Tetrahedron Letters No.16, pp. 1769-1772, 1966. Pergamon Press Ltd.
Printed in Great Britain.

THE SYNTHESIS OF ALANOSINE

[L-2-AMINO-3-(N-NITROSOHYDROXYLAMINO)PROPIONIC ACID]

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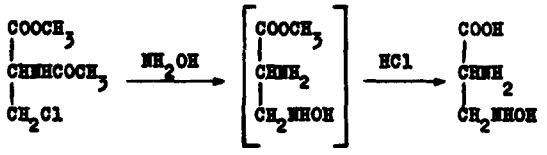
(Received 7 February 1966)

Alanosine is a new antibiotic isolated from the fermentation broth of Streptomyces alanosinicus n.sp., possessing an interesting antiviral and antitumor activity (1). Its structural formula, as elucidated from physico-chemical properties and catalytic reduction studies, is L-2-amino-3-(N-nitrosohydroxylamino)propionic acid (1-2).

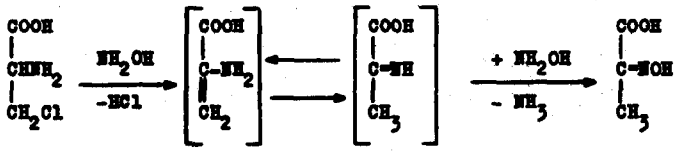
The synthesis of alanosine and of its enantiomer D-2-amino-3-(N-nitrosohydroxylamino)propionic acid are here reported.

Preliminary experiments showed that the last intermediate in the synthesis of alanosine could be 2-amino-3-hydroxylaminopropionic acid. In fact we have verified that the amino group of alanine was unaffected by treatment with $NaNO_2$ at 0° in slightly acid solutions, conditions at which alkyl hydroxylamines are nitrosated (2-3). Hence the introduction of the hydroxylamino group in the β position of alanine was attempted.

A mechanical mixture of anhydrous hydroxylamine and methyl 2-acetamido-3-chloropropionate was gently warmed to 30-35° and maintained at this temperature by cooling until a clear melted mass was obtained. After a few hours the unreacted hydroxylamine and the volatile reaction products were removed by evaporation under reduced pressure and an oily residue was obtained. Acid hydrolysis of this oil, which on the basis of its I.R. spectrum appeared to be an amino ester, afforded 2-amino-3-hydroxylamino propionic acid, obtained in a pure state by recrystallisation from water-ethanol, m.p. 165° (dec.).



An attempt to perform this reaction directly on 2-amino-3-chloropropionic acid was unsuccessful. The residue obtained after evaporation of the reaction mixture was identified as the pyruvic acid oxime, probably formed according to the scheme:

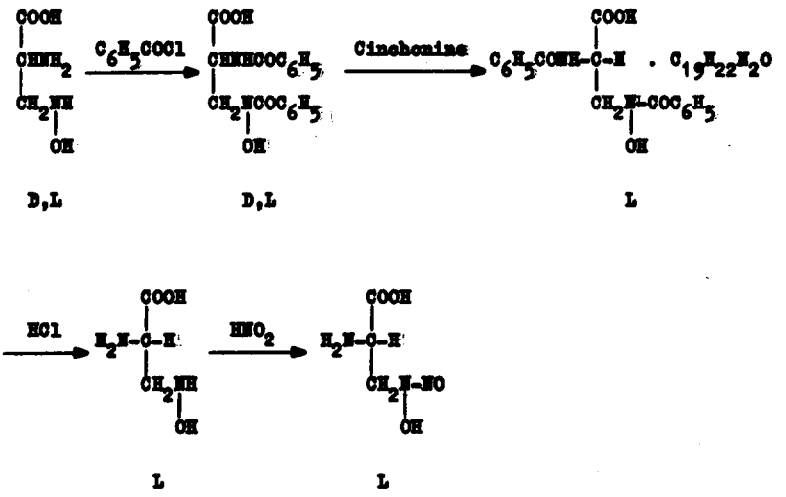


Treatment at 0° of the amino-hydroxylamino acid dissolved in dilute acetic acid with one molar equivalent of $NaNO_2$ yielded 2-amino-3-(N-nitrosohydroxylamino)propionic acid, recrystallized from water, m.p. 185° (dec.).

The above mentioned reactions had been carried out starting from racemic compounds; synthesis of the optically active derivatives was attempted starting from methyl L-2-acetamido-3-chloropropionate. However when this product was reacted with hydroxylamine an unexpected racemisation was observed, indicating that this reaction is not a simple replacement and D,L-2-amino-3-hydroxylaminopropionic acid was isolated.

The separation of the enantiomers was then studied. By treatment of the amino-hydroxylamino acid with benzoyl chloride, mixtures of N-benzoylhydroxylamino-benzoylamino and O-benzoyl-hydroxylamino-benzoylamino propionic acid were generally obtained, but a two step benzoylation in water with one molar equivalent of benzoyl chloride and one molar equivalent of NaOH each time gave, in practice, only 2-benzoylamino-3-(N-benzoylhydroxylamino)propionic acid (m.p. 170°). The optically active forms of this compound were then resolved as cinchonine salts by crystallisation from acetone-ether.

Acid hydrolysis of the L-dibenzoyl derivative gave L-2-amino-3-hydroxylaminopropionic acid, m.p. 163° (dec.); $[\alpha]_D$ = + 16.2 (c = 0.5% in N HCl). Nitrosation of this product, in the above mentioned conditions yielded alanosine, identical with the natural compound.



The D-2-amino-3-(N-nitrosohydroxylamino)propionic acid was obtained from the D-dibenzoyl-hydroxylamino-amino acid by the same procedure.

The synthesis of other α-amino-ω-nitrosohydroxylamino acids is in progress and will be published later with a more detailed account of the reactions here described.

References

1. Y.K.S. Murthy, J.E. Thiemann, C. Coronelli and P. Sensi, Nature, 1966 (in press).
2. C. Coronelli, C.E. Pasqualucci, G. Tamoni and G.G. Gallo, Il Farmaco, 1966 (in press).
3. J. Cason and F. Prout, J. Am. Chem. Soc., 71, 1219 (1949).