SYNTHESIS OF PAPAVERINE AND QUINOPAVINE SPECIFICALLY LABELED WITH ^{14}C

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SUMMARY

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisoquinoline (papaverine) labeled with ^{14}C in either the benzyl or 4-carbon position and 1-(3,4-dimethoxyphenyl) 6,7-dimethoxyisoquinoline (quinopavine) labeled with ^{14}C at the 1,4 or 4-methoxyphenyl position were synthesized. The 3,4-dimethoxybenzoic acid-carboxyl-^{14}C.(I) was employed as the precursor in the synthesis of all the above compounds except the 4-methoxyphenyl labeled where 3-methoxy-4-^{14}C-methoxybenzoic acid was employed (XII). The reduction of 3,4-dimethoxybenzoylchloride ^{14}C (VII) led to the formation of 3,4-dimethoxybenzaldehyde-carbonyl-^{14}C (VIII) from which 2-(3,4-dimethoxyphenyl)-2-methoxyethylamine-2-^{14}C (XI) was obtained through reduction of the corresponding ^{14}C-labeled substituted nitrostyrene (IX). 3,4-Dimethoxybenzoic acid-carboxyl-^{14}C (I) was employed in the synthesis of (3,4-dimethoxyphenyl)-acetonitrile-2-^{14}C (IV) from which a) 2-(3,4-dimethoxyphenyl)-ethylamine-2-^{14}C (VI) was obtained on reduction and b) (3,4-dimethoxyphenyl)-acetic acid-2-^{14}C (V) on alkaline hydrolysis. On heating together at 200° C the

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corresponding acids and amines in the absence as well as in the presence of decaline (solvent), or by a Schotten-Baumann reaction, the corresponding amines were obtained and then cyclized in the presence of phosphorus oxychloride. The 3,4-dihydro-products were dehydrogenated in the presence of palladium-pumice which acted as a catalyst. The cyclization of N-(3,4-dimethoxyphenyl-2-methoxyethyl-2-^{14}C) 3,4-dimethoxyphenyl-acetamide (XVI) gave straightaway the corresponding ^{14}C-marked papaverine.

Introduction:

Although 1-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline (papaverine), 1-(3,4-dimethoxyphenyl)-6,7-dimethoxyisoquinoline (quinopavine) and their derivatives are widely used in medicine, little useful information exists on the mode of action, distribution, and metabolism of these compounds. As the use of isotopically labeled compounds in the study of biological problems and especially in the study of metabolism has been proved to be most effective, the synthesis of ^{14}C-labeled substituted isoquinolines is reported in the present work. The results of the biological tests will in due time appear elsewhere.

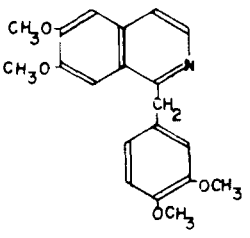
Discussion:

The present work deals with the synthesis of compounds having the general formulae in Figure 1.

These compounds marked with ^{14}C in different positions of the molecule were as follows:

I. a. 1-(3,4-Dimethoxybenzyl-^{14}C)-6,7-dimethoxyisoquinoline (XV)

b. 1-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisoquinoline-4-^{14}C (XVII) with specific activity 0.05 and 0.09 mCi/mmole, respectively.



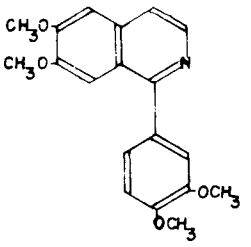


Figure 1

II. a. 1-(3,4-Dimethoxyphenyl)-6,7-dimethoxyisoquinoline-4-^{14}C (XIX)

b. 1-(3,4-Dimethoxyphenyl)-6,7-dimethoxyisoquinoline-1-^{14}C (XXI)

c. 1-(3-Methoxy-4-^{14}C methoxyphenyl)-6,7-dimethoxyisoquinoline (XXIII) with specific activity 0.05, 0.09 and 0.06 mCi/mmole, respectively.

The most important steps of labeling synthesis are shown in Figure 2.

