SYNTHESIS OF *p* ^{125}I-AMPHETAMINE

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SUMMARY

p-iodo-amphetamine was synthesized by the Sandmeyer reaction from iodine and *p*-NH_2-amphetamine, in which the amino aliphatic group was protected by an easily hydrolysable group : t-butyloxycarbonyl. Iodine was obtained by oxidation of Na ^{125}I with periodate in an acidic medium. The yield was 50 % with a specific activity of 25 mCi/mmol.

Key words : *p*-iodo-amphetamine, ^{125}I, Sandmeyer reaction.

INTRODUCTION

Iodophenylalkyl amines labelled with ^{125}I have been studied to develop a tracer which could be taken up in the brain (1). Among the substances studied isopropyl-*p*-iodo-amphetamine was selected to measure regional cerebral blood flow in man (2,3). *p*-iodo-amphetamine, a metabolite of isopropyl-*p*-iodo-amphetamine is also taken up in the brain with a high index (4). It was necessary to synthesize this new tracer with a high specific activity in order to test its properties.

The specific activity after the exchange reaction between *p*-iodo-amphetamine and radioactive iodine is always low and therefore we prefered to synthesize this molecule directly using the Sandmeyer reaction from radioactive iodine and *p*-amino-amphetamine (Scheme 1).

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RESULTS AND DISCUSSION

Nitration of the D-amphetamine using nitric acid (d = 1.49) (5) gave a mixture of nitro-D--amphetamine isomers from which the para isomer was obtained by distillation of the base and crystallisation of the hydrochloride (6.7). The amino aliphatic group was protected by the t-butyloxycarbonyl group (BOC) which was introduced by t-BOC-azide (8) and rapidly cleaved by mild acidic conditions. The aromatic nitro group was reduced by catalytic hydrazine reduction (9) instead of catalytic hydrogenation (7) to give the aromatic amino group. The Sandmeyer reaction could be carried out either in a chlorhydric aqueous medium which was incompatible with the presence of the BOC group, or in an anhydrous medium using an organic nitrite (10) instead of sodium nitrite. The reaction of amyl nitrite with arylamines generates aryl radicals and in the presence of iodine gives the corresponding aryl iodides (11). In addition to the expected product, non substituted amphetamine and a by-product which could be a dimere were found. Both of these were detected by gas chromatography. Their formation could be minimized using an excess of iodine, which was not feasible in the case of a synthesis using radioactive iodine. The percentage of by-products was kept to a minimum if there was an excess of iodine (1.2) and if amyl nitrite was added to the mixture of iodine and t-BOC-*p*-amino-amphetamine. The yield of *p*-iodo-amphetamine was increased using a large excess of amyl nitrite. Polymerisation was reduced to a minimum if the temperature did not exceed 105°C. Radioactive iodine was obtained by oxidation of Na ^{125}I using metaperiodate in an acidic medium, followed by extraction with the solvent used in the Sandmeyer reaction.

EXPERIMENTAL SECTION

Table I

Melting points were determined using a hot stage microscope (Reichert). Compound structures were established by IR (Perkin Elmer 457) and ^1H NMR (Jeol C-60 HL) spectra. Refraction index was measured at 22°C (O.P.L. refractometer). Thin layer chromatography was carried out on Merck 60 F 254 silica gel plates in $CHCl_3$ - AcOEt (4 : 1). Spots were visualized in UV at 250 nm and with I_2 vapours and ninhydrin. Purity of the final product was also verified by gas chromatography (Girdel 3000) : 2.10 m column packed with 3 % OV17 on chromosorb WHP, flame-ionization detector, column temperature 200°C, nitrogen carrier 30 ml/min.

p-nitro-amphetamine hydrochloride 2

100 g (0.74 mol) of dexamphetamine (De Laire) were added very slowly to a one liter three-necked flask containing 500 ml of HNO_3 (d = 1.49) frozen to - 20°C by dry ice . After stirring for 2 h at room temperature, the orange liquid was poured into 2 l of cold water and then extracted with 3 X 200 ml benzene. After neutralisation with 1.5 l NaOH 6N, the orange oily precipitate was extracted with 1 l and then 2 X 0.5 l benzene.The benzenic extracts were washed with water, dried on Na_2SO_4 and evaporated to an oily residue. This oil was distilled under 1 mm Hg pressure between 120-125°C. The distillate was dissolved in EtOH and saturated with gaseous HCl. The hydrochloride was precipitated by addition of ether and recrystallised from ethanol. Yield = 32 %.

t-BOC-*p*-NO_2-amphetamine 3

30 ml of an ether solution containing 50 mmol t-BOC-N_3, 10g MgO in suspension and 110 ml dioxanne were added 10 g (50 mmol) of *p*-NO_2-amphetamine-HCl dissolved in 40 ml water. After stirring for 24 h , the organic solvents were evaporated and the residue was extracted with 4 X 100 ml ether. The ether extract was washed with a citric acid solution, water and dried on Na_2SO_4.The solution was evaporated to dryness and the crystals were recrystallised from ether-hexane.

