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2-ARYL-4-METHYL-4-CHLOROCARBONYL-OXYMETHYL-2-OXAZOLINES

CHEMICAL REACTIVITY AND INFRA-RED SPECTRA

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Abstract—2-Aryl-4-methyl-4-chlorocarbonyl-oxymethyl-2-oxazolines have been shown to exhibit a particular reactivity towards nucleophilic reagents. This reactivity is to be attributed to the presence of the chlorocarbonic ester function. Reaction of the above 2-oxazolines with ammonia (or dimethylamine) results in ring opening, with the formation of benzamide (or N,N-dimethyl-benzamide) and 4-methyl-4-chloromethyl-oxazolidin-2-one (or 4-methyl-4-N,N-dimethylaminomethyl-oxazolidin-2-one). The presence of the chlorocarbonic ester function also affects the position of the C=N band in the infra-red spectrum of these 2-oxazoline derivatives; this band is shifted approximately 40 cm^{-1} towards lower wavelengths in comparison with the absorption band of structurally related compounds which do not possess the chlorocarbonic ester group. A possible reaction mechanism is proposed together with a correlation of the chemical and spectroscopical findings.

2-Aryl-4-methyl-4-chlorocarbonyl-oxymethyl-2-oxazolines (I) are stable, crystalline compounds. The presence of a chlorocarbonate group, however, confers on these oxazoline a rather remarkable chemical reactivity.

As previously reported,[1] these chlorocarbonates on heating with water undergo a complex reaction, giving the corresponding 4-methyl-4-aroyl-oxymethyl-oxazolidin-2-one (II).

While in the above reaction no fragmentation occurs except for the splitting of one mole of hydrogen chloride, the action of cold aqueous ammonia or dimethylamine results in the degradation of the oxazoline ring, benzamide or N,N-dimethyl-benzamide having been obtained quantitatively.

Under anhydrous conditions, carbamates (III) are obtained if the chlorocarbonates (I) react for long time at room temperature with a small excess of ammonia.[2] However, even under these mild conditions, a partial attack on the oxazoline ring occurs. In the case of the 2-*p*-chlorophenyl-4-methyl-4-chlorocarbonyl-oxymethyl-2-oxazoline (Ib), careful chromatographic separation showed that *p*-chlorobenzamide is present in small quantities, together with the corresponding carbamate (IIIb) and about 50 per cent of the unreacted starting material.

The course of the reaction, and consequently, the yield of the different carbamates, seem to depend on ammonia concentration and reaction time, rather than on temperature.

The relative stability of these chlorocarbonates towards nucleophilic reagents seems also to depend on the substituents in the benzene ring. When compound Ib reacts with excess ammonia under anhydrous conditions, the corresponding carbamate (IIIb) is formed in 50 per cent yield. On the contrary, chlorocarbonate (Ic)

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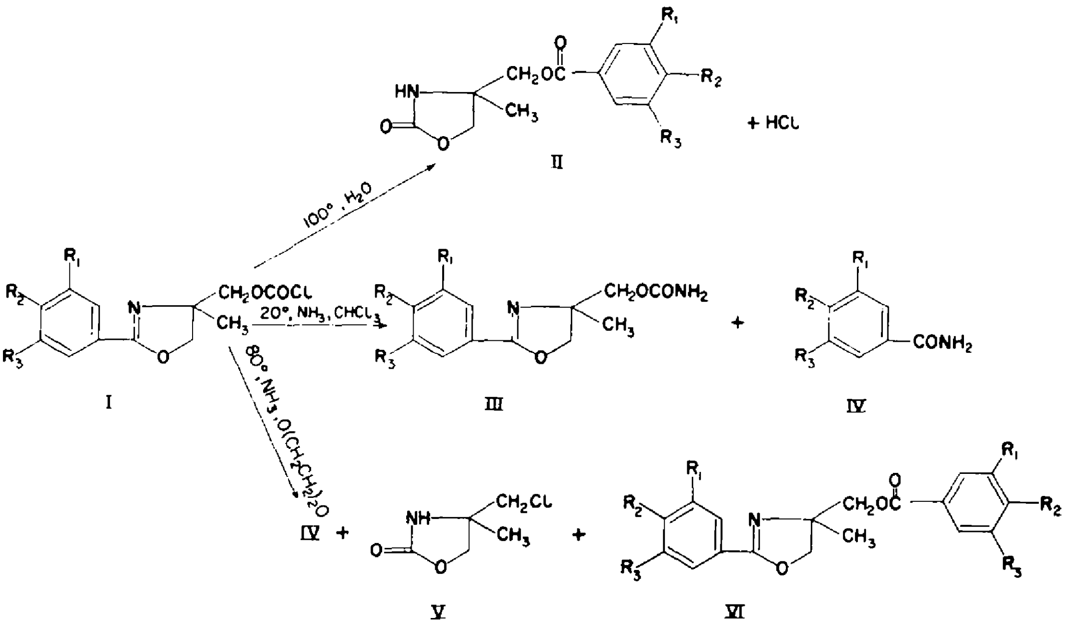
[1] V. Rosnati and D. Misiti, *Gazz. Chim. Ital.* **90**, 162 (1960).
[2] V. Rosnati and D. Misiti, *Gazz. Chim. Ital.* **90**, 171 (1960).