The 3,4-dimethoxybenzoic acid-carboxyl-^{14}C (veratric acid-carboxyl-^{14}C) (I) necessary in the present work was obtained from the reaction of p-bromoveratrole with n-butyllithium at liquid nitrogen temperatures followed by addition of carbon-^{14}C dioxide [1,2]. 3,4-Dimethoxybenzoyl chloride-^{14}C (VII) was then easily prepared and on reduction it gave 3,4-dimethoxybenzaldehyde-carbonyl-^{14}C (veratraldehyde-carbonyl-^{14}C) (VIII). From this 3,4-dimethoxy-2-nitrostyrene-2-^{14}C (IX) and then 2-(3,4-dimethoxyphenyl)-2-methoxy-1-nitroethane-2-^{14}C (X) were obtained [3,4,5,6,7,8,9,10,12] while reduction of the latter gave 2-(3,4-dimethoxyphenyl)-2-methoxyethylamine-2-^{14}C (XI). In another sequence of reactions starting with veratric acid-carboxyl-^{14}C (I) and through the intermediate steps of 3,4-dimethoxybenzyl alcohol-benzyl-^{14}C (II) and 3,4-dimethoxybenzyl chloride-benzyl-^{14}C (III), (3,4-dimethoxyphenyl)-acetonitrile-2-^{14}C (IV) was obtained [11,12,13,14,15] from which 2-(3,4-dimethoxyphenyl)-ethylamine-2-^{14}C (homoveratrylamine-2-^{14}C) (VI) was obtained on reduction [16] and (3,4-dimethoxyphenyl)-acetic acid-2-^{14}C (homoveratric acid-2-^{14}C) (V) on alkaline hydrolysis [17]. Finally 3-methoxy-4-^{14}C-methoxybenzoic acid (veratric acid-4-methoxy-^{14}C)(XII) was obtained by methylation of vanilic acid with methyl-^{14}C-iodide and this was reacted with thionyl chloride to give the corresponding chloride (XIII). The starting materials thus prepared were employed in the synthesis of the labeled alkaloids.

Heating homoveratric acid-2-^{14}C together with homoveratrylamine at 200° C gave the corresponding amide N-(3,4-dimethoxyphenylethyl)-3,4-dimethoxyphenylacetamide-^{14}C (XIV)which on cyclization in the presence of phosphorus oxychloride and subsequent dehydrogenation of the dihydropapaverine thus formed gave the desired 1-(3,4-dimethoxybenzyl-^{14}C)-6,7-dimethoxyisoquinoline (XV) [18,19].

In another sequence of reactions N-(3,4-dimethoxyphenyl-2-methoxyethyl-2-^{14}C)-3,4-dimethoxyphenylacetamide (XVI) was obtained through a Schotten-Baumann reaction starting with 2-(3,4-dimethoxyphenyl)-2-methoxyethylamine-2-^{14}C (XI) and on reaction with phosphorus oxychloride 1-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline-4-^{14}C (XVII) was formed in good yield [18,19].

With another Schotten-Baumann reaction starting with 3,4-dimethoxybenzoyl chloride-^{14}C (VII) the corresponding amide was prepared and this was cyclized with phosphorus oxychloride to give dihydroquinopavine labeled in the 1-position and on reduction this compound gave the desired quinopavine (XXI) [18,19]. By similar reactions the rest of the substituted isoquinolines marked at different positions were prepared the general route always being formation of the corresponding ^{14}C-labeled amides, cyclization and dehydrogenation.

