *71*, 246.
(9) Ulrich, H.; Sayigh, A. A. R. *J. Org. Chem.* **1965**, *30*, 2781.
(10) This compound has been claimed to be formed from methyl *N*-methylthionocarbamate and oxalyl chloride on heating: Stoffel, P. J. U.S. Pat. 3 252 988, 1966, to Monsanto Co.; *Chem. Abstr.* **1966**, *65*, 3883.

Table II. 3-Alkyl- and 3-Aryl-5,5-dichlorooxazolidine-2,4-diones 8[d] from Alkyl(Aryl) Isocyanates and Oxalyl Chloride

8	R	reactn condn, °C/h	yield, %	mp (bp), °C	^{13}C NMR shifts (δ [ppm]) C-2	C-4	C-5
a	CH_3[a]	50–58/3	70	(90–92/12 mm)	164.00	149.45	99.17
b	C_2H_5[a]	50–58/3	62	46–47 (31–32/0.1 mm)	163.59	148.94	98.79
c	n-C_3H_7[a]	90/18	quant	(45–46/0.1 mm)	164.10	149.30	98.97
d	i-C_3H_7	90–95/20	quant	64	163.72	148.50	98.43
e	n-C_4H_9[a]	110/3.5	96	(58–60/0.1 mm)	164.03	149.26	98.92
f	t-C_4H_9	110/120	38	50–51	164.52	148.54	98.20
g	C_6H_{11}	95/16	quant	71–72	163.79	148.62	98.39
h	$C_6H_5CH_2$[a]	130/2	68	63–65	163.60	148.95	98.94
i	4-$CH_3OC_6H_4CH_2$[a]	95/2.5	95	(160–163/0.1 mm)	163.59	147.02	98.94
k	2-$ClC_6H_4CH_2$[a]	75/20	quant	88–89	163.35	148.66	98.80 (?)
l	C_6H_5[a]	125/17	53[c]	135–136	162.69	148.03	98.77
m	4-$CH_3C_6H_4$[a]	110/120	70	95–96	162.84	148.18	98.50
n	4-$CH_3OC_6H_4$	78–124/22	62	108–109	162.95	*b*	*b*

[a] Isomeric isocyanate–oxalylchloride adducts **7** are detectable in the reaction mixtures but converted to **8** toward the end of the reactions or during distillative workup. [b] Signals not detectable. [c] The reaction was carried out in a closed system. [d] Satisfactory analyses (±0.25 for C, H, N, Cl) were reported for all **8**.

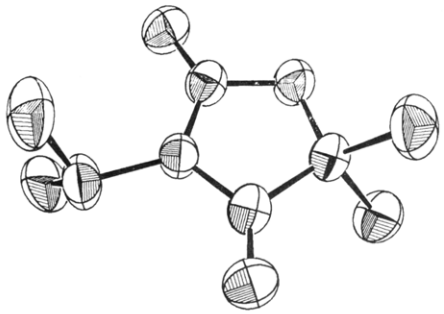
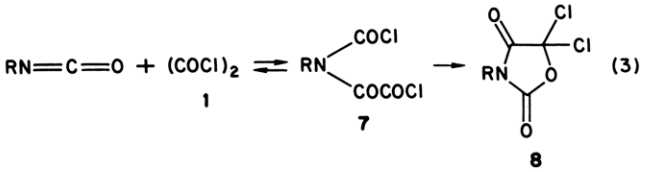


Figure 1. 3-Isopropyl-5,5-dichlorooxazolidine-2,4-dione.

tendency to rearrange on heating to the more stable adducts **8** (eq 3).

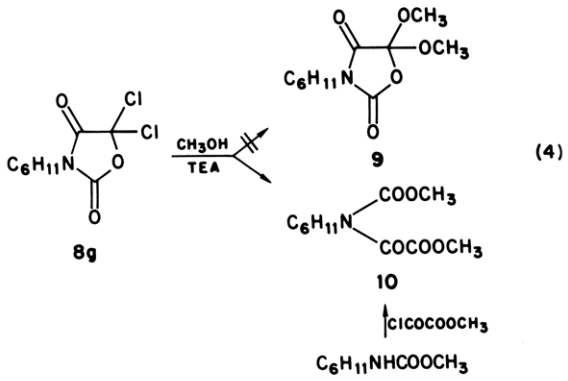


The formation of 5,5-dichlorooxazolidine-2,4-diones from aryl isocyanates and **1** was much slower than the reaction of aliphatic isocyanates and **1**. A mixture of phenyl isocyanate and **1** gave only a yield of 29% of **8l** after heating for 142 h at 80–110 °C. The yield was much improved (53%) on heating the components in a closed system at 125 °C for 17 h. Yields were higher and reaction times shorter with *p*-methoxyphenyl isocyanate probably due to increased electron density on the NCO group.

