

University of Groningen

## De synthese van zuurstofchlorides en peptiden met behulp van alpha-chloorethers

Heslinga, Lammert

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*

1959

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Heslinga, L. (1959). *De synthese van zuurstofchlorides en peptiden met behulp van alpha-chloorethers*. s.n.

### Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

### Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

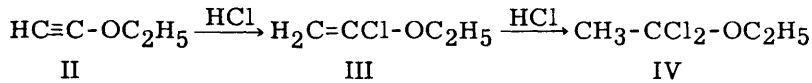
Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

## SUMMARY

## Chapter I

Formation of  $\alpha,\alpha$ -dichlorodiethyl ether (IV) and its use for the preparation of acyl chlorides.

Addition of two equivalents of hydrogen chloride to ethoxyacetylene (II) yields  $\alpha,\alpha$ -dichlorodiethyl ether (IV). This dichloro ether had not yet been described.



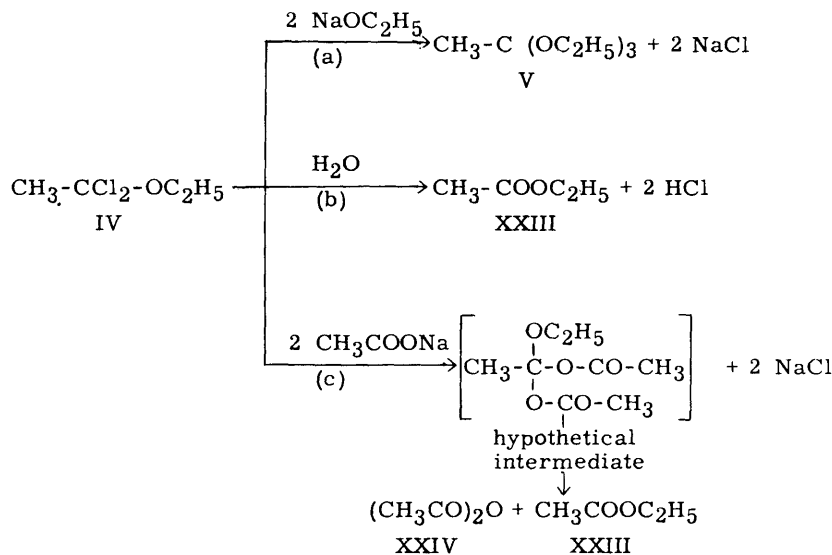
The intermediate ethyl  $\alpha$ -chlorovinyl ether (III) is a known substance.

The dichloro ether (IV) is a colourless liquid with b. p. 104.5-105.5°C (corrected) and  $n_D^{20}$  1.4261. The structure of this compound appeared from the following conversions.

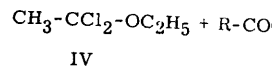
a) Reaction with sodium ethoxide in ethanol afforded ethylorthoacetate (V).

b) Ethyl acetate (XXIII) was formed by hydrolysis.

c) By reaction with sodium acetate, acetic anhydride (XXIV) and ethyl acetate (XXIII) were formed in good yields:



At about 40°C the dichloro ether (IV) easily reacted with carboxylic acids, yielding acyl chlorides (XXV) and ethyl acetate (XXIII). In some cases the reaction already started at room temperature.



We subjected several  $\alpha,\alpha$ -dichlorodiethyl ether acyl chlorides were obtained. The reaction times were short (about 10-15 minutes). The products were simple, ethylacetate, ethylacetate, etc. The results are listed in the report of this thesis).

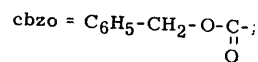
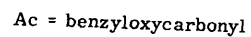
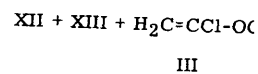
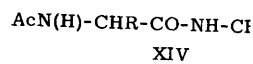
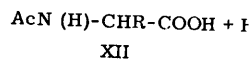
The use of the dichloro ether for the preparation of pure acyl chlorides is possible. The acyl chlorides must be prepared as  $\text{SOCl}_2$ ,  $\text{PCl}_3$  etc.

