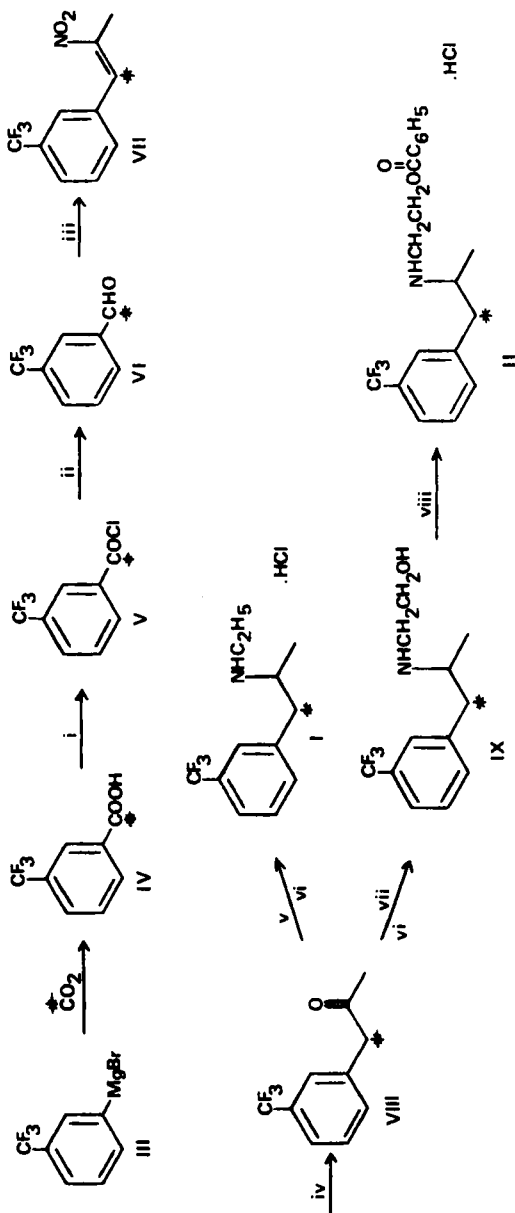




Scheme



\* denotes position of  $^{14}\text{C}$ -label

i =  $\text{SOCl}_2$ ; ii =  $\text{Pd}/\text{H}_2$ ; iii =  $\text{Pd}/\text{H}_2$ ; iv =  $\text{C}_2\text{H}_5\text{NO}_2/\text{Py}$ ; v =  $\text{Fe}/\text{HCl}$ ; vi =  $\text{C}_2\text{H}_5\text{NH}_2(\text{aq})$ ;  
 vii =  $\text{NaBH}_4$ ; viii =  $\text{H}_2\text{NCH}_2\text{CH}_2\text{OH}/n\text{-BuOH}$ ; ix =  $\text{C}_6\text{H}_5\text{COCl}$

## DISCUSSION

Carbonylation of Grignard reagent (III) derived from *m*-bromobenzotrifluoride with  $^{14}\text{CO}_2$  (total of 368 mCi) afforded the carboxylic acid (IV) with only a slight loss in activity<sup>1</sup>. Conventional treatment of the acid with thionyl chloride produced the acid chloride (V) in excellent yield, and this was smoothly reduced to the aldehyde (VI) under Rosenmund conditions<sup>2</sup>, provided that the acid chloride had been distilled. This reaction was conveniently monitored by IR spectroscopy - the acid chloride  $\text{C}=\text{O}$  absorption at  $1765\text{ cm}^{-1}$  being replaced by that of the aldehyde at  $1710\text{ cm}^{-1}$ . The aldehyde itself was not isolated; instead, the solution obtained from the reaction was used directly in the next stage. Although a variety of conditions were tried in this (condensation) reaction<sup>3</sup> using inactive material, the best overall conversion of acid chloride to the  $\beta$ -methyl- $\beta$ -nitrostyrene (VII) that could be achieved was only of the order of 40%. Treatment of this nitroolefin with iron and hydrochloric acid yielded the labelled phenylacetone (VIII) in 65% yield<sup>3</sup>. The ketone obtained in this manner was contaminated with a small amount of less polar material, but was of sufficient purity to be used in the next step.