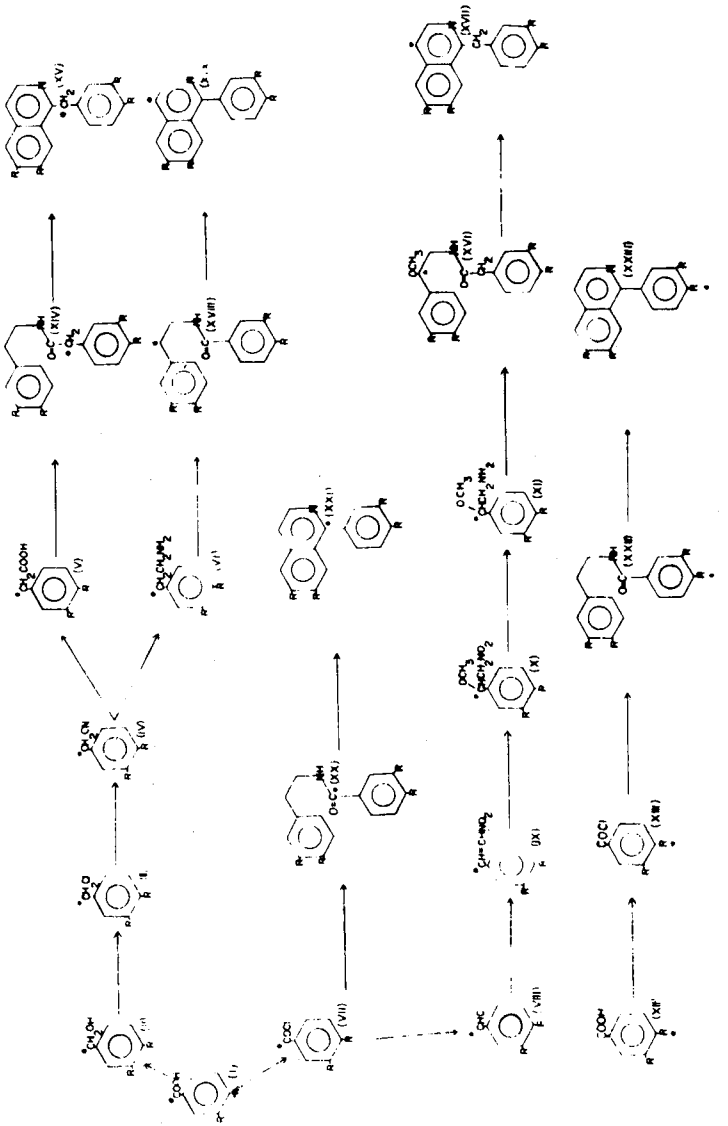


Figure 2

R = CH_3O-

The notation (•) indicates labeling with ^{14}C.

The reactions reported in this section were first carried out without radioactive isotopes and the product of each step was characterized by its physical constants (Table I), elemental analysis and infrared spectroscopy. The reactions were then repeated with labeled compounds and the final products were characterized by their physical constants, Kjeldahl determination of nitrogen and by comparison of their infrared spectra with those of their nonradioactive counterparts.

During the labeling synthesis the intermediate compounds were used in subsequent steps without further purification.

Experimental:

3,4-Dimethoxybenzoic acid-carboxyl-^{14}C (Veratric acid-carboxyl-^{14}C)(I).

n-Butyllithium (16 g, 249.78 mmoles) dissolved in petroleum ether was added to a flask connected with a gas-inlet, a separatory funnel and a vacuum system. The solvent was removed by aspiration, the colorless residue was cooled with liquid nitrogen and 25 ml of ether (peroxide free) was added. Dry nitrogen was passed through the flask, followed by the addition of p-bromoveratrole (3.5g, 10.00 mmoles) and the mixture was left for 15 min. This was followed by passage of carbon-^{14}C dioxide obtained as follows: Hydrochloric acid was added dropwise into a mixture of dry barium carbonate (0.8g, 4.05 mmoles) and barium carbonate-^{14}C (0.25g, 1.27 mmoles, 3 mCi). The carbon-^{14}C dioxide was suitably dried and was passed through the reaction mixture. Hydrochloric acid (8 ml) was then added; the mixture after reaching room temperature was ether-extracted. The combined ether extracts were treated with dilute sodium hydroxide and the aqueous layer was acidified with hydrochloric acid to give a fine precipitate; this was washed with cold water and dried to give 3,4-dimethoxybenzoic acid-carboxyl-^{14}C.