## Chapters II and III.

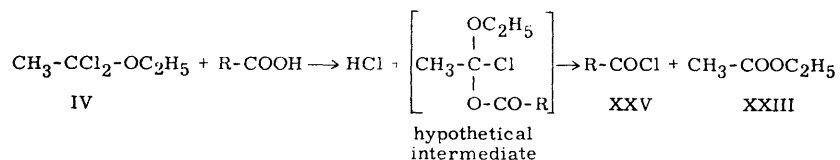
## Synthesis of peptides

Two new methods for the synthesis of acyl peptide esters (XXVI) were described. One method used dry ethyl acetate and the other used amino acid ester hydrochlorides. The reaction of  $\alpha,\alpha$ -dichlorodiethyl ether (IV) with amino acid ester hydrochlorides yielded  $\alpha,\alpha$ -dichlorodiethyl ether (III).

## Reaction C: One step



The method has been applied to the synthesis of  $\alpha,\alpha$ -dichlorodiethyl ether (IV) and phth-di-ethyl ether (XIII). In all experiments good results were obtained. The syntheses of  $\alpha,\alpha$ -dichlorodiethyl ether (IV) were performed by heating



We subjected several carboxylic acids to treatment with  $\alpha, \alpha$ -dichlorodiethyl ether (IV), without a solvent. The pure acyl chlorides were obtained in good yields (70-100%); the reaction times were short (about 30 min). The isolation of the reaction-products was simple, because of the formation of volatile by-product, ethylacetate.

The results are listed in table I, chapter I, (page 1-9<sup>a</sup>, 9<sup>b</sup> of this thesis).

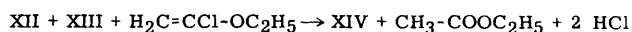
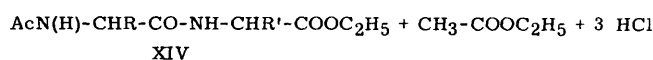
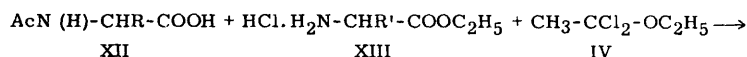
The use of the dichloro ether (IV) for the preparation of very pure acyl chlorides may be advantageous in cases where these chlorides must be completely free from the usual reagents such as  $\text{SOCl}_2$ ,  $\text{PCl}_3$  etc., and their reaction products.

#### Chapters II and III.

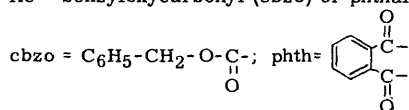
##### *Synthesis of peptides by means of $\alpha$ -chlorinated ethers.*

Two new methods of peptide-synthesis were developed. N-acyl peptide esters (XIV) were easily prepared by refluxing in dry ethyl acetate a mixture of a N-acylamino acid (XII), an amino acid ester hydrochloride (XIII) and one of the chlorinated ethers,  $\alpha, \alpha$ -dichlorodiethylether (IV), or ethyl  $\alpha$ -chlorovinyl ether (III):

##### *Reaction C: One step procedure.*



Ac = benzyloxycarbonyl (cbzo) or phthalyl (phth) group;



The method has been applied for the preparation of a number of cbzo- and phth-di- and a few tripeptide esters.

In all experiments optically pure acyl peptide esters (XIV) were isolated. Especially with  $\alpha, \alpha$ -dichlorodiethyl ether (IV) good results were obtained.

The syntheses of a number of *phth* peptide esters were also performed by heating the reactants without a solvent. In these

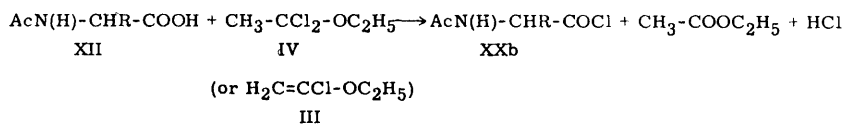
cases the reactions were very fast: reaction time 10-15 min.

