SYNTHESIS OF 2-TRICHLOROMETHYLOXAZOLIDIN-5-ONES BY REACTION OF CHLORAL WITH N,O-TRIMETHYLSILYL DERIVATIVES OF AMINO ACIDS

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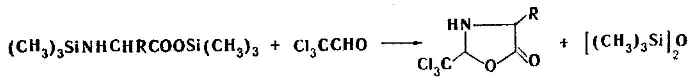
The corresponding 2-trichloromethyloxazolidin-5-ones were obtained by reaction of chloral with trimethylsilyl (TMS) derivatives of some amino acids. The corresponding oxazolidin-5-ones could not be obtained by the action of chloral on aspartic and glutamic acids.

We have synthesized 2-trichloromethyloxazolidin-5-one derivatives of amino acids in order to verify the possibility of their use in peptide synthesis.

It is known that chloral reacts with glycine, alanine, serine, and cysteine to give oxazolidin-5-ones with complex structures containing two chloral residues. Proline and phenylalanine form oxazolidin-5-ones when one molecule of chloral is added [1, 2]. The preparation of 2-trichloromethyloxazolidin-5-ones from chloral and benzyloxycarbonylglycine [3] or barium and calcium salts of glycine [4] has also been described. Replacement of all of the hydrogen atoms attached to the nitrogen atom occurs in all cases (except for phenylalanine) in the formation of the oxazolidinone ring.

This paper is devoted to a study of the reaction of chloral with trimethylsilyl (TMS) derivatives of amino acids. It was found that N,O-bis- and N,O,O'-tris-TMS derivatives of amino acids react with chloral considerably more readily than the free amino acids. Some amino acids (for example, aspartic and glutamic acids) do not react with chloral even when a considerable excess of chloral is present and when the temperature is raised, whereas their N,O,O'-tris-TMS derivatives form the corresponding oxazolidinones at room temperature. The method for the preparation of 2-trichloromethyloxazolidin-5-ones is extremely simple and involves only mixing of the reagents. We have obtained the corresponding 2-trichloromethyloxazolidin-5-ones in the crystalline state in high yields from the TMS derivatives of phenylalanine, methionine, and leucine (Table 1).



I a-e

II a-e

I–II a $R = CH_2C_6H_5$; b $R = CH_2CH_2SCH_3$; c $R = CH_2CH(CH_3)_2$; d $R = CH_2COOSi(CH_3)_3$
e $R = CH_2CH_2COOSi(CH_3)_3$

Only one molecule of chloral reacts with all of the TMS derivatives (Ia-e) of amino acids. 4-Trimethylsilyloxycarbonylmethyl and 4-trimethylsilyloxycarbonylethyl derivatives (IId, e) of 2-trichloromethyloxazolidin-5-ones respectively were isolated as the primary reaction products even in the case of N,O,O'-tris-TMS derivatives of aspartic and glutamic acids. This indicates the reduced reactivity of the TMS-oxycarbonyl groups in the side chain of these amino dicarboxylic acids. These groupings are unaffected in the presence of excess chloral at high temperatures.

The 2-trichloromethyloxazolidin-5-ones obtained (IIa-e) are white crystalline substances that decompose slowly on storage. The compositions and structures of the synthesized products were confirmed by the results of elementary analysis and the IR spectroscopic data. All of the 2-trichloromethyloxazolidin-5-ones (II) have characteristic absorption bands at 3300 (NH) and 1800 cm^{-1} (ring C=O). The IR spectra of products IId, e contain, in addition

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TABLE 1. 2-Trichloromethyloxazolidin-5-ones (II)

Compound	R	mp, °C	Found, %				Empirical formula	Calc. %				Yield, %
			C	H	Cl	N		C	H	Cl	N	
IIa	Benzyl	130—133 (dec.)	45,0	3,5	35,4	5,0	$C_{11}H_{10}Cl_3NO_2$	44,9	3,4	36,1	4,8	84
IIb	$CH_2CH_2SCH_3$	69—70	30,5	3,7	38,6	5,5	$C_7H_{10}Cl_3NO_2S$*	30,2	3,6	38,2	5,1	98
IIc	iso-butyl	98,5--100	37,1	4,7	—	5,3	$C_8H_{12}Cl_3NO_2$	36,9	4,6	—	5,4	70
IId	$CH_2COOSi(CH_3)_3$	124--125	32,6	4,1	31,9	4,6	$C_9H_{14}Cl_3NO_4Si$	32,3	4,2	31,8	4,2	78
IIe	$CH_2CH_2COOSi(CH_3)_3$	177—178	34,6	4,9	30,8	4,1	$C_{10}H_{16}Cl_3NO_4Si$	34,5	4,6	30,5	4,0	54

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*Found: S 11.6%. Calculated: S 11.5%.

to the indicated bands, absorption bands characteristic for TMS-esters — intense absorption at 1740 (C=O) and at 1250 and 850 cm^{-1}, which is typical for vibrations of the Si—CH_3 bond.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with an IKS-22 spectrometer. Analysis by gas—liquid chromatography was accomplished with a Khrom-2 chromatograph with a 2-m-long column; the support was Chromaton N-AW DMCS (0.2-0.25 mm), the starting phase was SKT-FT-50 fluorinated silicone rubber, the helium flow rate was 30 ml/min, and the column temperature was 110°C.

2-Trichloromethyl-4-benzyloxazolidin-5-one (IIa). A mixture of 6.72 g (21.8 mmole) of N,O-bis-TMS-L-phenylalanine and 3.22 g (21.8 mmole) of chloral was allowed to stand for 3 days, and the solidified reaction mass was then dissolved in ether. The ether solution was treated with petroleum ether in portions until the solution became turbid, and the resulting precipitate was removed by filtration and dried in vacuo at room temperature. The mother liquor was evaporated, and petroleum ether was added to the residue to give another portion of IIa. Recrystallization from ether—petroleum ether (3:1) without heating gave 5.4 g (84%) of oxazolidinone IIa. Hexamethyldisiloxane was identified in the filtrate by GLC.

Oxazolidinones IIb-e were obtained by the same method.

4-Trimethylsilyloxycarbonylmethyl-2-trichloromethyloxazolidin-5-one (IId). A mixture of 6.14 g (20 mmole) of N,O,O'-tris-TMS-aspartic acid and 8.90 g (60 mmole) of chloral was allowed to stand for 3 days, after which it was heated at 70°C for 4 h. It was then worked up as in the preceding experiment to give 4.2 g of IId.

A mixture of 2.7 g (20 mmole) of aspartic acid and 8.9 g (60 mmole) of chloral was shaken for 10 days, after which it was heated at 80°C for 5 h. No products of addition of chloral were detected.

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