The reaction was repeated and the combined yields gave: Yield: 2.90 g (15.92 mmoles), 70.3% based on $Ba^{14}CO_3$, m.p. 181-182° C. Radiochemical yield: 4.22 mCi (1.46 mCi/g, 0.27 mCi/mmole).

3,4-Dimethoxybenzyl alcohol-benzyl-^{14}C (II).

Lithium aluminum hydride (2.74 g, 72.22 mmoles) as a suspension in anhydrous ether (500 ml) was put into a flask supplied with a Soxhlet extractor containing a mixture of veratric acid (3.90 g, 21.40 mmoles) and veratric acid-carboxyl-^{14}C (1.09 g, 5.98 mmoles, 1.59 mCi). The flask was heated for 12 hr, then it was allowed to cool and water (2.5 ml) was added, and the inorganic material was filtered off, the filtrate was dried ($MgSO_4$) and the solvent was removed to leave 3,4-dimethoxybenzyl alcohol-benzyl-^{14}C. Yield: 3.55 g (21.11 mmoles), 80.5% based on amount of I used. Radiochemical yield: 1.28 mCi (0.36 mCi/g, 0.06 mCi/mmole).

3,4-Dimethoxybenzyl chloride-benzyl-^{14}C (III).

Thionyl chloride (2 ml) was added dropwise to a mixture of calcium chloride and 3,4-dimethoxybenzyl alcohol-benzyl-^{14}C (3.55 g, 21.11 mmoles, 1.28 mCi). Calcium carbonate and anhydrous ether were then

added and the mixture was left overnight. The inorganic material was then filtered off, and the ether was distilled off to leave 3,4-dimethoxybenzyl chloride-benzyl-^{14}C. Yield: 3.6 g (19.29 mmoles), 87.5% based on II. Radiochemical yield: 1.12 mCi (0.31 mCi/g, 58.06 mCi/mmole).

(3,4-Dimethoxyphenyl)-acetonitrile-2-^{14}C (IV).

Potassium cyanide (1.95 g, 29.95 mmoles) in dimethyl sulfoxide (15 ml) was stirred for 10 min, then 3,4-dimethoxybenzyl chloride-benzyl-^{14}C (3.6 g, 19.29 mmoles, 1.12 mCi) was added and the mixture was stirred at room temperature for 6 hr. Water (100 ml) was then added and the aqueous layer was extracted with 1:1 ether-petroleum ether (b.p. 40-60° C); the organic layer was washed with water, dried, and the free solvent was distilled off to leave (3,4-dimethoxyphenyl)-acetonitrile-2-^{14}C. Yield: 3.30 g (18.62 mmoles), 91.1% based on III. Radiochemical yield: 1.02 mCi (0.31 mCi/g, 54.78 mCi/mmole).

(3,4-Dimethoxyphenyl)-acetic acid-2-^{14}C (Homoveratric acid-2-^{14}C) (V)

(3,4-Dimethoxyphenyl)-acetonitrile-2-^{14}C (1.52 g, 8.58 mmoles, 0.47 mCi) and potassium hydroxide (6 g) were added to a solution of water (6 ml) in ethylene glycol (15 ml) and the mixture was heated under reflux at 140° C for 12 hr. The mixture was then allowed to cool, acidified and extracted with ether. The ether layer was dried and the solvent was distilled off to leave (3,4-dimethoxyphenyl)-acetic acid-2-^{14}C. Yield: 1.6 g (8.15 mmoles), 95.5% based on the amount of IV used. Radiochemical yield: 0.45 mCi (0.28 mCi/g, 0.055 mCi/mmole).

2-(3,4-Dimethoxyphenyl)-ethylamine-2-^{14}C (Homoveratrylamine-2-^{14}C (VI).