The ^{13}C NMR spectra of all 5,5-chlorooxazolidine-2,4-diones **8** show a characteristic signal for the chlorine bearing carbon at 98–99 ppm downfield from Me_4Si. A similar chemical shift value of 104 ppm has recently been reported for the CCl_2 carbon of 3,4,5,5-tetrachloro-3-oxolenone-2.[11] The two carbonyl carbons of all oxazolidinediones gave signals at approximately 148–149 ppm (C-4) and 164–165 ppm (C-2). Spectra of mixtures containing *N*-(chlorocarbonyl)-*N*-(chlorooxalyl)amines **7** show additional carbonyl carbon signals, one at 152 and two at 159–160 ppm.

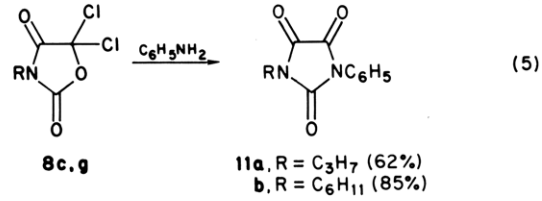
5,5-Dichlorooxazolidine-2,4-diones **8** are much less susceptible to hydrolysis than 2,2-dichlorothiazolidine-4,5-diones, derived from **1** and isothiocyanates. Treatment of **8l** (R = C_6H_5) with methanol in absence of acid or base also does not alter this molecule. In presence of triethylamine (TEA), however, the ring is cleaved to yield phenyl isocyanate and dimethyl oxalate. Evidence for the formation of 5,5-dimethoxy-3-phenyloxazolidine-2,4-dione as an intermediate was not obtained. In excess methanol with *p*-toluenesulfonic acid as a catalyst, dimethyl oxalate and methyl phenylcarbamate were the only products.

Ring opening was also observed on treatment of **8g** (R = cyclohexyl) with methanol/TEA although the product in this case was methyl *N*-cyclohexyl-*N*-(methoxycarbonyl)oxamate (**10**) (eq 4). The ^{1}H NMR spectrum of



10 shows two methyl signals (at 3.90 and 3.95 ppm) and the ^{13}C NMR spectrum three carbonyl carbon signals (between 154 and 163 ppm), which definitely rules out a cyclic product **9** with geminal methoxy groups. **10** was also obtained by reacting methyl cyclohexylcarbamate with methyloxalyl chloride.

Treatment of **8c** (R = C_3H_7) and **8g** with aniline gave the corresponding 1-alkyl-3-phenylimidazolidine-2,4,5-triones **11a,b** in high yield (eq 5). Formation of these

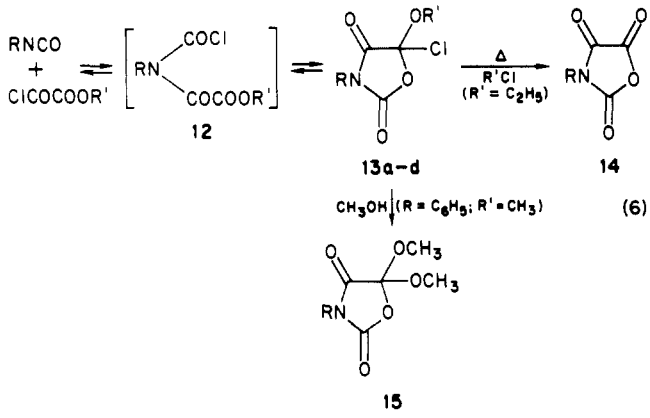


heterocycles most likely involves ring opening and closing steps related to the chlorine exchange by amino groups on isobenzofuran derivative.[12]

(11) Kimpenhaus, W.; Auf der Heide, W. *Liebigs Ann. Chem.* **1983**, 378.

(12) Kubota, Y.; Tatsuno, T. *Chem. Pharm. Bull.* **1971**, *19*, 1226.

3. Isocyanate–Alkyloxalyl Chloride Adducts. Alkyl and aryl isocyanates were also found to give adducts with methyl- and ethyloxalyl chloride on heating the components at 95 °C or above. Based on IR and ^{13}C NMR spectroscopic comparison with cycloadducts of type **8**, it became apparent that these adducts are 3-alkyl(aryl)-5-chloro-5-alkoxyoxazolidine-2,4-diones **13** and are also formed in a stepwise cyclization quite similar to the oxalyl chloride reactions. Here too alkyl isocyanates were found to react much faster than phenyl isocyanate. Isopropyl isocyanate required only 18 h of heating with ethyloxalyl chloride to produce 83% of **13b** while adduct **13c** (R = C_6H_5) was obtained in only 69% yield after heating phenyl isocyanate with methyloxalyl chloride for 120 h (eq 6).