Because of the known sensitivity of N-benzoyloxycarbonyl-amino acyl chlorides (which most probably are intermediates) towards heat, this variation could not be applied for the analogous synthesis of N-cbzo peptide esters.

The various results are listed in tables IV, V, VIII, IX and X, (chapters II and III of this thesis, pages II-4, 5, 11, 12 and III-2.)

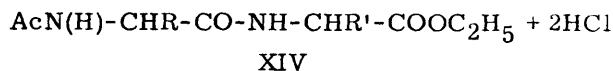
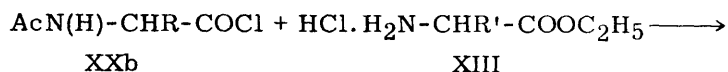
These new peptide syntheses most probably proceed as follows:

*Reaction A: formation of N-acyl aminoacyl chloride (XXb).*



Ac = N-protecting group (phth or cbzo).

*Reaction B: formation of peptide bond.*



These two steps (A and B) could also be performed separately.

Evidence for the occurrence of the acyl chloride (XXb) as an intermediate, during the synthesis of phth-gly-gly-Et with  $\alpha, \alpha$ -dichloro ether (IV) (reactions A, B and C) was obtained, by performing the reactions at 40°C and 77°C, and interrupting the processes before completion (see tables XI and XII, chapter III, pages III-7 and III-8 of this thesis).

Most probably, also in the peptide syntheses with ethyl  $\alpha$ -chlorovinyl ether (III) these acyl chlorides (XXb) are intermediates.

Some free phth-peptides were obtained by refluxing a mixture of phth-aminoacyl chloride (XX) and free amino acid in ethyl acetate.

Of the two reagents for the synthesis of protected peptides, proposed here  $\alpha, \alpha$ -dichlorodiethyl ether (IV) is to be preferred.

The new method has the following attractive features:

- simple, "one step" procedures: isolation of intermediates is not necessary.
- short reaction times (0.5 - 1.5 h).
- good yields of optically pure N-acyl peptide esters.
- easy isolation of the crystalline reaction products.

- 1) E. Fischer, Ber.
- 2) E. Fischer, en
- 3) W. Grassmann  
stoffe 13, 444
- 4) Th. Curtius en
- 5) E. Brand, B. F.  
1849, (1952).
- 6) W. L. Le Quesn
- 7) J. C. Sheehan e
- 8) J. F. Arens, R.  
Festschrift A
- 9) H. J. Pannema  
binnenkort in
- 10) A. E. Favorsk  
15, 394, (1945
- 11) Th. R. Rix en  
Wetenschap.
- 12) J. F. Arens en
- 13) T. L. Jacobs e
- 14) Y. A. Sinnema
- 15) R. Broekema,  
chim. 77, 258
- 16) Th. R. Rix en  
Wetenschap.
- 17) H. Crompton e  
(1920).
- 18) I. B. Douglas e  
(1956).
- 19) L. Heslinga, C  
76, 969, (195
- 20) G. Imbert, Ko  
222194, (1910  
Fortschr. d. 7
- 21) H. Crompton e
- 22) P. V. Mc Kie,
- 23) D. Ben Ishaï e
- 24) M. Bergmann
- 25) M. Bergmann
- 26) E. Drechsel,
- 27) J. C. Sheehan  
(1950).
- 28) J. C. Sheehan
- 29) H. Leuchs, B
- 30) S. Gabriel, B
- 31) F. E. King, J.  
J. Chem. Soc.
- 32) K. Yamashita  
Soc. Japan 27
- 33) J. C. Sheehan
- 34) T. Curtius en
- 35) J. C. Sheehan,  
Soc. 74, 382
- 36) D. A. van Dor  
chim. 70, 289