Lithium aluminum hydride (0.5 g) suspended in anhydrous ether (500 ml) was added to a flask supplied with a Soxhlet extractor containing (3,4-dimethoxyphenyl)-acetonitrile-2-^{14}C (1.75 g, 9.89 mmoles, 0.54 mCi) and the mixture was heated under reflux for 12 hr. Water (4 ml) was then added, the inorganic material was filtered off and the ether layer was dried. The solvent was then removed to leave a yellowish liquid. This was treated with glacial acetic acid and the amine was generated from the acetate by treatment with 6N sodium hydroxide and extraction with ether. The ether extracts were dried and the solvent was distilled off to leave 2-(3,4-dimethoxyphenyl)-ethylamine-2-^{14}C. Yield: 1.71 g (.44 mmoles), 96.3% based on the amount of IV used, b.p. 170-172° C, n_D^{25} 1.4660. Radiochemical yield: 0.52 mCi (0.3 mCi/g, 0.055 mCi/mmole).

3,4-Dimethoxybenzoyl chloride-^{14}C (VII).

A mixture of veratric acid (3.2 g, 17.57 mmoles), veratric acid-carboxyl-^{14}C (1.74 g, 9.6 mmoles, 2.55 mCi) and thionyl chloride (15 ml) was heated under reflux at 150° C for 5 hr. The mixture was then left at room temperature for 12 hr. and the excess of thionyl chloride was removed under vacuum. This removal was aided by the addition of anhydrous benzene (5X10 ml) and evaporation of the solvent under vacuum. The yellowish powder thus obtained was recrystallized from

petroleum ether to give 3,4-dimethoxybenzoyl chloride-^{14}C. Yield: 5.25 g (26.17 mmoles), 91.4% based on the amount of I used, m.p. 70-71° C. Radiochemical yield: 2.33 mCi (0.44 mCi/g, 0.09 mCi/mmole).

3,4-Dimethoxybenzaldehyde-Carbonyl-^{14}C (Veratraldehyde-Carbonyl-^{14}C) (VIII).

3,4-Dimethoxybenzoyl chloride-^{14}C (4.1 g, 20.44 mmoles, 1.82 mCi) were dissolved in anhydrous xylene (20 ml) containing traces of quinoline-sulfur catalyst and palladium-barium sulfate 5% (0.15 g) catalyst. Hydrogen gas was bubbled through the mixture which was stirred for 5 hr.; the inorganic material was then filtered off and the solvent was distilled off to leave 3,4-dimethoxybenzaldehyde-carbonyl-^{14}C. Yield: 1.76 g (10.59 mmoles), 56% based on the amount of VII used. Radiochemical yield: 1.02 mCi (0.58 mCi/g, 0.1 mCi/mmole).

3,4-Dimethoxy-2-nitrostyrene-2-^{14}C (IX).

Nitromethane (0.5 g), glacial acetic acid (0.1 g), and benzylamine (0.12 g) were added to a solution of veratraldehyde-carbonyl-^{14}C (1.76 g, 10.59 mmoles, 1.02 mCi) in ethanol (20 ml). The mixture was heated under reflux at 50° C with stirring for 10 hr. It was then allowed to cool, filtered, washed with cold ethanol, and dried to give yellow crystals of 3,4-dimethoxy-2-nitrostyrene-2-^{14}C. Yield: 1.65 g (7.89 mmoles), 94.1% based on VIII. Radiochemical yield: 0.96 mCi (0.58 mCi/g, 0.12 mCi/mmole).

2-(3,4-Dimethoxyphenyl)-2-methoxy-1-nitroethane-2-^{14}C (X).

3,4-Dimethoxynitrostyrene-2-^{14}C (1.65 g, 7.89 mmoles, 0.96 mCi) as a suspension in cold methanol was strongly stirred while sodium methoxide (15 g, as metallic sodium dissolved in 20 ml of anhydrous methanol) was added dropwise; after the reaction was complete, glacial acetic acid (2.5 ml) was added and most of the alcohol was removed under vacuum. Water was then added in excess and 2-(3,4-dimethoxyphenyl)-2-methoxy-1-nitroethane-2-^{14}C was obtained as a precipitate. Yield: 1.89 g (7.83 mmoles), 96.9% based on X. Radiochemical yield: 0.93 mCi (0.49 mCi/g, 0.12 mCi/mmole).

2-(3,4-Dimethoxyphenyl)-2-methoxyethylamine-2-^{14}C (XI).