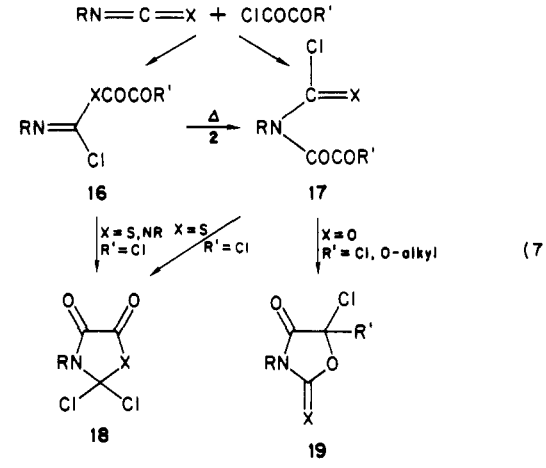


The IR spectra of the novel liquid and solid adducts **13** show two characteristic bands in the double-bond region at 1840 cm^{-1} (weak) and 1750–1760 cm^{-1} (strong). IR spectra taken during the reactions showed no evidence for the presence of intermediates of type **12**. The C-5 signal of the heterocycles is found at 109 ppm in the ^{13}C NMR spectra which is in agreement with the proposed cyclic structure. The liquid or low melting 5-chloro-5-alkoxyoxazolidine-2,4-diones were purified by distillation at reduced pressure without noticeable decomposition although prolonged heating of **13b** (R = *i*-C_3H_7, R' = C_2H_5) to 90 °C lead to partial dissociation back to the starting materials and at the same time to partial loss of ethyl chloride and formation of 3-isopropyloxazolidine-2,4,5-trione **14**. Treatment of **13c** (R = C_6H_5, R' = CH_3) with excess methanol results in exchange of the chlorine within minutes, affording 5,5-dimethoxy-3-phenyloxazolidine-2,4-dione (**15**). This facile Cl/CH_3O exchange is strikingly different from the behavior of 5,5-dichloro-3-phenyloxazolidine-2,4-dione (**8l**) toward methanol, which lead under basic as well as acidic conditions to ring degradation. It appears likely that the exchange of the first chlorine in **8l** to the monomethoxy derivative **13c** is much slower than the succeeding steps leading to **15** and subsequently to dimethyl oxalate and phenyl isocyanate (or methyl phenylcarbamate).

The introduction of a second methoxy group in position 5 on **15** induces a further downfield shift of the carbon-13 NMR signal to 112.5 ppm. This value compares well with orthocarbonic acid derivatives, such as tetramethyl orthocarbonate and 2,2-dimethoxy-3-phenylthiazolidine-4,5-dione (**3d**) which show chemical shifts of 120.9 and 118.9 ppm, respectively, for the central carbons. As expected, **15** has only one CH_3 signal in the ^1H NMR spectrum for the identical methoxy groups.

The structures assigned to adducts **8** and **13** based on ^{13}C NMR spectroscopic evidence were further supported by X-ray crystallographic analysis. The isopropyl derivative **8d** was shown to have both chlorines attached to carbon 5 and not to carbon 2 (see Figure 1).[13]

4. Cyclization Mechanism. The structural differences between (alkyl) oxalyl chloride adducts derived from isothiocyanates and isocyanates clearly indicate a difference in the cyclization mechanisms. As has been pointed out earlier, the cyclization of isothiocyanates with **1** is closely related to the formation of 1,3-disubstituted 2,2-dichloroimidazolidine-4,5-dione from carbodiimides and **1**. In each case the orthocarbonic acid derivatives are formed with both double bonds of the heterocumulene participating in the cyclization. Initial attack of **1** on isothiocyanates could take place on either the C=S or C=N bond and give intermediates **16** or **17** (X = S) on the way to **18** (see eq 7). Ring closure to adducts of type **18** can take



place on either of these precursors. It has been documented that both double bonds of isothiocyanates are indeed capable of selectively reacting with a number of substrates, and we believe that initial attack of **1** takes place only on the C=N bond. Our assumption is based on the observation that the C=S group in carbon disulfide is not attacked by **1** at room temperature (molar mixtures remained unchanged for 14 days). The isocyanate–oxalyl chloride reactions could also involve both linear adducts **16** and **17** (X = O, R' = Cl); however, if indeed an O-acylated product is formed, rapid rearrangement to the N-acylated intermediate **17** (R' = Cl) is likely. The final cyclization **17** → **19** is brought about by attack of one electrophilic chlorocarbonyl group on the oxygen of another such group followed by Cl migration. This step is reminiscent of a cyclization involving N,N-disubstituted α-chloro- or α-phenylacetamide and **1**, yielding 5-amino-2,2-dichloro-(2*H*)furan-3-ones.[14] It has also been pointed out that certain dicarboxylic acid dichlorides may exist in an isomeric, cyclic form (2,2-dichlorofuran-5-one derivatives);[15] perchloro crotonylchloride was found to isomerize on heating in presence of catalysts to yield hexachlorodihydrofuran.[16] In this context it might be added, that the recently described addition of dimethyl dithionooxalate to *N,N'*-dialkylcarbodiimides, which yields 4,4-dimethoxyimidazolidine-2,5-dithiones, is likely to proceed via a related cyclization mechanism, although the authors[17]

(13) X-ray crystallographic services were performed by Molecular Structure Corp., College Park Station, TX. Tables of crystallographic data, information about the methodology, full experimental details (crystal data, intensity measurements), and bond distances and angles are available as supplementary material.