The transformation of this ketone to the final products was accomplished in both cases by condensation with the appropriate primary amine and reduction of the resulting imine with sodium borohydride<sup>4</sup>. It was found that a thin layer chromatogram of the imine obtained from ethanolamine exhibited two spots of similar  $R_f$  values, one of which was identical to that of the ketone. However, since the IR spectrum of the mixture showed no carbonyl absorption whatsoever, but a new ( $\text{C}=\text{N}$ ) peak at  $1665\text{ cm}^{-1}$ , and subsequent reduction afforded a single amine (IX) in near-quantitative yield, it was concluded that the two spots corresponded to the *syn*- and *anti*-forms of the imine.

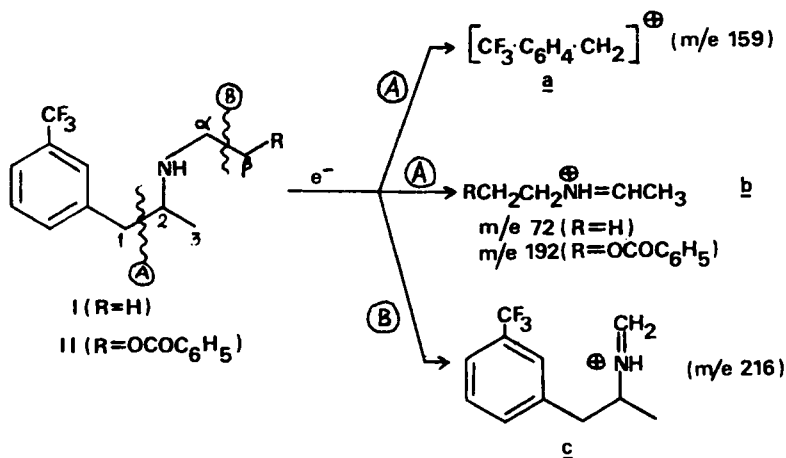
The free bases obtained in this manner were converted to the corresponding hydrochloride salt, and in the case of the ethanolamine derivative, subsequently esterified with benzoyl chloride. Purification of the final products was effected simply by recrystallising until TLC, in conjunction with autoradiography, indicated that the compound contained less than 2% of impurities. The combined activities of the two pure products so obtained amounted to 23.5 mCi, representing an overall radiochemical yield of 9%.

## MASS SPECTROMETRY

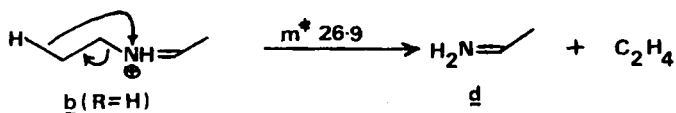
Mass spectrometry was used to confirm the identities and purity of all intermediates and final products. \*

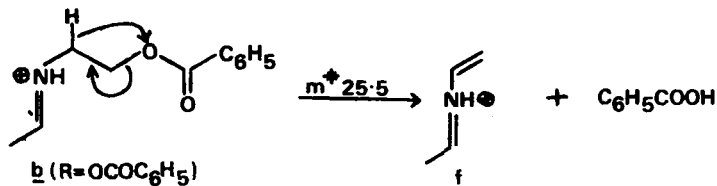
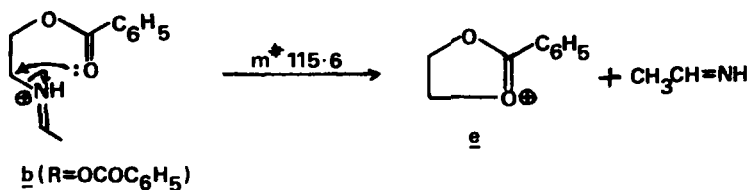
\*Mass spectra were recorded on a Hitachi Perkin Elmer RMS - 4 spectrometer at 70eV using the direct insertion probe. The two amines were introduced as the hydrochloride but vapourised as the free base.