A solution of 2-(3,4-dimethoxyphenyl)-2-methoxy-1-nitroethane-2-^{14}C (1.89 g, 7.83 mmoles, 0.93 mCi) in 200 ml of anhydrous tetrahydrofuran was added to a mixture of anhydrous ether (300 ml) and lithium aluminum hydride (0.6 g), and the mixture was refluxed for 4 hr. After cooling, 3 ml of water was added. The inorganic residue so formed was filtered off. The ether extracts were dried and the solvent was distilled off to leave 2-(3,4-dimethoxyphenyl)-2-methoxy-1-nitroethane-2-^{14}C as a transparent yellow oil. Yield: 1.16 g (5.49 mmoles), 69.9% based on XI. Radiochemical yield: 0.65 mCi (0.56 mCi/g, 0.12 mCi/mmole).

3-Methoxy-4-^{14}C-methoxybenzoic Acid (Veratric acid-4-methoxy-^{14}C)(XII).

3-Methoxy-4-hydroxybenzoic acid (1.55 g, 9.22 mmoles) was heated over a steambath while aqueous potassium hydroxide (1.7 g) in water

(10 ml) and methyl-^{14}C iodide (1.42 g, 10.0 mmole, 0.51 mCi) were added dropwise in a way ensuring the continuous alkalinity of the mixture. The heating was continued for one hour after the addition; the mixture was then allowed to cool and hydrochloric acid was added; the precipitate thus formed was washed with cold water until the filtrate was chloride free to give white crystals of 3-methoxy-4-^{14}C-methoxybenzoic acid. Yield: 1.25 g (6.86 mmoles), 82.4% based on methyl-^{14}C iodide. Radiochemical yield: 0.42 mCi (0.34 mCi/g, 0.06 mCi/mmole).

3-Methoxy-4-^{14}C-methoxybenzoyl chloride (XIII).

It was prepared in the way described in paragraph VII starting with 3-methoxy-4-^{14}C methoxybenzoic acid (1.25 g, 6.86 mmoles, 0.42 mCi) to give 3-methoxy-4-^{14}C methoxybenzoyl chloride. Yield: 1.26 g (6.28 mmoles), 92.9% based on XII. Radiochemical yield: 0.39 mCi (0.31 mCi/g, 0.06 mCi/mmole).

N-(3,4-Dimethoxyphenylethyl)-3,4-dimethoxyphenylacetamide-^{14}C (XIV).

Homoveratric acid-2-^{14}C (1.6 g, 8.15 mmoles, 0.45 mCi) was added to homoveratrylamine (2.7 g, 14.9 mmole) and stirred under reflux at a temperature of 190° C for 4 hr. The mixture was then allowed to cool and a little acetone was added. The white precipitate thus obtained was recrystallized from ethyl acetate to give N-(3,4-dimethoxyphenylethyl)-3,4-dimethoxyphenylacetamide-^{14}C. Yield: 2.75 g (7.65 mmoles), 93.3% based on V. Radiochemical yield: 0.42 mCi (0.15 mCi/g, 0.05 mCi/mmole).

1-(3,4-Dimethoxybenzyl-^{14}C)-6,7-dimethoxyisoquinoline (XV).

N-(3,4-dimethoxyphenylethyl)-3,4-dimethoxyphenylacetamide-^{14}C (2.75 g, 7.65 mmoles, 0.42 mCi) in xylene (100 ml) and 6.5 ml phosphorus oxychloride was heated to 160° C under inert atmosphere for 90 min. The mixture was then allowed to cool when pet. ether (b.p. 40-60° C) was added an oily liquid was obtained which was dissolved in methanol and made alkaline with dilute aqueous potassium hydroxide. Cold water was added until a little precipitate appeared. Most of the methanol was removed under vacuum and the remainder was extracted with benzene, dried, and the solvent removed under vacuum. The remainder together with tetralin (15 g) was added to a 10% palladium on pumice catalyst (3.5 g) and the mixture was heated for 3 hr at a temperature of 200° C under inert atmosphere; it was then left standing at room temperature for 12 hr, and the solvent was removed under vacuum and the remainder extracted with hot chloroform (5X50 ml). Most of the chloroform was then removed and pet. ether (b.p. 40-60° C) was added to the remaining concentrated solution to give a cream-colored precipitate. This was dried and recrystallized from ethanol-ether to give 1-(3,4-dimethoxybenzyl-^{14}C)-6,7-dimethoxyisoquinoline. Yield: 2.03 g (5.98 mmoles), 76.2% based on XIV, m.p. 146-148° C. Radiochemical yield: 0.32 mCi (0.16 mCi/g, 0.05 mCi/mmole).

