LABELING PHARMACEUTICALS
WITH
RADIOACTIVE ISOTOPES

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MASTER

Monte Blau and Merril A. Bender
Department of Nuclear Medicine
Roswell Park Memorial Institute
666 Elm Street
Buffalo, New York 14203

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ABSTRACT

The objective of this program is to synthesize γ -emitting analogs of aliphatic amino acids which may be clinically useful for the localization of pancreas. The γ -radionuclides to be incorporated include ^{131}I , ^{123}I and ^{77}Br .

We have prepared β -chloro- α -aminobutyric acid which on interchange with ^{131}I would yield I-for-methyl analog of valine. This interchange is being currently studied. The bromo derivative has also been prepared and should be a more reactive substrate for halogen interchange reactions or direct isotope exchange with ^{77}Br .

Concurrently, we are synthesizing the I-for-methyl analog of leucine. In this connection, we have prepared two intermediates, namely, allyl glycine and α -amino- γ -valerolactone.HCl. Allyl glycine on reaction with HI should yield the desired leucine analog. The lactone on the other hand, should open with HI to yield the desired compound. The iodo analog of leucine will be labeled by isotopic exchange with ^{131}I or ^{123}I .

PREPARATION OF γ -EMITTING AMINO ACID ANALOGS

In order to achieve I-for-methyl substituted amino acid analogs two approaches are being considered, namely, halogen interchange¹ and isotopic exchange². Halogen interchange will involve the preparation of some appropriate chloro- or bromo-substituted amino acid derivatives with subsequent replacement of the halogen moiety with labeled iodine. On the other hand, isotopic exchange involves first preparing a 'cold' iodo-amino acid analog followed by exchange of the 'cold' iodine atom with the labeled one.

A. I-for-methyl analog of valine

With the ultimate aim to synthesize the desired valine analog (I),

Valine

(I)

a chloro-substituted amino acid derivative, β -chloro- α -aminobutyric acid (Ia) has been prepared in sufficient amounts for halogen interchange reactions according to the following reaction scheme:

dl-Threonine was esterified using thionyl chloride and methanol³ in order to protect the carboxyl group. This reaction gave a 95% yield of compound (2) (m.p. 123-125°, Literature 125°; I.R (KBr) C=O at 1725 cm⁻¹; T.L.C. one spot). Esterification⁴ of the threonine using HCl gas and methanol gave lower yields (68%). The ester.HCl (2) yielded the β -chloro derivative (3) upon reaction with PCl₅ in chloroform suspension⁵ (yield, 88%; m.p. 172-173°, lit. 173°; I.R (KBr) C=O at 1750 cm⁻¹, NH₃⁺ at 2010 cm⁻¹ and C-Cl at 610 cm⁻¹; T.L.C., one spot). The literature⁶ process

was modified by substituting chloroform for acetyl chloride as this improved the yield from 50% to 88%. Compound (3) was hydrolysed⁶ to the corresponding acid (4) with 20% aq. HCl. The compound (4) without isolation was dissolved in minimum amount of absolute ethanol and neutralized⁶ with pyridine to pH 6. Compound (Ia) separated out as white solid (yield, 72%; m.p. 168-170°, lit. 150-176; I.R. (KBr) absence of ester C=O at 1750 cm⁻¹ and appearance of a broad acid C=O 1655, 1575 cm⁻¹, C-Cl at 608 cm⁻¹; T.L.C., one spot; sodium fusion and Beilstein tests were positive for Cl). It could be recrystallized from hot water indicating good chemical stability.

The solution phase iodine interchange experiments on compounds Ia and (3) are in progress. Preliminary experiments indicate that β-Cl interchanged to β-I to the extent of 37% in case of compound (3). Labeled (I) was not prepared in these preliminary studies.

In order to increase the yield of the halogen interchange, the corresponding β-bromo-α-aminobutyric acid was prepared. The intermediate bromo-ester HBr corresponding to (3) in the above reaction scheme has been prepared in sufficient amounts (yield, 44%; m.p. 154-156°, lit. unknown; I.R. (KBr) C=O 1740 cm⁻¹, NH₃⁺ 1915 cm⁻¹, C-Br 553 cm⁻¹; elemental analysis being awaited; T.L.C., one spot; positive test for halogen). At the time of writing the bromo-derivative corresponding to (Ia) is being crystallized. In addition to the iodine interchange, the bromo-derivative will also be exchanged with a suitable bromine isotope and studied for its organ localizing properties.

B. I-for-methyl analog of leucine

With a view to prepare the desired leucine analog (II)

Leucine

(II)

the synthesis of γ -chloro- α -aminovaleric acid (IIa) was in progress at the time of our last annual report according to the following scheme:

In continuation of the condensation reaction between diethyl acetamidomalonate (6) and 1,2-dichloropropane (5), different condensing agents have been tried eg. NaOC_2H_5 ⁷, NaH ⁸ and K_2CO_3 ⁹. In these experiments (6) was recovered and no desired condensation product (8a) resulted.

(8)

Owing to the greater reactivity of (9) and dibromopropane, (6) and (5) were replaced with ethyl acetamidocyanoacetate (9) and 1,2-dibromopropane in some of the above condensation reactions. However, the desired condensation product (8b) could not be obtained despite prolong heating and other forcing reaction conditions.

As a result of the above unsuccessful attempts, another approach for the synthesis of γ -halo- α -aminovaleric acid was utilized.

(9)

(10)

(11)

(12)

Pyridine

(IIa)

OR

(11)

(13)

HX

(IIa)

where X=Cl, Br, I

The condensation product (10) was prepared according to Matsumoto⁹ (yield, quantitative; m.p. 87-88° (Lit. 88-89°); I.R. (KBr) C=O at 1750 and 1655 cm⁻¹; T.L.C., one spot). (10) was then acid or base hydrolysed to allyl glycine (11) as reported by Albertson¹⁰ (yield, 44%, lit. 34%; m.p. 253-255° (dec.), lit. 255-258°; I.R. (KBr) acid C=O at 1655 cm⁻¹, NH₃⁺ at 2080 cm⁻¹). HI is known¹¹ to add to a double bond in accordance with Markownikoff's rule. However, initial attempt to add HI to (11) when generated in situ to obtain (12) and finally our target compound (IIa) has been unsuccessful to date.

The lactone intermediate (13) was prepared according to Dittmer et. al.¹². The lactone when reacted with aqueous HI at various temperatures or under pressure in a glass bomb appears to open to possibly (IIa.HI) as evidence by paper chromatography, but reverts back to lactone structure during subsequent chemical steps as established by melting point, infra-red spectrum and thin layer chromatography.

In order to ensure that the reversion does not take place, anhydrous methanol and dry HI gas will be employed to open the lactone (13), but this last step has not been carried out.

Compound (IIa) will be used for labeling experiments as described for compound (Ia).

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