Ia, IIa, IIIa, IVa, VIa : R₁, R₂, R₃=H
Ib, IIb, IIIb, IVb, VIb : R₁, R₃=H R₂=Cl
Ic, IIc, IIIc IVc : R₁, R₂, R₃=OCH₃

under similar conditions yields no carbamate but instead 3,4,5-trimethoxy-benzamide is obtained quantitatively.

As the formation of benzamide or substituted benzamides accounts for only a part of the total chlorocarbonate, a careful study resulted in the isolation of other products and led to a theory of a possible reaction mechanism.

The chlorocarbonates Ia, Ib, Ic when treated with a large excess of ammonia in anhydrous dioxane, undergo complete degradation of the oxazoline ring, yielding in all cases benzamide (or substituted benzamides) and a new compound $C_5H_8ClNO_2$.

The latter compound is neutral with the chlorine easily removable by treatment with alkaline carbonates. Its infra-red spectrum shows a strong band at 1764 cm^{-1} (suggesting the presence of a carbonyl group in a five-membered lactone ring) and a weak band at 3484 cm^{-1}, in the region of the N—H absorption. On the basis of chemical and spectroscopical data, compound $C_5H_8ClNO_2$ was identified as 4-methyl-4-chloromethyl-oxazolidin-2-one (V), not yet described in the literature.

The assignment of structure V to compound $C_5H_8ClNO_2$ was confirmed by its synthesis through chlorination of known 4-methyl-4-hydroxy-methyl-oxazolidin-2-one with thionyl chloride.

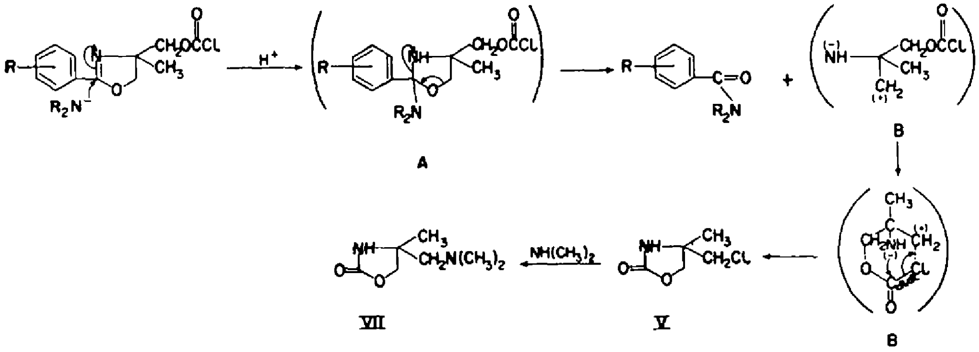
In the case of chlorocarbonate Ib, in addition to compound $C_5H_8ClNO_2$, another product of empirical formula $C_{18}H_{15}Cl_2NO_3$ was isolated, but in very small amount. This compound is neutral with the chlorine atoms unaffected by alkaline treatment. Its infra-red spectrum shows a strong band at 1733 cm^{-1}, indicative of an aryl ester function, and another strong band at 1653 cm^{-1}, which is attributed to the C=N stretching vibration of a 2-oxazoline ring. On this basis compound $C_{18}H_{15}Cl_2NO_3$ was identified as 2-*p*-chlorophenyl-4-methyl-4-*p*-chlorobenzoyl-oxymethyl-2-oxazoline

(VIb). Final confirmation was obtained by esterification of 2-*p*-chlorophenyl-4-methyl-4-hydroxymethyl-2-oxazoline to VIb.