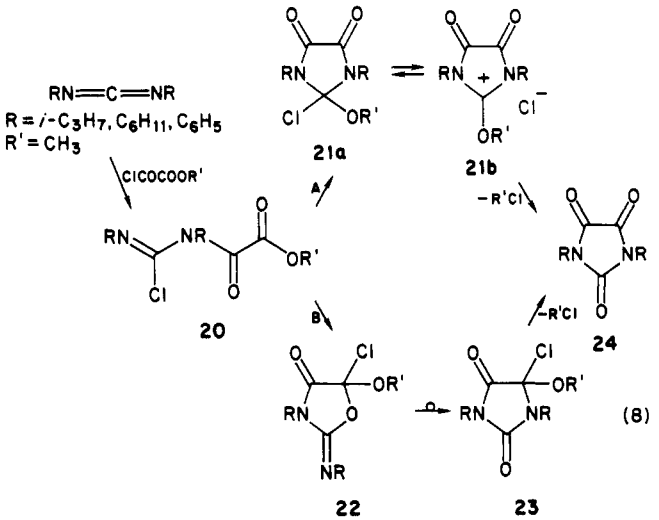
(14) Speziale, A. J.; Smith, L. R.; Fedder, J. E. *J. Org. Chem.* **1965**, *30*, 4303.

(15) Reinheckel, H.; Haage, K.; Gensike, R. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 785. Ott, K. *Liebigs Ann. Chem.* **1912**, *392*, 245. Cason, J.; Reist, E. *J. Org. Chem.* **1958**, *23*, 1492.

(16) Maass, G. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 787.

suggest a very different one involving a four-membered-ring intermediate. A related Cl migration during formation of a five-membered-ring heterocycle was described recently which involves a reaction between isocyanates, isothiocyanates, and sulfuryl chloride.[18]

We believe that the 5-chloro-5-alkoxyoxazolidine-2,4-diones **13** are also formed via a pathway as shown in eq 7 with RO as migrating groups. For comparison we tried to react isothiocyanates and carbodiimides with alkyloxalyl chloride to see which type of adduct (**18** or **19**) would be formed. No adduct was obtained from methyl isothiocyanate and methyloxalyl chloride; *N,N'*-diphenylcarbodiimide, on the other hand, reacted exothermically in chloroform solution (eq 8). The initially formed adduct,



believed to be **20**, has bands at 1660, 1715 (both strong), and 1745 cm^{-1} (weak) in the double bond region of its IR spectrum. This compound decomposes within hours in solution to afford 1,3-diphenylimidazolidine-2,4,5-trione (**24**, R = C_6H_5) in virtually quantitative yield.

Much slower is the corresponding reaction between *N,N'*-diisopropylcarbodiimide and methyloxalyl chloride which can be followed by ^{13}C NMR spectroscopy. The complexity of the spectrum during the process is evidence for the involvement of several intermediates: a transient signal at 111.0 ppm is indicative of formation of an orthocarbonic acid derivative of type **21** (see eq 8). These compounds are expected to be labile since ureas are not known to be alkylated by R'Cl, hence loss of methyl chloride will lead to **24**. Cyclization to **21** is coupled with CH_3O migration. A related case of PhO or PhS group migration during cyclization of *N*-(benzoylformyl)-*N*-[(phenylthio)carbonyl]amines or phenyl *N*-(benzoylformyl)-*N*-phenylurethane has been reported recently.[19] An alternative pathway B leading to **24** can almost certainly be ruled out. Although cyclization to **22** (in analogy to isocyanate–oxalyl chloride ring closure) as well as Dimroth rearrangement to **23** is feasible, loss of R'Cl is unlikely to occur at room temperature.

On comparing the experimental results of all these addition reactions, it becomes apparent that the course of cyclization, taking place between heterocumulene and **1** or alkyloxalyl chloride, is determined largely by the nucleophilicity of the two double bonds of the N=C=X group: electron rich =S and =NR attached to the C=N group favor the participation of both double bonds in the formation of the cycloadduct **18** while isocyanates react only on the C=N group to yield **19**.

Experimental Section

Infrared spectra were recorded on a Beckman Acculab 4 spectrophotometer with chloroform as medium; ^1H NMR spectra were determined on a Varian T60 spectrometer and ^{13}C NMR spectra on a Varian CFT-20 spectrometer with $CDCl_3$ as solvent and Me_4Si as internal standard; elemental analyses were performed by Galbraith Laboratories, Knoxville, TN; melting points are uncorrected.

General Procedure for the Preparation of 2,2-Dichlorothiazolidine-4,5-diones 2a–g. Mixtures of equimolar amounts of alkyl or aryl isothiocyanate and **1** in the range of 0.01 to 0.1 mol are kept at room temperature in a flask fitted with a drying tube ($CaCl_2$) while the progress of the reactions is periodically checked by IR spectroscopy: The bands at 2100–2200 cm^{-1} (N=C=S) will disappear completely and the broad double band at 1750–1800 cm^{-1} for **1** will change as the adducts are formed which show a sharp band at 1750 cm^{-1} only. In the case of methyl or ethyl isothiocyanates, the reactions are over within hours. Benzyl, *n*-butyl, and cyclohexyl isothiocyanates require from 4–6 days to be converted to the adducts which in most cases is indicated by solidification of the flask content. The reaction mixtures of phenyl or *p*-methoxyphenyl isothiocyanate and **1** are kept for 25 and 40 days, respectively, during which time crystals will separate.

