ETHYL ESTERS OF ω -CARBOXAMIDOALIPHATIC ACIDS -$^{14}CONH_2$.

V.Tolman, J.Cabak, J.Benes.
Isotope Laboratory of the Institutes for Biological Research
Czechoslovak Academy of Sciences, Prague.
Received on September 18, 1973.

SUMMARY

Ethyl esters of 2- cyanoacetic, 3- cyanopropionic and 4-cyanobutyric acids - ^{14}CN were prepared by reaction of the appropriate halogenated esters with potassium cyanide-^{14}C. Conversion of these cyanoesters into iminoether hydrochlorides and subsequent thermal decomposition gave ethyl esters of malonamic, succinamic and glutaramic acids -$^{14}CONH_2$.

Introduction

One of the functional groups in the molecule of antibiotic Tetracycline is the carboxamido group bound in position 2 of the Tetracycline skeleton. When searching for potential biosynthetic precursors of this antibiotic it seemed to be advantageous to synthetize some compounds containing the ^{14}C - carboxamido group. Amidoesters Ia - Ic were the substances of choice.

Of these compounds, Ic was not yet known in the literature, as well as all the three ^{14}C - labelled amidoesters. Being not possible to prepare the radioactive compounds Ia - Ic by usual synthetic methods, a new procedure was elaborated briefly described as follows.

As the starting radioactive material potassium cyanide - ^{14}C was used. Its interaction with halogenesters IIa - IIc gave the corresponding cyanoesters IIIa - IIIc. Using dimethylsulpho-

$H_2NO^{14}C - / CH_2 /_n - CO_2C_2H_5$

Ia ... n = 1

Ib ... n = 2

Ic ... n = 3

$X - / CH_2 /_n - CO_2C_2H_5$

IIa ... X = Br, n = 1

IIb ... X = Cl, n = 2

IIc ... X = Br, n = 3

$N^{14}C - / CH_2 /_n - CO_2C_2H_5$

IIIa ... n = 1

IIIb ... n = 2

IIIc ... n = 3

xide as a solvent[1] the nitrilation step is best carried out. Nevertheless, in the preparation of compound IIIa, this solvent could not be separated from the product due to the close boiling points. Ethanol was substituted for dimethylsulphoxide even though the yield of IIIa was remarkably lower.

The substances IIIa - IIIc were converted into iminoether hydrochlorides[2], thermal decomposition of which led to the desired amides Ia - Ic. These products were chromatographically homogeneous with the exception of Ic, this containing trace amounts of ammonium chloride which, however did not inhibit its further use.

Experimental

Potassium cyanide - ^{14}C was the product of Zentralinstitut für Kernforschung, Dresden, DDR / produced in 1967, radiochemical purity 3[illegible] - 39 % /. Radioactivity was measured on Mark I liquid scintillation counter / Nuclear Chicago /. TLC analyses were performed on Silufol^R in ether - ethanol / 9 : 1 /; detection by chlor - tolidine reagent[3]. Radioactive chromatograms were measured on Frieseke and Hoepfner apparatus.

Ethyl malonamate - 3 - ^{14}C / Ia /. The mixture of potassium cyanide / 140 mg; 2 mmoles /, potassium cyanide - ^{14}C / 1.6 mg; specific radioactivity = 6.5 mCi/mmole / and ethyl bromoacetate / 334 mg; 2 mmoles / in dry ethanol / 3 ml / was refluxed while stirring for 5 hours. Ethanol was evaporated and the product was extracted 8 hours with dry ether. After evaporation of ether 97 mg / 42.5 % / of ethyl cyanoacetate - ^{14}CN / IIIa / was isolated by distillation / 35 Torr, bath temperature 90 - 155° C /.

Dry hydrogen chloride was passed for 10 min. in a mixture of ester IIIa / 97 mg /, dry ethanol / 67 μl / and dry ether / 3 ml / cooled at -15° C. The mixture was allowed to stand overnight at 0° C and then ether was evaporated, while excluding the influence of moisture. The remaining iminoether hydrochloride was carefully heated to bath temperature 105° C/20 Torr, when the decomposition began. During 15 min. the mixture was slowly warmed to 115° C and cooled. The oily residue solidified within a week in a refrigerator. Yield, 68 mg / 62 % /, specific radioactivity 28.6 μCi/mmole. Inactive preparation had m.p. 43 - 45° C / lit.,[4] 45 - 46° C /.

Ethyl succinamate - 4 - ^{14}C / Ib /. The mixture of ethyl 3 - chloropropionate / 175 mg /, potassium cyanide / 107 mg / and potassium cyanide - ^{14}C / 26 mg; specific radioactivity = 6.5 mCi/mmole/ in dry dimethylsulphoxide / 3 ml / was stirred for 5 days in argone atmosphere, then water / 6 ml / was added and the nitrile IIIb was extracted with dry ether while stirring for 1 hour. The extract was evaporated, this being repeated twice with a small amount of chloroform. Dry ester IIIb was distilled and fraction boiling within the range 65 - 105° C/16 Torr was collected. Yield, 154 mg / 66 % / of ethyl 3 - cyanopropionate - ^{14}CN / IIIb /.

Ester IIIb / 134 mg / and dry ethanol / 55 μl / in dry ether / 2 ml / was saturated with dry hydrogen chloride for 45 min. at 0° C. The mixture was allowed to stand overnight in the refrigerator and then evaporated. The decomposition was carried out at bath temperature 94° C/15 Torr and was complete after 45 min. The crude product was sublimed at bath temperature 100 - 110° C and under the pressure 0.05 Torr. Yield, 125 mg / 71.3 % /; specific radioactivity 331 μCi/mmole. Inactive preparation had m. p. 66 - 70° C / lit.,[5] 70 - 74° C /.

Ethyl glutaramate - 5 - ^{14}C / Ic /. Ethyl 4 - cyanobutyrate - - ^{14}CN / IIIc / was prepared by the procedure described for ester IIIb. Ester IIc / 340 mg /, potassium cyanide / 70 mg /, potassium cyanide - ^{14}C / 50 mg; specific radioactivity = 5.1 mCi/mmole/ and dimethylsulphoxide / 3 ml / were used.

Yield, 230 mg / 93.2 % / of the product, which was distilled at bath temperature 110 - 145° C/0.15 Torr.

The mixture of ester IIIc / 230 mg /, dry ethanol / 85 μl / and dry ether / 2.5 ml / was saturated with dry hydrogen chloride at 0° C and further worked up by the same manner as in the case of compound Ib. The crude substance solidified on cooling. Yield, 118 mg / 45.6 % /, specific radioactivity was 976 μCi/mmole. Inactive preparation melted at 48 - 50° C / ether /. Analysis: found C, 52.65; H, 7.88; N, 9.18. Calc. for $C_7H_{13}NO_3$, C, 52.93; H, 8.21; N, 8.80 %.

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