NEW IODINATED AMPHETAMINES BY RAPID SYNTHESIS FOR USE AS BRAIN BLOOD FLOW INDICATORS

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Our initial observations of the first-pass brain uptake of III (4-^{123}iodo-2,5-dimethoxyamphetamine)(1,2,3) have led to development by others of iodoamphetamines having different ring and nitrogen substitution patterns (4). Although ^{123}I is an ideal isotope for single photon tomographic imaging, a positron emitting isotope is required for Positron Emission Tomography (PET). The preferred isotope for this latter purpose is 3.6 min ^{122}I, a daughter of 20 hr ^{122}Xe; a generator system for the production of ^{122}I has been described (5). The iodoamphetamine derivatives described in (4) were radiolabelled, without exception, by exchange reactions which are inherently too slow for the short-lived ^{122}I. We have thus reinvestigated compounds that maintain the 2,5-dimethoxy ring pattern, as it allows the possibility of rapid iodination by direct substitution.

We have found that tertiary amines of the general formula I can be iodinated directly without attack on the basic nitrogen. In the preliminary biological investigations of various R^1 and R^2 nitrogen substituents in II, iodine isotopes with more conventional half lives were used (usually ^{131}I). Two labelled precursors, III and IV, allowed a broad versatility of nitrogen substitution. 4-Iodo-2,5-dimethoxyamphetamine (III) reacted readily with an appropriate aldehyde in the presence of $NaCNBH_3$ to yield II in which $R^1 = R^2$. Similarly, 4-iodo-2,5-dimethoxyphenylacetone (IV) was reacted with amines in the presence of $NaCNBH_3$. Primary amines (R^1NH_2) were the more effective, yielding II, with R^2 being hydrogen.

We have found that the direct labelling reaction of I → II ($R^1 = R^2 = CH_3$) provided maximum incorporation of radioiodine within one minute, and hence represents a practical procedure for synthesis with ^{122}I.

Using II labelled with ^{131}I and $R^1 = R^2 = CH_3$ (IIa) and $R^1 = R^2 = CH_2CH_3$ (IIb), we have measured brain, blood and other organ uptake in the rat. Compound IIa was studied in the dog by whole body scanning; brain uptake was 3.6 % at 5 min, and the maximum brain/blood ratio of 8.7 occurred at 8 min.

This type of compound thus appears to provide an excellent basis for radiopharmaceuticals which can provide a measure of regional brain blood flow with PET. The short $T_{\frac{1}{2}}$ of ^{122}I will result in a low patient radiation dose and the possibility of sequential measurements at short intervals. The ^{122}Xe → ^{122}I generator system can provide the isotope to institutions some distance from a production cyclotron.

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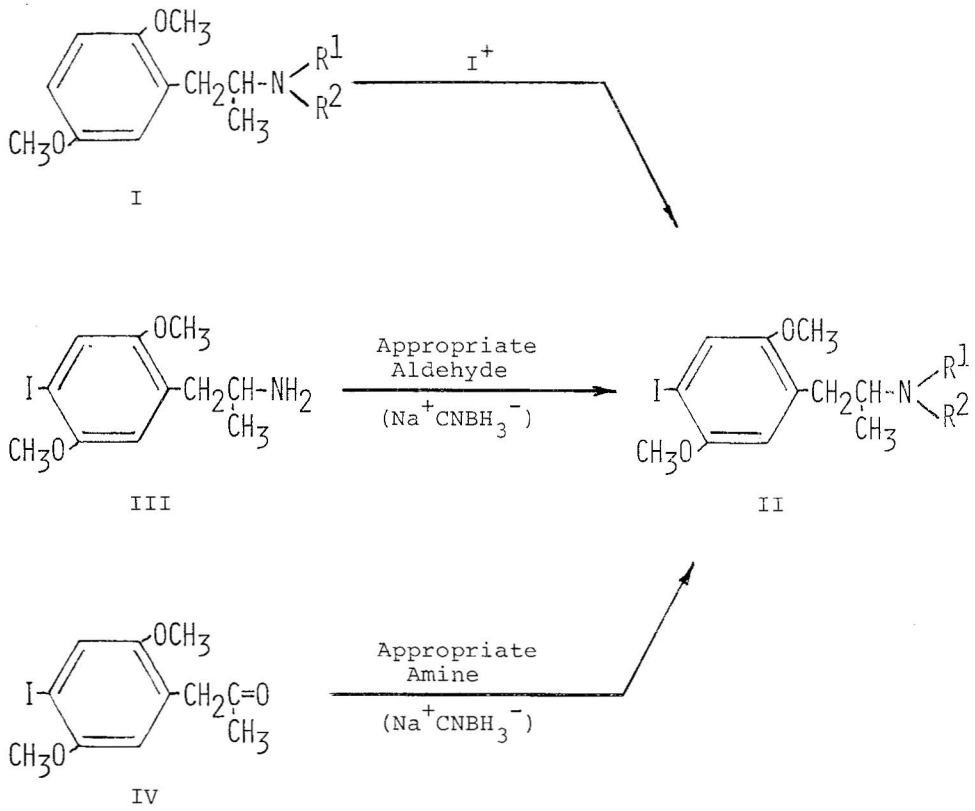
OCH3
CH2CH-N
CH3
R1
R2
CH3O
I+
I
III
Appropriate
Aldehyde
(Na+CNBH3-)
II
CH2C=O
Appropriate
Amine
IV