Solid or partially solidified products are treated with *n*-hexane (to remove traces of unchanged starting materials) and filtered; samples for analytical purposes are reprecipitated from $CHCl_3$/*n*-hexane or recrystallized from *n*-hexane. Liquid products are distilled at reduced pressure; melting points and boiling points are given in Table I.

3-Methylthiazolidine-2,4,5-trione (6).[10] A sample of 4.0 g (0.02 mol) of **2a** is suspended in 20 mL of water. On stirring the suspension rapidly, the starting material changes visibly without going into solution. Filtration after 15 min, brief washing of the residue with cold water, and drying at 45–50 °C leaves 1.50 g (51%) of colorless crystals: mp 102–107 °C ($CHCl_3$/*n*-hexane); IR ($CHCl_3$) 1715 cm^{-1} (C=O). Anal. Calcd for $C_4H_3NO_3S$: C, 33.12; H, 2.08; N, 9.66. Found: C, 33.36; H, 2.14; N, 9.73.

General Procedure for the Preparation of 2,2-Dialkoxythiazolidine-4,5-diones 3a–f. Samples of the 2,2-chlorothiazoline-4,5-diones **2** in the range of 1.0 to 3.0 g are treated with approximately 10 to 30 mL each with methanol or ethanol while the reaction flasks are immersed in an ice bath. The starting materials are dissolved rapidly followed occasionally by precipitation of products **3**. Diluting the reaction mixtures after 5 to 7 min with ice water causes precipitation of the dialkoxythiazolidinediones as crystalline solids. Samples of the products are purified for elemental analysis by recrystallization from hexane: yield, mp, and ^{13}C chemical shifts of ring carbons are given in Table I. IR spectra show one strong carbonyl band between 1725 and 1740 cm^{-1}; the band at higher wavenumber will often have a shoulder at 1710/1720 cm^{-1}. This trend is reversed in the case of **3e** where the strongest band appears at 1710 and a weaker shoulder at 1735 cm^{-1}.

General Procedure for the Preparation of 3-Alkyl- and 3-Aryl-5,5-dichlorooxazolidine-2,4-diones 8. Alkyl, benzyl, and aryl isocyanates are mixed each with equimolar amounts of **1** in the range of 0.1 to 0.2 mol each and heated for a duration as given in Table II. Progress of the reactions is frequently checked by IR spectroscopy in following the decrease or complete disappearance of characteristic bands of the starting materials (N=C=O at 2260–2280 cm^{-1}, C=O of **1** at 1750–1800 cm^{-1}). Reactions carried out with aryl isocyanates are terminated before all the starting materials have been converted. In cases where adducts of type **7** are also formed as precursors of **8**, heating is continued after the starting materials have been consumed until the IR bands of **7** in the double-bond region (at 1720 and 1750 cm^{-1}) have disappeared or reached a minimum. Methyl isocyanate and **1** are reacted at room temperature but the cycloaddition is completed by brief heating to 50–58 °C. The mixture of phenyl isocyanate and **1** is kept in an autoclave at 125 °C for 18 h to speed up the adduct formation. Unreacted starting materials are re-

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Table III. 3-Alkyl- and 3-Aryl-5-chloro-5-alkoxyoxazolidine-2,4-diones 13[e] from Alkyl(Aryl) Isocyanates and Alkyloxalyl Chlorides

13	R	R′	yield, %	mp (bp), °C	^{13}C NMR shifts (δ [ppm]) C-2	C-4	C-5
a	i-C_3H_7	CH_3	44[a]	(56–58/0.1 mm)	163.52	149.66	109.66
b	i-C_3H_7	C_2H_5	83[b]	(66–67/0.1 mm)	163.48	149.56	109.06
c	C_6H_5	CH_3	69[c]	48–50 (112–114/0.1 mm)	162.29	148.91	109.81
d	C_6H_5	C_2H_5	28[d]	65–66	162.48	149.09	109.35

[a] Components kept at 70–75 °C for 75 h. [b] Components kept at 90–95 °C for 18 h. [c] Components kept at 140–145 °C for 120 h. [d] Components kept at 130–140 °C for 54 h. [e] Satisfactory analyses (±0.35 for C, H, N, Cl) were reported for all **13**.

moved by distillation and the crude products are purified by distillation or recrystallization from n-hexane or chloroform/n-hexane (see Table II for yields and spectral data).