Yield = 65 %.

t-BOC-*p*-NH_2-amphetamine 4

4 g (14 mmol) of t-BOC-*p*-NO_2-amphetamine were dissolved in 150 ml ethanol and an excess of hydrazine (70 mmol). The solution was refluxed with 100 mg Pd 10 % on C. The end of the reaction was verified by TLC. The catalyst was filtered, the solvent was evaporated and the oil was dissolved in cyclohexane and allowed to crystallise. Yield = 70 %.

t-BOC-*p*-I-amphetamine 5

20 mg (0.08 mmol) of t-BOC-*p*-NH_2-amphetamine in 2 ml benzene were added to a 100 ml flask containing 12.6 mg (0.1 mmol) iodine then a solution of 47 mg (0.4 mmol) of amyl nitrite (n = 1.3860) in 3 ml benzene was added dropwise. After 1 h of refluxing,in an oil bath heated to 105°C,the benzene was evaporated.

p-I-amphetamine hydrochloride 6

The product obtained by the method above was stirred together with chlorhydric ethanol. When the reaction was complete, the solvent was evaporated and the orange solid obtained was purified by extraction, followed by crystallisation from ethanol. Yield = 50 %.

Retention times of the bases in GC :

amphetamine : 2.3 min

p-I-amphetamine : 2.8 min

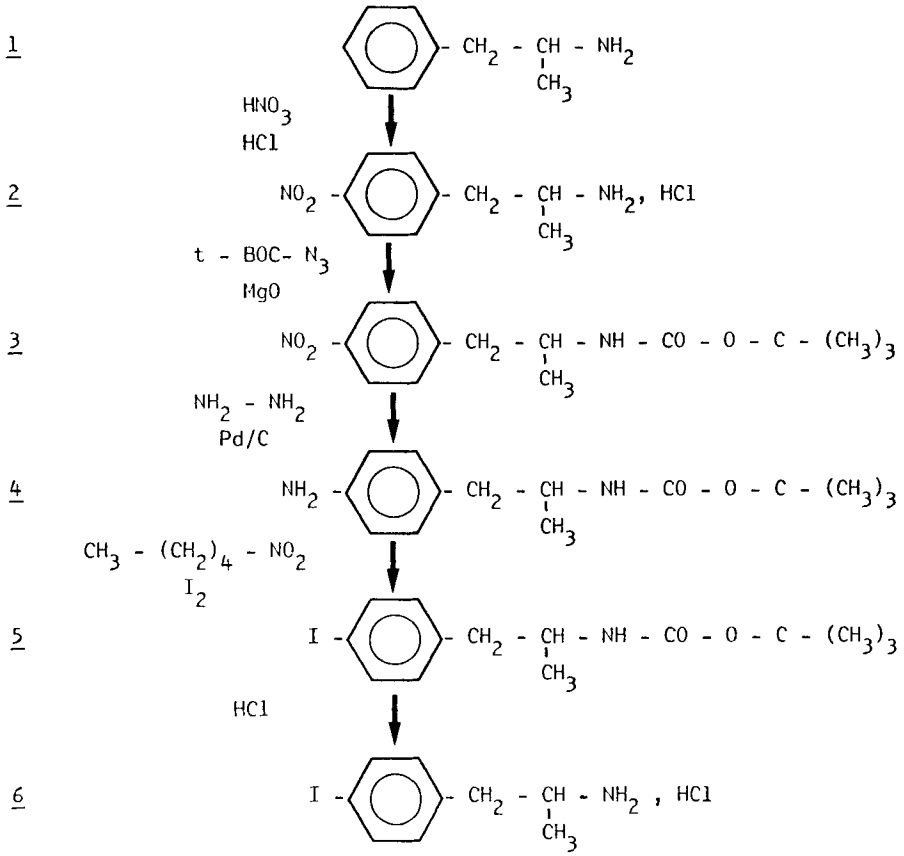
by-products : 6.3 and 9.6 min.

p ^{125}I-amphetamine, HCl

12.3 mg (0.83 mmol) NaI , 3.6 mg (0.17 mmol) KIO_3, 3 ml benzene and 5 ml H_2SO_4 0.1 N were added Na ^{125}I (2.5 mCi)(carrier free - CEA Saclay).The iodine produced 12 mg (SA 12.5 mCi/mmol) was extracted with benzene.The aqueous phase was again

extracted with 2 X 3 ml benzene. The 9 ml of solution obtained were used for the Sandmeyer modified reaction. The *p* ^{125}I-amphetamine, HCl can be used without purification and it is possible to enhance the specific activity by using a larger dose of Na ^{125}I.

Scheme 1



$$NaIO_3 + 3H_2SO_4 + 5Na\ I \longrightarrow 2\ Na_2SO_4 + Na_2SO_4 + 6I + 3H_2O$$

Table 1

Physicochemical properties of R  $CH_2 - CH(CH_3) - NH - R_2$

R_1	R_2	N°	Salt	M.W.	F	Yield	Cryst. Solv.	Rf	NMR
NO_2	H	2	HCl	216.5	194	32	EtOH	0.95*	7.86 (q) 3.8 à 2.8 (m) 1.24 (d)
NO_2	BOC	3	-	280	136	65	Et_2O + hexane	0.87	7.70 (q) 4.46 (m) 3.90 (m) 2.84 (m) 1.40 (s) 1.10 (d)
NH_2	BOC	4	-	250	48	70	cyclohexane	0.44	6.64 (q) 4.40 (m) 3.60 (m) 2.46 (m) 1.34 (s) 0.92 (d)
I	BOC	5	-	360	137	-	hexane	0.95	7.3 (q) 4.38 (m) 3.90 (m) 2.74 (m) 1.46 (s) 1.08 (d)
I	H	6	HCl	297.5	220	50	EtOH + Et_2O	0.40*	7.38 (q) 3.8 à 2.4 (m) 1.14 (d)

TLC in $CHCl_3$ - AcOEt (4 : 1) * + NH_3 vapours

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