The nucleophilic attack on these oxazoline chlorocarbonates was also carried with dimethylamine to determine whether the nitrogen atom in compound V was the one originally incorporated in the oxazoline ring or whether it came from the ammonia. From the reaction of 2-*p*-chlorophenyl-4-methyl-4-chlorocarbonyl-oxymethyl-2-oxazoline (Ib) and dimethylamine, *p*-chloro-N,N-dimethyl-benzamide was isolated together with a new compound $C_7H_{14}N_2O_2$, which, on the basis of spectroscopical data, was identified as a derivative of compound V, namely 4-methyl-4-N,N-dimethyl-aminomethyl-oxazolidin-2-one (VII). This same compound VII was obtained directly by reaction of dimethylamine with the intermediate V.

The importance of the chlorocarbonic group in determining the oxazoline ring opening is fully illustrated by the fact that 2-*p*-chloromethyl-phenyl-2-oxazoline is converted, by excess diethylamine at 100°, to 2-*p*-diethylaminomethyl-phenyl-2-oxazoline, the oxazoline ring remaining intact.[3]

The following scheme summarizes the above findings and the proposed reaction mechanism:



According to this scheme, the first step of the reaction between chlorocarbonate (I) and ammonia (or dimethylamine) can be visualized as an addition of the nucleophilic reagent to the carbon–nitrogen double bond of the oxazoline ring. The nucleophilic attack should be initiated by an anion R_2N^- attack on carbon atom in position 2 of the ring, where an electron deficiency exists, owing to the proximity of a benzene ring, and two atoms possessing high electron affinity.

The postulated intermediate A, by means of the indicated electron shifts, clearly accounts for the formation of benzamide, or substituted benzamides.

The zwitterion B could also be formed, and, through a concerted mechanism involving migration of the chlorine atom and formation of a new carbon–nitrogen bond, compound V could be formed.

The infra-red absorption spectra offer a rational interpretation of the chemical reactivity of these 2-oxazoline chlorocarbonates. Thus, oxazoline derivatives of type VIII, which are stable towards nucleophilic reagents, regularly show the C=N absorption bond between 1653 and 1647 cm^{-1}, depending on the substituents on the

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[3] M. T. Leffler and R. Adams, *J. Amer. Chem. Soc.* 59, 2252 (1937).