Ring Opening of 8l (R = C_6H_5) and 8g (R = C_6H_{11}) with Methanol. 1. An ice-cooled solution of 2.45 g (0.01 mol) of **8l** in 40 mL of chloroform is treated dropwise with a solution of 0.65 g (0.02 mol) of methanol and 2.0 g (0.02 mol) of triethylamine in 10 mL of chloroform over a period of 45 min, and the mixture is kept for another hour at ice-bath temperature. Infrared analysis of the reaction solution indicates that all of the **8l** has reacted; strong bands at 2280 cm^{-1} (NCO) and at 1770 and 1745 cm^{-1} (C=O) are evidence for the formation of phenyl isocyanate and dimethyl oxalate; a mixture of authentic samples of these compounds gives spectral patterns identical with those of the products.

2. A suspension of 2.45 g (0.01 mol) of **8l** in 25 mL of methanol is treated with a crystal of p-toluenesulfonic acid and briefly heated to reflux to dissolve the starting material. The resulting solution is kept at room temperature for 18 h after which excess methanol is removed in vacuo, leaving a tan oil consisting of methyl phenylcarbamate (NH at 3420 and C=O at 1740 cm^{-1}) and dimethyl oxalate according to IR evidence; spectral comparison with authentic samples verified the identity of the products.

3. A solution of 1.28 g (0.04 mol) of methanol and 4.00 g (0.04 mol) of triethylamine in 10 mL of chloroform is added dropwise with stirring over a period of 1 h to 5.00 g (0.02 mol) of **8g**, dissolved in 30 mL of chloroform, at ice-bath temperature. The resulting mixture is allowed to reach room temperature and is kept for 24 h after which it is extracted several times with water to remove triethylamine hydrochloride. IR spectra of the resulting $CHCl_3$ solution show traces of phenyl isocyanate (2280 cm^{-1}). Evaporation of solvent and vacuum distillation yields 2.50 g (50%) of methyl N-(cyclohexyl)-N-(methoxycarbonyl)oxamate (**10**): bp 98–100 °C (0.1 mm); IR ($CHCl_3$) 1700, 1740 cm^{-1} (C=O). Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.34; H, 7.05; N, 5.83. A small amount of a forerun is collected which solidifies in the receiver and is identified as dimethyl oxalate, mp 50–54 °C.

Authentic **10** is prepared from 7.8 g (0.05 mol) of methyl cyclohexylcarbamate and 7.0 g (0.057 mol) of methyloxalyl chloride at room temperature (330 h). The crude reaction product is purified by distillation, affording 10.7 g (88%) of **10**, bp 100 °C (0.1 mm), identical in IR comparison with material obtained above.

1,3-Disubstituted Imidazolidine-2,4,5-triones 11a and 11b. 1. To a solution of 2.12 g (0.01 mol) of **8c** in 20 mL of chloroform is added dropwise with stirring 2.79 g (0.03 mol) of aniline. The reaction is exothermic and accompanied by formation of aniline hydrochloride. The mixture is kept at room temperature for 18 h after which it is heated to reflux for 4 h. Removal of solvent in vacuo leaves a semisolid residue which is taken up in methanol. Gradual addition of water leads to precipitation of 1.45 g (62%) of **11a**: mp 72–73 °C (from methanol/water); IR ($CHCl_3$) 1745 cm^{-1} (C=O). Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.24; H, 5.15; N, 12.08.

2. 1-Cyclohexyl-3-phenylimidazolidine-2,4,5-trione (**11b**) is prepared similarly in methanolic solution and obtained in 82% yield: mp 149 °C (lit.[20] mp 149 °C); IR ($CHCl_3$) 1735 cm^{-1} (C=O); identical in IR comparison with authentic material prepared from N-cyclohexyl-N'-phenylurea and **1**.[9]

General Procedure for the Preparation of 3-Alkyl-(aryl)-5-chloro-5-alkoxyoxazolidine-2,4-diones 13. Equimolar mixtures of isopropyl or phenyl isocyanate with methyl- or ethyloxalyl chloride in the range of 0.1 to 0.3 mol are maintained at 90 to 145 °C for 6 to 120 h. Reactions with isopropyl isocyanate lead to a nearly complete disappearance of the starting materials in the reaction mixtures (according to IR evidence) while those with phenyl isocyanate are incomplete even after 120 h. After terminating the cyclizations, unchanged starting materials are distilled off at reduced pressure and the residual adducts are either taken up in n-hexane (solids) and isolated by filtration or distilled in vacuo (see Table III for yields and spectral data). In the case of **13a** and **b** excessive heating beyond the completion of the reaction has to be avoided since loss of methyl or ethyl chloride will lead to formation of 3-isopropyloxazolidine-2,4,5-trione (see below).

Thermolysis of 3-Isopropyl-5-chloro-5-ethoxyoxazolidine-2,4-dione (13b). A sample of 8.0 g (0.036 mol) of **8b** is kept at 180–190 °C in a flask equipped with a short distillation head. Isopropyl isocyanate (2.45 g) is collected in the receiver over a period of 5 h. The liquid flask residue (4.45 g) is first distilled at aspirator vacuum (bp 29–30 °C, yield 2.20 g, mixture of isopropyl isocyanate and ethyloxalyl chloride) and later at oil pump vacuum to yield 0.80 g of 3-isopropyloxazolidine-2,4,5-trione (**14**); bp 63–65 °C (0.1 mm), which solidifies: mp 89–90 °C (n-hexane); IR ($CHCl_3$) 1770 (strong), 1820 cm^{-1} (C=O). Anal. Calcd for $C_6H_7NO_4$: C, 45.86; H, 4.49; N, 8.92. Found: C, 45.58; H, 4.73; N, 8.76.

