Tetrahedron Letters No. 18, pp. 28-30, 1960. Pergamon Press Ltd. Printed in Great Britain

AMINOOXY-PEPTIDE DERIVATIVES OF DL-CANALINE

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(Received 7 July 1960)

ETHYL N^{α},N^{ω}-dibenzoyl-DL-canalinate (DL-α-benzamido-γ-benzamido-oxybutyric acid ethyl ester), prepared by condensation of benzhydroxamic acid with α-benzamido-γ-halogenobutyric acid ethyl ester[1], could be freed from the benzoyl rest attached to the γ-aminooxy group without cleavage of the α-benzamidic linkage or hydrolysis of the ester, by refluxing in 10% ethanolic hydrogen chloride, resulting in ethyl N^{α}-benzoyl-DL-canalinate hydrochloride (I) (m.p. 162°; anal. found: C,50.9; H,6.3; N,9.5; Cl,12.0; OC_2H_5,14.8. $C_{13}H_{19}N_2O_4Cl$ requires C,51.5; H,6.2; N,9.3; Cl,11.7; OC_2H_5, 14.9; the compound gave the orange-red colour with alkaline picrate (Jaffe's test) specific for the free aminooxy group, and a negative ninhydrin test). The canalinate (I) served for the following reactions carried out on the γ-aminooxy group: intermolecular peptidic selfcondensation, intramolecular condensation, peptidic acylation by an N-protected amino acid and amidination to the guanidinoxy derivative.

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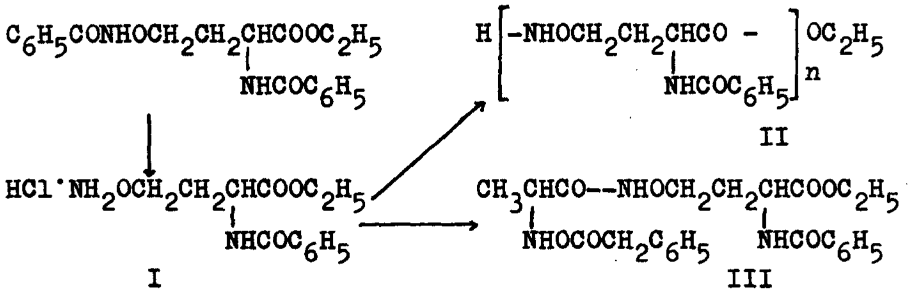
[1] Y. Knobler and M. Frankel, J. Chem. Soc. 1629 (1958).



When ethyl N$^{\alpha}$-benzoyl-DL-canalinate was freed from hydrogen chloride with potassium acetate and then refluxed in ethanol for a few hours, a condensation product was obtained, from which an (average) aminooxy-tripeptide (II) was isolated (m.p. 95-100°; anal. found: C,60.1; H,5.8; N,11.9; OC_2H_5,6.9. $C_{35}H_{42}N_6O_{10}$ requires C,59.5; H,5.9; N,11.9; OC_2H_5,6.4).

The ethyl N$^{\alpha}$-benzoyl-N$^{\omega}$-[N$^{\alpha}$-benzoyl-N$^{\omega}$-(N$^{\alpha}$-benzoyl-DL-canalyl)-DL-canalyl]-DL-canalinate (II) represents a new type of a peptidic compound, linking the carboxyl group of an α-amino acid with the aminooxy group of the α-amino acid canaline, which occurs in nature in the L-form.

On the other hand, condensation of the free ester of I according to the high dilution principle leads through intramolecular cyclisation to the lactamic N-benzoyl derivative of DL-canaline (N$^{\alpha}$-benzoyl-DL-homocycloserine); this is indicated by the specific blue colour test reaction with sodium nitritopentacyanoferroate[2].

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[2] L.R. Jones, Anal. Chem. **28**, 39 (1956).

The aminooxy peptidic linkage was also built up between the canalinate I and another α-amino acid, *e.g.* DL-alanine. After liberation of I by triethylamine in methylene chloride, the free canalinate was condensed with N-benzyloxycarbonyl-DL-alanine by the aid of N,N'-dicyclohexyl carbodiimide, resulting in ethyl N^{α}-benzoyl-N^{ω}-(N-benzyloxycarbonyl-DL-alanyl)-DL-canalinate (III) (found: N,9.1; OC_2H_5,9.4. $C_{24}H_{23}N_3O_7$ requires N,9.0; OC_2H_5,9.7; Jaffe's test - negative).

The N^{α}-benzoyl-DL-canalinate freed as above from I, was also used for amidination of the aminooxy group by the aid of S-methyl*iso*thiourea sulphate. The DL-canavanine derivative thus obtained gives the characteristic magenta colour reaction of the guanidinoxy group of canavanine, tested with activated sodium nitroprusside[3].

Syntheses parallel to those above were also carried out with aminooxyacetic acid ethyl ester, prepared by condensation of benzhydroxamic acid with ethyl bromoacetate and removal of the benzoyl rest, in the same manner as for I.

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[3] W.R. Fearon and E.A. Bell, *Biochem. J.* **59**, 221 (1955).