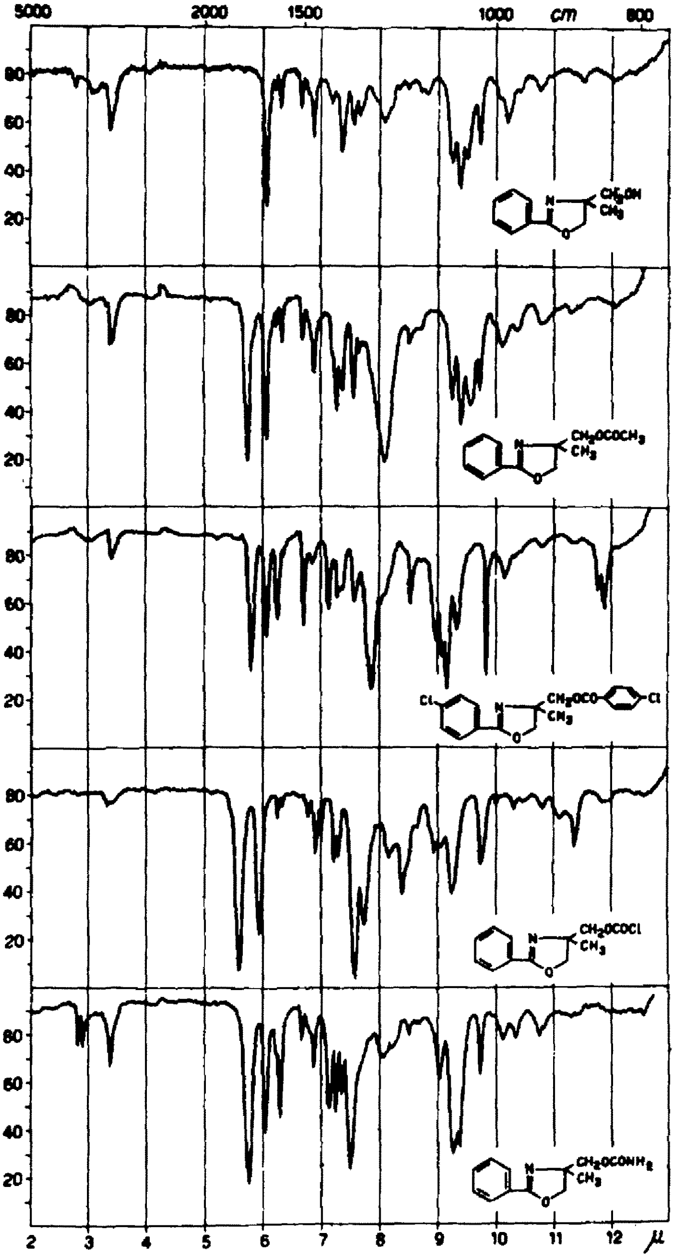

Fig. 1.

benzene ring (Fig. 1). These values are in good agreement with those reported in the literature.[4]

Instead, chlorocarbonates (I) show in their infra-red spectra two strong bands in the carbonyl region: one is constantly at 1795 cm^{-1} and it is due to the C=O

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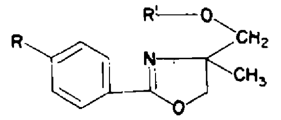
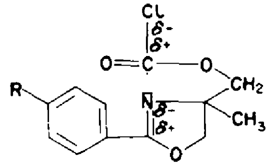
[4] R. B. Barnes, R. C. Gore, U. Liddel and W. Van Zandt, *Infra-red Spectroscopy*. Reinhold, New York (1944); L. J. Bellamy, *The Infra-red Spectra of Complex Molecules* p. 227. Methuen, London (1956).

vibration of the chlorocarbonate moiety;[5] the other band, which is in the region between 1692 and 1686 cm^{-1} depending on the substituents in the benzene ring, is attributed to the C=N stretching vibration of the oxazoline ring. Therefore chlorocarbonates (I), which are unstable towards nucleophilic reagents, show the absorption band of the C=N group at frequencies increased by approximately 40 cm^{-1}. These facts may depend on the effect of the chlorocarbonic group on the carbon-nitrogen double bond in the ring: the relative spatial interaction of these two groups could account for both the chemical and spectroscopical properties of these chlorocarbonates. Formula IX may well visualize the actual interaction of the two groups, the highly polarized carbon-chlorine bond being responsible of the induced polarization of the neighbouring C=N double bond.



VIII



IX

$R=H;\ Cl;\ R'=H;\ COCH_3, COC_6H_5, COC_6H_4{-}pCl, CONH_2.$

According to this view, the polarization of the carbon-nitrogen double bond must be considered the driving force of the process which ultimately leads to the ring opening.

At the same time, the increased polarization of the carbon-nitrogen double bond may well account, in these chlorocarbonates, for the observed shift of the C=N band towards shorter wavelengths. Structure IX could also explain the experimental finding that these chlorocarbonates do not give the corresponding hydrochlorides when treated with dry hydrochloric acid in anhydrous chloroform solution: in fact the nitrogen electron pair, which normally participates in the salt formation, is here partially screened off from the approaching proton.

On the contrary, compound of type VIII, under similar conditions, give stable, crystalline hydrochlorides.[2,6]

EXPERIMENTAL*

Reaction between 2-phenyl-4-methyl-4-chlorocarbonyl-oxymethyl-2-oxazoline (Ia) *and ammonia.* Compound Ia (3·3 g) was heated in a sealed tube for 24 hr at 80° with a saturated solution of anhydrous ammonia in dry dioxane (150 cc). After filtration and removal of solvent (red press), the residue was treated with cold, dry benzene, leaving a residue. The latter after recrystallization from benzene, yielded 1·2 g of crystals (m.p. 127–129°). Found: C, 69·59; H, 6·09; N, 11·66. C_7H_7NO requires: C, 69·40; H, 5·83; N, 11·56%). This product was identified by mixed melting point and infra-red

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* Melting and boiling points are uncorrected. Elementary micro-analyses were carried out by Dr. M. Marzadro and Dr. A. M. Pirelli of the Micro-analysis Laboratory of the Istituto Superiore di Sanità, Rome. Infra-red absorption spectra were recorded for all the substances described on a Perkin Elmer 21 spectrophotometer.

