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REARRANGEMENT OF ORTHO-O-AMINOACYL,N-ACYLAMINOPHENOL

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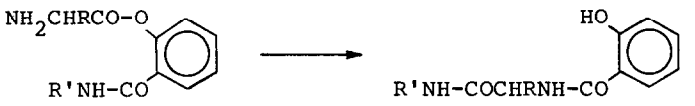
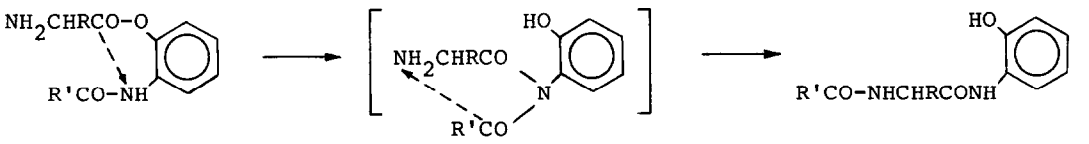
It is known that rearrangement of aminoacyl esters of amides of salicylic acid leads to the formation of a new peptide bond.[1]



We have found that aminoacyl esters of ortho-acylaminophenols (I) also undergo an analogous rearrangement:



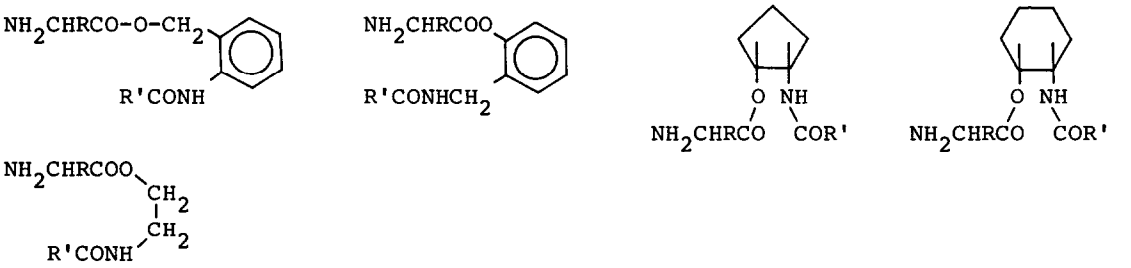
I II III

This reaction, being an aminoacyl incorporation, also leads to the formation of a peptide bond (resulting in compound III). However, in contrast to the rearrangement described by Brenner, the peptide chain grows from the carboxyl end.

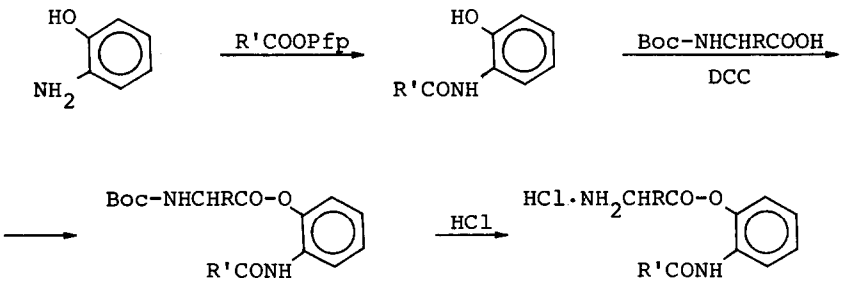
It can be assumed that an intermediate compound is diacylamide (II), which readily forms peptide analogously to the described transformation of N,N-bis-aminoacylimides.[2,3]

β-Amino acid esters can also rearrange, although the rate of the reaction is noticeably lower than that for α-amino acid esters. γ-Amino acid esters cannot

rearrange at all. Esters of the following type do not rearrange either:



Esters IV are the starting compounds for rearrangement. The aminoacyl part of these esters contains easily removable protecting groups (e.g. the Boc-group).[4] Amide esters IV are easily synthesized proceeding from ortho-amino phenol, for example:



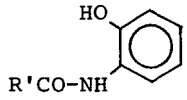
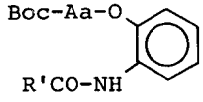
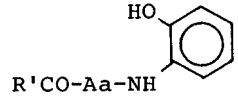
IV V

Treatment of amide esters IV with trifluoroacetic acid or HCl in dioxane leads to the splitting of the Boc-masking group resulting in stable salts V. Salts V, without any changes, can be dissolved in polar solvents such as dimethylformamide, dioxane, water, alcohol, etc. But a rapid rearrangement takes place when tertiary amine is added (pH>7). The rate of the rearrangement does not depend on the concentration and is completed in a few minutes.

Z-Gly-NHC$_6$H$_4$OH (ortho) is synthesized from 2.18 g (20 mmol) ortho-amino phenol and 3.75 g (10 mmol) Z-Gly-OPfp in 10 ml of dimethylformamide. The yield of Z-Gly-NHC$_6$H$_4$OH is 2.58 g (86%), m.p. 176-177°.

