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TOTAL SYNTHESIS OF TETRAACETYL CLIONAMIDE

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Abstract: Tetraacetyl clionamide, a 6-bromotryptophan derivative from the sponge Cliona celata was synthesized from gallic acid.

Enamide[1] residues have been found in several natural compounds, e. g. in peptide alkaloids[2] from Rhamnaceae and Sterculiaceae, in linear peptide alkaloids[3] from the sponge Cliona celata, and in alkaloids of Peripterygia marginata[4]. Having constructed the peptide alkaloids zizyphine A and B[5], we now describe the synthesis of tetraacetyl clionamide (1) (R,R'=acetyl), an enamide from Cliona celata which was isolated and structure elucidated in form of its tetraacetyl derivative[6].

Recently W.Steglich[1c,d] described two methods for the synthesis of enamides, but E/Z mixtures were obtained. In contrast to this the linear natural compounds are exclusively E-isomers and the cyclic peptide alkaloids Z-isomers. In our synthesis of peptide alkaloids pure Z-enamides were prepared by elimination reactions of acylamino-selenoxides. But in the field of the non rigid linear enamides the selenoxideelimination forms E-isomers exclusively. In this way we synthesized tetraacetyl-clionamide and triacetyl-BOC-clionamide.

Regarding the lability of the enamide function of clionamide the four protective groups of the three phenolic functions and the amino group should be easily removable. Our first experiments with the tris-methoxy-methyl derivative 1 led without difficulties to the clionamide derivative 3 (Br=H, R=CH_2--O-CH_3; R'=BOC), but reagents for deblocking (BCl_3; Me_3SiI; HCl/H_2O) failed

with the exception of $(Me_3Si)SO_4$; the yield was rather small and not reliable to be reproduced.

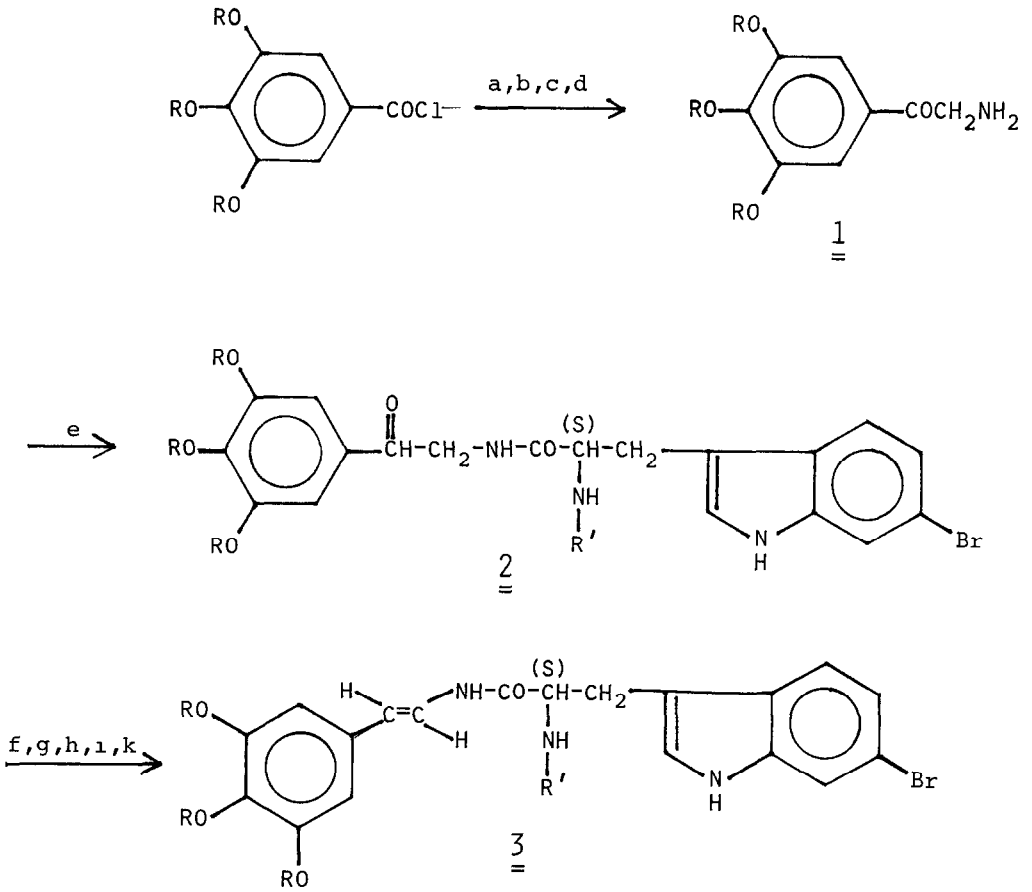
The methoxycarbonyl protective group - frequently used by Emil Fischer in the synthesis of depsides - allowed the synthesis of the protected enamide 3 (Br=H; R=$COOCH_3$; R'=BOC). Also the triacetyl-BOC-derivative 3 (R=CH_3CO; R'=BOC) could be prepared. Both bear the possibility to be transformed easily into clionamide by removing the acetyl groups with ammonia, isolating BOC--clionamide, and splitting off the BOC group.

The synthesis started with triacetyl gallic acid chloride which was reacted successively with diazomethane, hydrogen chloride, and sodium azide to the azido ketone which was hydrogenated in the presence of one mol hydrogen chloride forming the amino ketone hydrochloride 1. In all steps attention has to be payed on the very easily deacetylating and transacetylating reactions of the triacetoxyphenyl compounds. Thus acylation with S-BOC-6-bromo-tryptophan [7] pentafluorophenyl ester and one mol triethylamine proceeded quickly in order to avoid O→N transacetylation. $NaBH_3$-CN reduction formed the alcohol 2. Redox--condensation[10] with p-nitrophenylselenocyanate and tributylphosphine led to the selenide, the oxidative elimination of which formed triacetyl-BOC-clionamide. Removing the BOC group with trifluoroacetic acid and acetylation formed tetraacetyl clionamide. Its spectroscopic characteristics were in accord with the values described by J.Andersen. In addition we were able to find the mass peak. ($|\alpha|_D^{20} = +46.8^o$(c = 0.16, acetone); $|\alpha|_D^{lit\ 6} = +45^o$(c = 0.7, acetone)).

Physical constants

2: R = acetyl mp. = 139-141°C $|\alpha|_D^{20} = -9.8^o$ (c = 1.29 in $CHCl_3$)
R'= BOC

3: R = acetyl mp. = 191-192°C $|\alpha|_D^{20} = +5.9^o$ (c = 1.2 in $CHCl_3$)
R'= BOC



a CH_2N_2

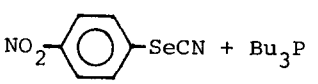
b HCl

c NaN_3

d H_2/Pd

e S-BOC-6-bromotryptophan pentafluorophenylester

f $NaBH_3CN$

g 

h $NaJO_4$

ı CF_3COOH

k $(CH_3CO)_2O$

Yıeld of 3 (R,R' = acetyl): 45 % from tetraacetyl gallıc acıd chloride.

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