[5] This value is in good agreement with those reported in the literature, although no detailed information is available concerning the infra-red absorption of different chlorocarbonates. H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangl, *Infra-red Determination of Organic Structures*. Van Nostrand, New York (1949) have given a value of 1785 cm^{-1} for ethyl chlorocarbonate. N. B. Colthup, *J. Opt. Soc. Amer.* **40**, 397 (1950) quotes a range of 1790–1770 cm^{-1} based on this unpublished work.

[6] V Rosnati and D. Misiti, *Gazz. Chim. Ital.* **90**, 155 (1960).

spectrum as benzamide. The remaining benzene solution, after removal of the solvent at reduced pressure, gave an oily residue (2·3 g), which was dissolved in a mixture (75 cc) of benzene–petrol ether 4:1. This solution was fractioned using an alumina column 11 cm high and 3 cm in diameter (20 g alumina). Fractions 1 to 4 inclusive (75 cc each) were eluted with a 1:1 benzene–petrol ether solution and yielded 80–90 mg of an oil, which, on the basis of infra-red spectra, appeared to be a mixture of the cyclic urethane (V), the predominant component, and a 2-oxazoline derivative having an aromatic ester function.*

The latter compound was not easily separable either by chomatography or fractional distillation; thus, the 2-oxazoline derivatives (presumably the ester VIa) could not be isolated in a pure state. Fractions 5–14 (75 cc each) were eluted with benzene and gave a colourless oil (1·1 g), which was fractionated at low pressure.

A small quantity of a white crystalline product (m.p. 127–129°, b.p. 110–115° at 0·1 mm) was obtained in the first fraction; this was identified as benzamide by its mixed melting point and infra-red spectrum. The main portion of the distillation product was a colourless oil b.p. 135–140° at 0·1 mm, which on standing formed crystals m.p. 75–85°. After repeated recrystallizations from benzene–petrol ether, the m.p. was raised to 89–91°. (Found: C, 40·33; H, 5·33; N, 9·55; Cl, 23·50. $C_5H_8ClNO_2$ requires: C, 40·15; H, 5·39; N, 9·36; Cl, 23·72%). These crystals showed no depression on admixture with authentic 4-methyl-4-chloromethyl-oxazolidin-2-one (V) prepared as described below. The infra-red spectra of both these samples were also identical.

4-Methyl-4-chloromethyl-oxazolidin-2-one (V). 4-Methyl-4-hydroxymethyl-oxazolidin-2-one[1] (7 g) suspended in anhydrous chloroform (50 cc) was treated with thionyl chloride (20 cc) and the reaction mixture allowed to stand at room temp until solution was complete and then refluxed for 4 hr. Chloroform and thionyl chloride were removed at reduced pressure and the residue (8 g) was fractionated *in vacuo*. The first fraction (4 g) was collected between 138–144° at 0·1 mm; the remainder of the distillate (1·5 g), (b.p. 166–172° at 0·1 mm) consisted of unreacted starting material (m.p. 115–117° and identical infra-red spectrum). After redistillation, the first fraction gave colourless oil (b.p. 135–136° at 0·1 mm) which on standing solidified completely (m.p. 75–86°). Repeated recrystallization from benzene–petrol ether gave pure crystals of V, m.p. 90–92°. (Found: C, 40·14; H, 5·41; N, 9·14; Cl, 23·68. $C_5H_8ClNO_2$ requires: C, 40·15; H, 5·39; N, 9·36; Cl, 23·72%). Infra-red absorption ($CHCl_3$): 3472 (w), 3263 (w), 1773 (s), 1761 (s), 1381 (m) cm^{-1}.