A sample of **14** is obtained in quantitative yield on mixing 0.01 mol each of methyl isopropylcarbamate and **1** at room temperature (48 h) in analogy to a literature procedure for preparation of other oxazolidine-2,4,5-triones.[21] A gas evolves from the liquid which slowly solidifies; the solid is broken up with n-hexane and the product is isolated by filtration; the material is identical in spectral and mp comparison with **14** prepared above.

3-Phenyl-5,5-dimethoxyoxazolidine-2,4-dione (15). On dissolving 1.0 g (0.004 mol) of **13c** in 10 mL of methanol an exothermic reaction takes place. After 3 min the mixture is diluted with water causing separation of colorless crystals which are collected by filtration: 0.5 g (51%); mp 74–75 °C (n-hexane); IR ($CHCl_3$) 1835 (weak), 1765 cm^{-1} (C=O); ^{13}C NMR ($CDCl_3$) 112.53 (C-5), 150.67 (C-4), 164.05 ppm (C-2). Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.69; H, 4.67; N, 5.91. Found: C, 55.71; H, 4.78; N, 5.99.

Addition of Methyloxalyl Chloride to Carbodiimides. An exothermic reaction takes place on mixing 6.0 g (0.03 mol) of N,N'-diphenylcarbodiimide with 3.70 g (0.03 mol) of methyloxalyl chloride in 30 mL of chloroform. IR spectra taken immediately after mixing fail to show the characteristic N=C=N band at 2160 cm^{-1} while bands in the double-bond region at 1660, 1715, and 1745 cm^{-1} (weak) indicate adduct formation. After 48 h, the spectrum of the mixture shows a decrease of the bands at 1660 and 1715 cm^{-1} while the one at 1745 cm^{-1} gains in intensity. Brief heating to 60–65 °C speeds up this process; the flask content solidifies to yield 6.50 g (81%) of 1,3-diphenylimidazolidine-2,4,5-trione (**24**, R = C_6H_5), mp 203–204 °C (lit.[22] mp 204 °C). The reactions between N,N'-diisopropyl- or N,N'-dicyclohexylcarbodiimide with methyloxalyl chloride are performed similarly. To speed up the conversion of the intermediate adducts, heating (after removal of solvent) to 120 °C for a brief period is required; 1,3-diisopropylimidazolidine-2,4,5-trione (**24**, R = i-C_3H_7) (88%), mp 90 °C (lit.[8] mp 93 °C); 1,3-dicyclohexylimidazolidine-2,4,5-

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trione (86%), mp 172–174 °C (lit.[9] mp 174–175 °C).

Registry No. 1, 79-37-8; **2a**, 91466-83-0; **2b**, 91466-84-1; **2c**, 91466-85-2; **2d**, 91466-86-3; **2e**, 91466-87-4; **2f**, 91466-88-5; **2g**, 91466-89-6; **3a**, 91466-90-9; **3b**, 91466-91-0; **3c**, 91466-92-1; **3d**, 91466-93-2; **3e**, 91466-94-3; **3f**, 91466-95-4; **6**, 6495-70-1; **7a**, 91466-96-5; **7b**, 91466-97-6; **7c**, 91466-98-7; **7e**, 91466-99-8; **7h**, 91467-00-4; **7i**, 91467-01-5; **7k**, 91467-02-6; **7l**, 91467-03-7; **7m**, 91467-04-8; **8a**, 91467-05-9; **8b**, 91467-06-0; **8c**, 91467-07-1; **8d**, 91467-08-2; **8e**, 91467-09-3; **8f**, 91467-10-6; **8g**, 91467-11-7; **8h**, 91467-12-8; **8i**, 91467-13-9; **8k**, 91467-14-0; **8l**, 91467-15-1; **8m**, 91467-16-2; **8n**, 91467-17-3; **10**, 91467-18-4; **11a**, 91467-19-5; **11b**, 30593-00-1; **13a**, 91467-20-8; **13b**, 91467-21-9; **13c**, 91467-22-0; **13d**, 91467-23-1; **14**, 91467-24-2; **15**, 91467-25-3; **20** (R = Ph, R′ = Me), 91467-26-4; **21a** (R = $CHMe_2$, R′ = Me), 91467-27-5; **21b** (R = $CHMe_2$, R′ = Me), 91467-28-6; **24** (R = Ph), 6488-59-1; **24** (R = $CHMe_2$), 3621-68-9; **24** (R = C_6H_{11}), 3621-71-4; CH_3-NCS, 556-61-6; C_2H_5-NCS, 542-85-8; C_4H_9-NCS, 592-82-5; C_6H_{11}-NCS, 1122-82-3; $C_6H_5CH_2$-NCS, 622-78-6; C_6H_5-NCS, 103-72-0; 4-$CH_3OC_6H_4$-NCS, 2284-20-0; CH_3-NCO, 624-83-9; C_2H_5-NCO, 109-90-0; C_3H_7-NCO, 110-78-1; *iso*-C_3H_7-NCO, 1795-48-8; C_4H_9-NCO, 111-36-4; *t*-C_4H_9-NCO, 1609-86-5; C_6H_{11}-NCO, 3173-53-3; $C_6H_5CH_2$-NCO, 3173-56-6; 4-$CH_3OC_6H_4CH_2$-NCO, 56651-60-6; 2-$ClC_6H_4CH_2$-NCO, 55204-93-8; C_6H_5-NCO, 103-71-9; 4-$CH_3C_6H_4$-NCO, 622-58-2; 4-$CH_3OC_6H_4$-NCO, 5416-93-3; dimethyl oxalate, 553-90-2; methyl phenylcarbamate, 2603-10-3; methyl cyclohexylcarbamate, 5817-68-5; aniline, 62-53-3; methoxalyl chloride, 5781-53-3; ethoxalyl chloride, 4755-77-5; methyl isopropylcarbamate, 5602-90-4; *N,N′*-diphenylcarbodiimide, 622-16-2; *N,N′*-diisopropylcarbodiimide, 693-13-0; *N,N′*-dicyclohexylcarbodiimide, 538-75-0.