To synthesize ester IV (R = CH_3, R' = Z-NHCH$_2$), 0.45 g (2.2 mmol) dicyclohexylcarbodiimide is added to the solution of 0.6 g (2 mmol) Z-Gly-NHC$_6$H$_4$OH and 0.76 g (4 mmol) Boc-Ala-OH in 10 ml ethylacetate and 1 ml dimethylformamide at 0°. After 30 min 0.28 ml (2 mmol) triethylamine is added and the mixture is stirred for 18 hours. After a standard treatment, 0.9 g (96%) of chromatographically homogeneous amorphous ester IV (R = CH_3, R' = Z-NHCH$_2$) is obtained; R_f 0.7 (chloroform:MeOH 95:5). The product is treated for 30 min with 5 N HCl in dioxane

Table 1. Starting substances for the rearrangement and resulting products

 *				 *				 *		
R'CO	Yield (%)	M.p. (°C)	R_f	Aa	Yield (%)	M.p. (°C)	R_f	Yield (%)	M.p. (°C)	R_f
Gly	86	176-178	0.30 (A)**	Ala	98	amorph.	0.70 (A)	93	113-115	0.23 (A)
				β-Ala	90	amorph.	0.68 (A)	51	182-183	0.26 (A)
Cys(Bzl)	73	170-171	0.71 (A)	Pro	84	amorph.	0.45 (B)	90		0.83 (A)
Gly-Ile	95	137-139	0.24 (A)	Gly	40	141-145	0.39 (A)	80	178-180	0.23 (A)
Gly-Ala	64	113-115	0.23 (A)	Leu	90	amorph.	0.56 (A)	64	amorph.	0.30 (A)
Ile	62	129-131	0.41 (B)	Phe	86	114-115	0.85 (A)	94	183-185	0.55 (A)

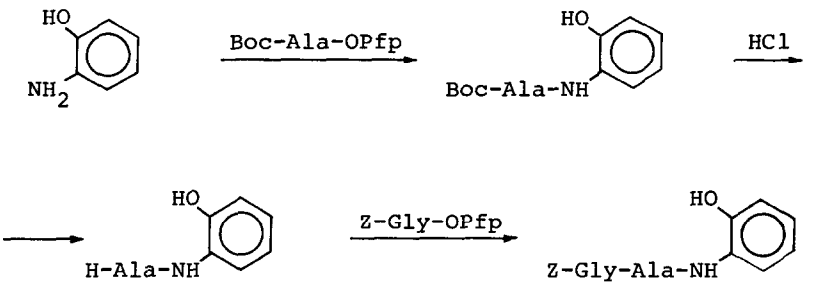
*Results of the element analysis correspond to the values calculated.

**Solvent for thin layer chromatography: (A), chloroform:methanol 95:5;

(B), chloroform:methanol:hexane 95:5:100.

which is then removed in a rotary evaporator, the residue is treated with ether and 0.8 g (98%) of chromatographically homogeneous salt V (R = CH_3, R' = Z-$NHCH_2$) is obtained; R_f 0.46 (n-butanol:AcOH:H_2O 4:1:1). Other compounds used for the rearrangement were synthesized in the same way (Table 1).

For the rearrangement to take place, salt V (R = CH_3, R' = Z-$NHCH_2$) is dissolved in 20 ml dioxane and 0.28 ml (2 mmol) triethylamine is added to the solution. After 5 min ethylacetate is added, and the mixture is washed with 5% HCl and then with water. After removing the solvent, the residue is treated with a mixture of ether with petroleum ether (1:1). The yield of product of rearrangement III (R = CH_3, R' = Z-$NHCH_2$) is 93%, m.p. 113-115°, R_f 0.23 (chloroform:MeOH 95:5). In its properties the obtained substance, Z-Gly-Ala-NHC_6H_4OH (ortho), is completely identical to the product obtained by the synthesis:



Some products of the rearrangement are given in the right column of Table 1. The problem of splitting peptides off the aminophenol ring as well as determining the degree of possible racemization is being studied.

REFERENCES

1. M. Brenner, G. P. Zimmermann, J. Wehrmüller, P. Quitt, and I. Photaki, Experientia, 11, 397 (1955).
2. T. Wieland, and H. Mohr, Liebigs Ann. Chem., 599, 222 (1956).
3. T. Wieland, and H. Urbach, Liebigs Ann. Chem., 613, 84 (1958).
4. Abbreviations of amino acids and other reagents used in peptide synthesis are given according to IUPAC nomenclature (see J. Biol. Chem. 247, 977 (1972)). Other abbreviations: Pfp, pentafluorophenyl; DCC, dicyclohexylcarbodiimide.

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