Reaction between 2-p *chlorophenyl*-4-methyl-4-*chlorocarbonyl-oximethyl-2-oxazoline* (Ib) *and ammonia*. A solution of a compound Ib (1·3 g) in dry dioxane (50cc) was saturated at room temp with anhydrous ammonia and the reaction mixture was heated at 80° for 12 hr in a sealed tube. After removal of the solvent (red press) the crystalline residue was dissolved in the least quantity of hot benzene. Upon standing, crystals (0·3 g, m.p. 179–180°) were obtained. Found: C, 53·90; H, 4·06; N, 8·93; Cl, 22·72. C_7H_6NOCl requires: C, 54·03; H, 3·89; N, 9·00; Cl, 22·79%). This product was identified by mixed melting point and infra-red spectrum as *p*-chlorobenzamide. The remaining benzene solution, after removal of the solvent (red press) gave an oily residue (0·6 g) which was dissolved in benzene–petrol ether 3:1 (25 cc) and chromatographed over alumina (21 g). Elution was carried out with benzene–petrol ether 3:1. The first three fractions (25 cc each) yielded 0·1 g (VIb), m.p. 122–123° (from petrol ether). (Found: C, 59·23; H, 4·17; N, 3·91; Cl, 19·30. $C_{18}H_{15}Cl_2NO_3$ requires: C, 59·35; H, 4·15; N, 3·85; Cl, 19·47%). This product showed no depression of the m.p. with VIb prepared as described below. The infra-red spectra of both materials were also identical. Subsequent fractions (4–11) afforded 0·5 g of a crystalline compound m.p. 87–93°. Crystallization from benzene–petrol ether gave needles of V with m.p. 90–92°. (Found: C, 40·15; H, 5·52; N, 9·46; N, 9·46; Cl, 23·49. $C_5H_8ClNO_2$ requires: C, 40·14; H, 5.52; N, 9·37; Cl, 23·70%). The crystals m.p. 90–92° were not depressed upon admixture with V prepared as described above. The infra-red spectra of both these compounds were identical.

Reaction between 2-p-*chlorophenyl-4-methyl-4-chlorocarbonyl-oxymethyl-2-oxazoline* (Ib) *and dimethylamine*. A solution of compound Ib (4 g) and anhydrous dimethylamine (12 g) in dry dioxane (100 cc) was heated in a sealed tube for 24 hr at 80–85°. After filtration and removal of the solvent

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* Infra-red spectra of these fractions showed two strong bands in the region of the carbonyl: one at 1770 (s) cm^{-1}, which can be attributed to the carbonyl of the cyclic urethane (V) and the other at 1733 (s) cm^{-1}, suggesting the presence of an aromatic ester function. Further evidence for the presence of a benzene ring is given by two bands at 1610 (w) cm^{-1} and 1499 (w) cm^{-1}. The appearance of a strong band at 1653 (s) cm^{-1} clearly indicates the presence of an oxazoline ring.

(red press), the residue was dissolved in benzene–petrol ether 1 : 1 (30 cc) and the solution chromatographed over alumina (120 g). The first seven fractions (100 cc each; elution with benzene–petrol ether 1 : 1) gave an oily material which solidified upon standing; the crude product (2 g; m.p. 50–55°), after crystallization from benzene–petrol ether, gave crystals m.p. 56–58°. (Found: C, 58·63; H, 5·51; N, 7·76; Cl, 19·20. $C_9H_{10}ClNO$ requires: C, 58·86; H, 5·49; N, 7·63; Cl, 19·31%). This product was identified by mixed m.p. and infra-red spectrum as 4-chloro-N,N-dimethyl-benzamide. Subsequent fractions (eluted with benzene and benzene–ether 1 : 1) gave a colourless oil (2 g) which, after distillation *in vacuo*, gave 1·7 g (VII), b.p. 69–73° at 0.03 mm. After long standing, crystals m.p. 55–59° were obtained. (Found: C, 53·13; H, 8·91; N, 17·69. $C_7H_{14}N_2O_2$ requires: C, 53·14; H, 8·92; N, 17·71%). The I.R. spectrum of this compound was identical to that obtained with VII prepared as described below.

4-*Methyl*-4-N,N-*dimethylaminomethyl-oxazolidin*-2-*one* (VII). A solution of V (3 g) and anhydrous dimethylamine (7 g) in dry dioxane (100 cc) was heated in a sealed tube for 24 hr at 80–85°. After filtration and removal of the solvent (red press) the oily residue was fractionated *in vacuo*. Compound VII was thus obtained as a colourless oil (2·3 g; b.p. 70–74° at 0·03 mm) which after long standing solidified completely, giving crystals m.p. 54–59°. (Found: C, 52·89; H, 9·12; N, 17·44. $C_7H_{14}N_2O_2$ requires: C, 53·14; H, 8·92; N, 17·71%). Infra-red absorption ($CHCl_3$): 3333 (w) broad, 1764 (w), 1664 (s), 1653 (s), 1412 (m) cm^{-1}.