The mass spectra of fenfluramine (I) and its  $\beta$ -benzoyloxy derivative (II) are, predictably, both dominated by fission of the 1,2 side-chain bond, since this is  $\beta$  to both the nitrogen atom and the aromatic ring. This gives rise to benzylic (a) and immonium (b and c) ions, whose stabilities are well known<sup>5</sup>:



Metastable peak analysis reveals that the extremely abundant ions b in both spectra undergo extensive secondary fragmentation. Thus, in the case of fenfluramine (I), elimination of 28 amu (presumably a neutral ethylene molecule) is the major decomposition pathway of this species - thereby generating ion d (m/e 44) - whereas in the case of the benzoyloxyethylamino derivative (II), rearrangement with concomitant loss of C<sub>2</sub>H<sub>5</sub>N - a reaction which is impossible for fenfluramine - produces ion e (m/e 149), and elimination of the elements of benzoic acid produces ion f (m/e 70), possibly in the manner outlined below:





## EXPERIMENTAL

### m-Trifluoromethylbenz- $^{14}\text{C}$ zoic acid (IV)

In the usual evacuated manifold apparatus<sup>1</sup>, barium carbonate  $^{14}\text{C}$  (368 mCi; specific activity 51.2 mCi/mmol - The Radiochemical Centre, Amersham) was treated cautiously with excess concentrated sulphuric acid, and the  $^{14}\text{CO}_2$  liberated was trapped in a flask containing 20 mmoles of m-trifluoromethylphenylmagnesium bromide (III) in THF (30 ml), cooled in liquid nitrogen. When the evolution and absorption of the gas were complete, the reaction solution was poured into dilute hydrochloric acid and the mixture extracted with ether. The organic phase was then extracted several times with 10% sodium hydroxide solution, and the combined ether-washed aqueous layers were acidified. Extraction with ether provided the product (1.456g) as a colourless, crystalline solid, shown to be identical with an authentic sample of IV by TLC, m.pt. and mixed m.pt. Total activity 346 mCi (94% radiochemical yield).

### m-Trifluoromethylbenz- $^{14}\text{C}$ oyl Chloride (V)

The above radioactive acid was diluted with unlabelled acid (5.894g), treated with thionyl chloride (30 ml), and heated under reflux for two hours. The solution was then evaporated to dryness and the residue distilled at atmospheric pressure as a colourless liquid (6.72g; 85%), b.pt.  $184^\circ\text{C}$ ;  $\nu_{\text{max}}$   $1765\text{ cm}^{-1}$ .

### m-Trifluoromethylbenz- $^{14}\text{C}$ aldehyde (VI)

A solution of the acid chloride (6.72g) in toluene (60 ml; dried over sodium) was treated with 5% Pd/BaSO<sub>4</sub> (2g) and 1% sulphur-quinoline poison<sup>2</sup> (5 drops),

then stirred and refluxed whilst a stream of dry hydrogen gas was slowly passed through it. After three hours, an IR spectrum showed that reaction was complete (see Discussion). The mixture was filtered, the residue washed with hot toluene (20 ml), and the solution of the aldehyde used directly in the next stage.

1-m-Trifluoromethylphenyl-2-nitropropene-1- $\text{-}^{14}\text{C}$  (VII)

The toluene solution from the previous reaction was treated with nitroethane (30 ml), pyridine (40 ml), and piperidine (1 ml), then stirred under reflux for 5 hours. The resulting brown solution was evaporated to dryness *in vacuo*, finally at 0.1 mm, and the residue was chromatographed on silica gel MFC (250 g). Elution with benzene (750 ml) provided the pure product as a golden oil (2.84 g; 38% overall yield from the acid chloride),  $\nu$  max 1530  $\text{cm}^{-1}$  (C:C-NO<sub>2</sub>) and 1665  $\text{cm}^{-1}$  (Ar-C=C-).