Supplementary Material Available: Tables of crystallographic data, information about methodology, full experimental details, and bond distances and angles for 8 (12 pages). Ordering information is given on any current masthead page.

Synthesis of DL-Slaframine

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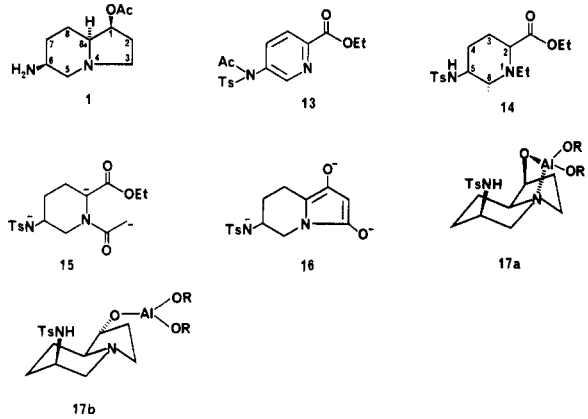
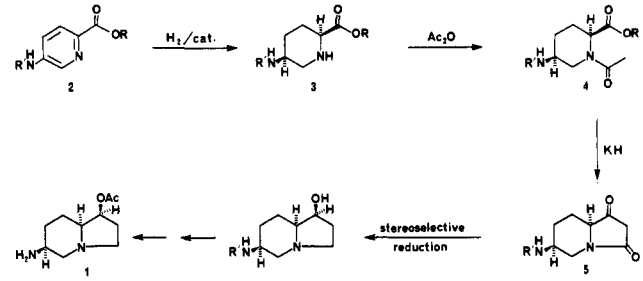
A stereoselective synthesis of DL-slaframine (1) is described, beginning with ethyl 5-nitropicolinate (6). The key step is formation of the octahydroindolizine nucleus via a potassium hydride cyclization of *N*-acetylpipecolate ester 8 to give β-keto lactam 9. Relative stereochemistry of C-6 and C-8a of 1 is set during catalytic reduction of picolinate ester 2, and this cis relationship of substituents is retained during the cyclization process. The relative configuration of C-1 is established via a stereoselective reduction of β-keto lactam 9 with L-Selectride (Aldrich). The yield of slaframine obtained from 6 is 12%.

The mycotoxin slaframine (1), produced by *Rhizoctonia leguminicola*, has been of interest since its isolation and identification as the agent responsible for excessive salivation in livestock consuming mold-infested legume feeds.[1]



The structure,[2] biosynthesis,[3] and metabolism[3a] of this alkaloid have been studied. Slaframine is of interest as a stimulator of the parasympathomimetic exocrine glands.

Scheme I. General Synthetic Approach



Studies have indicated that the stimulation is brought about by a metabolite of slaframine rather than by the alkaloid itself.

Three syntheses of DL-slaframine have been published. The initial one, reported in 1970 by Rinehart and coworkers, was based on the catalytic reduction of an appropriately substituted picolinic acid derivative followed by a potassium *tert*-butoxide catalyzed cyclization to close the five-membered ring.[4] This synthesis lacked stereoselectivity, giving a mixture of all possible diastereoisomers; the overall yield of slaframine was less than 0.1%. Subsequent work in Rinehart's laboratory by Christophel produced some improvements in the synthesis, most notably in the preparation of the key picolinate.[5] In 1973, Gensler and Hu published a stereoselective synthesis based on glutamic acid in which both rings were formed by Dieckmann cyclizations and the requisite cis,cis stereochem-

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