2-p-*Chlorophenyl* 4-*methyl*-4-p-*chlorobenzoyl-oxymethyl*-2-*oxazoline* (VIb). To compound Ib (2·2 g) dissolved in toluene (50 cc), *p*-chlorobenzoylchloride (1.7 g) was added and the mixture was refluxed for 2 hr. After removal of the solvent (red press), the residue was taken up in ether, the solution washed with 50% K_2CO_3 and dried over K_2CO_3. After removal of the solvent, the residue was dissolved in benzene–petrol ether 2 : 1 (30 cc), and chromatographed over alumina (30 g), each fraction (25 cc) being eluted with benzene–petrol ether 2 : 1. The first three fractions gave an oily residue; subsequent fractions gave 2 g of a crystalline product, which after crystallization from petrol ether yielded the pure ester (VIb), with m.p. 122–123°. (Found: C, 59·24; H, 4·31; N, 3·72; Cl, 19·28. $C_{18}H_{15}Cl_2NO_3$ requires: C, 59·35; H, 4·15; N, 3·85; Cl, 19·47%). Infra-red spectrum ($CHCl_3$): see Fig. 1.

Reaction between 2-(3′, 4′, 5′-*trimethoxyphenyl*)-4-*methyl*-4-*chlorocarbonyl-oxymethyl*-2-*oxazoline* (Ic) *and ammonia*. Chlorocarbonate Ic (1 g) was heated in a sealed tube for 24 hr at 80° with a saturated solution of anhydrous ammonia in dry dioxane (25 cc). After filtration and removal of the solvent (red press), the residue was treated with cold benzene, to give 0·5 g of crystals m.p. 178–179°. (Found: C, 56·66; H, 6·13; N, 6·67. $C_{10}H_{13}NO_4$ requires: C, 56·86; H, 6·20; N, 6·63%). This compound was identified as 3, 4, 5-trimetoxybenzamide by mixed m.p. and infra-red spectrum. The remaining benzene solution was evaporated to dryness (red press) and the oily residue (0·45 g), after treatment with absolute ether, gave crystalline material m.p. 65–75°. After repeated crystallizations from benzene–hexane, crystals of pure V m.p. 90–92° were obtained. (Found: C, 40·36; H, 5·29; N, 9·19; Cl, 23·85. $C_5H_8ClNO_2$ requires: C, 40·14; H, 5·39; N, 9·36; Cl, 23·70%). These crystals gave no m.p. depression with authentic V prepared as described. Their infra-red spectra were also identical.

The reaction between Ic and ammonia was also carried out at room temp according to the following procedure: a continuous stream of anhydrous ammonia was passed for 8 hr through a solution of Ic (0·439 g) in anhydrous chloroform (150 cc) then allowed to stand for several days, infra-red spectra being recorded from time to time. After the first 3 hr the infra-red spectrum was much the same as that of the starting material. Subsequent spectra, taken at intervals of about 8–10 hr, showed a progressive weakening of the band at 1795 cm^{-1}, together with the appearance of a new band of increasing intensity at 1764 cm^{-1}, and the persistance of a strong band in the region between 1684–1675 cm^{-1}.*

The reaction was discontinued only after a constant infra-red spectrum was obtained. Removal of

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* The progressive disappearance of the chlorocarbonate derivative from the reaction mixture was responsible for the weakening of the 1795 cm^{-1} band. The new band at 1764 cm^{-1} was attributed to the carbonyl group present in the five-membered lactone ring of the cyclic urethane V, which was eventually isolated. The intense absorption between 1684–1675 cm^{-1} in the initial spectra was attributed to the C=N stretching vibration of the oxazoline ring of the chlorocarbonate (Ic). However, since this product is gradually degraded by nucleophilic attack, the presence of such a band, even in the crude final product, must be due to the CO—NH absorption of the 3,4,5-trimethoxybenzamide; in fact, the latter shows in chloroform solution a strong absorption band at 1681 cm^{-1}.

the solvent and unreacted ammonia left a residue which, by treatment with a mixture of benzene–absolute ether 5:1, gave a solid material (0·25 g m.p. 172–174°). Crystallization from benzene yielded crystals m.p. 176–178°. (Found: C, 56·66; H, 6·13; N, 6·67. $C_{10}H_{13}NO_4$ requires: C, 56·86; H, 6·20; N, 6·63%). This substance was identified by mixed m.p. and infra-red spectrum as 3, 4, 5-trimethoxybenzamide. The remaining benzene–ether solution after removal of the solvents gave an oily residue which after long standing solidified completely. By repeated crystallizations from benzene–hexane, crystals of V were obtained m.p. 89–91°.