1-m-Trifluoromethylphenylacetone-1- $\text{-}^{14}\text{C}$  (VIII)

To a rapidly stirred mixture of the above nitro-olefin, toluene (30 ml), water (75 ml), iron powder (20 g) and ferric chloride (0.6 g) maintained at 80°C, concentrated hydrochloric acid (36 ml) was added over 30 minutes. After one hour at 80°C, a further portion of acid (20 ml) was added and the mixture was then heated and stirred at 100°C for 90 minutes. After cooling, the mixture was filtered and the separated organic phase evaporated to dryness. The residue was dissolved in acetone (10 ml) and treated dropwise with Jones' reagent<sup>6</sup> (ca. 1 ml) until in excess. The solution was then diluted, extracted with ether and the product isolated in the normal manner. This material (2.03 g) was chromatographed on silica gel MFC (150 g) in benzene. A further portion (300 ml) of benzene eluted a less polar impurity (0.25 g), whereas 5% ether-benzene provided the slightly impure product as a yellow oil (1.62 g; 65%,  $\nu$  max 1720  $\text{cm}^{-1}$ ).

1-m-Trifluoromethylphenyl-2-N-ethylaminopropane- $\text{-}^{14}\text{C}$ hydrochloride (I)

A solution of the above ketone (0.77 g) in aqueous ethylamine (70% w/w) was allowed to stand for 6 hours at room temperature ( $\nu$  max 1665  $\text{cm}^{-1}$ ; C=N), then treated with sodium borohydride (0.6g) and stirred overnight. The resulting mixture was cautiously added to excess dilute hydrochloric acid and extracted well with ether. The aqueous phase was separated, basified (50% NaOH solution), extracted with ether, washed, dried (MgSO<sub>4</sub>) and evaporated. The residual colourless oil (0.50 g; 58%) was dissolved in ether and treated with excess ethereal HCl. The resulting precipitate was filtered, washed with ether and recrystallised from methanol/ethyl acetate as colourless needles (0.49 g; 48%), m. pt. 169-170°C, not depressed upon admixture with a sample of authentic fenfluramine hydrochloride;  $\nu$  max 2750 and 1590  $\text{cm}^{-1}$  (R<sub>2</sub>NH<sub>2</sub>); specific activity 37.3  $\mu\text{Ci}/\text{mgm}$  (9.97 mCi/mmole); total activity 18.1 mCi. A silica gel thin layer chromatogram, developed in CHCl<sub>3</sub>/MeOH/NH<sub>4</sub>OH

(200:50:1 v/v; Rf 0.70) was subjected to autoradiography. Liquid scintillation counting showed the radiochemical purity to be >98%.

1-m-Trifluoromethylphenyl-2-N- $\beta$ -benzoyloxyethylaminopropane [ $^{14}\text{C}$ ]-hydrochloride (II)

A solution of the ketone (VIII; 0.85 g) and ethanolamine (0.45 g; 1.5 equivalents) in n-butanol (5 ml) was heated under reflux for eight hours, then cooled to 100°C, treated with sodiumborohydride (0.6 g) and stirred overnight. The resulting mixture was worked up in the same fashion as that described above for fenfluramine, to provide the N- $\beta$ -hydroxyethylamino derivative as a colourless, chromatographically-homogeneous oil (0.98 g; 94%). This was dissolved in benzene, treated with excess ethereal HCl and evaporated to dryness. The residual oily hydrochloride (1.00 g) was treated with benzoyl chloride (0.7 ml; 1.5 equivalents) and heated at 90°C for 1.5 hours. The mixture was allowed to cool, di-isopropyl ether (10 ml) was added and the resulting precipitate cooled to 0°C. The product was filtered, washed several times with di-isopropyl ether, and recrystallised twice from ethyl acetate as colourless needles (0.60 g; 37%), m.pt. and mixed m.pt. 159-160°C;  $\nu_{\text{max}}$  2760, 1590 ( $\text{R}_2\text{NH}_2$ ) and 1720  $\text{cm}^{-1}$  (Ar-COOR); specific activity 25.7  $\mu\text{Ci}/\text{mgm}$  (9.97 mCi/mmol); total activity 15.4 mCi. Radiochemical purity (determined after TLC in 100% methanol; Rf 0.59) was determined to be > 99%.

ACKNOWLEDGEMENTS

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4. The steps involving synthesis of the nitro-olefin and its reduction to the ketone were adapted from the procedures outlined in Org. Synthesis, Coll. Vol. 4, 573, and J. Labelled Compounds, Vol. VI, No. 3, 289.

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