N-(3,4-dimethoxyphenyl-2-methoxyethyl-2-^{14}C)-3,4-dimethoxyphenylacetamide (XVI).

3,4-Dimethoxyphenylacetyl chloride (1.5 g, 6.99 mmoles) in ether (5 ml) and a 10% potassium hydroxide solution (5 ml) were added to

2-(3,4-dimethoxyphenyl)-2-methoxyethylamine-2-^{14}C (1.16 g, 5.49 mmoles, 0.65 mCi) in ether (10 ml) and the mixture was heated under reflux with stirring for 90 min. The mixture was then extracted with benzene, the extracts were dried and the solvent was distilled off to leave transparent brownish crystals of N-(3,4-dimethoxyphenyl-2-methoxyethyl-2-^{14}C)-3,4-dimethoxyphenylacetamide. Yield: 1.77 g (4.54 mmoles), 61.5% based on XI. Radiochemical yield: 0.40 mCi (0.23 mCi/g, 0.09 mCi/mmole).

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisoquinoline-4-^{14}C (XVII).

Phosphorus oxychloride (5 ml) in xylene (100 ml) was added to N-(3,4-dimethoxyphenyl-2-methoxyethyl-2-^{14}C)-3,4-dimethoxyphenylacetamide (1.77 g, 4.54 mmoles, 0.40 mCi) and the mixture was heated under reflux for 45 min; it was then extracted with hot water and the aqueous layer was allowed to cool and made alkaline. The white precipitate thus obtained was extracted with ether, and after the ether layer was dried the solvent was distilled off to leave a cream-colored precipitate, which was recrystallized from ethanol-ether to give 1-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline-4-^{14}C. Yield: 1.10 g (3.24 mmoles), 70.0% based on XVI. Radiochemical yield: 0.28 mCi (0.25 mCi/g, 0.09 mCi/mmole).

N-(3,4-Dimethoxyphenylethyl-2-^{14}C)-3,4-dimethoxybenzamide (XVIII).

3,4-Dimethoxybenzoyl chloride (2.8 g, 13.96 mmoles) was added with stirring to homoveratrylamine-2-^{14}C (1.71 g, 9.44 mmoles, 0.52 mCi) in anhydrous ether (10 ml) while care was taken to keep the temperature low. The mixture was stirred at room temperature for 6 more hr. The solvent was then distilled off and the white powder thus obtained was recrystallized from ethyl acetate to give N-(3,4-dimethoxyphenylethyl-2-^{14}C)-3,4-dimethoxybenzamide. Yield: 2.93 g (8.48 mmoles), 88.46% based on VI. Radiochemical yield: 0.46 mCi (0.16 mCi/g, 0.05 mCi/mmole).

1-(3,4-Dimethoxyphenyl)-6,7-dimethoxyisoquinoline-4-^{14}C (XIX).

Phosphorus oxychloride (6.5 ml) was added to solution of N-(3,4-dimethoxyphenylethyl-2-^{14}C)-3,4-dimethoxybenzamide (2.93 g, 8.48 mmoles, 0.46 mCi) in toluene (100 ml) and the mixture was stirred and heated under reflux at 150-155° C for 90 min under an inert atmosphere; the solvent and the excess of phosphorus oxychloride were removed under vacuum and the remainder was dissolved in water and extracted once with a little ether. The aqueous layer was rendered alkaline with ammonium hydroxide and the precipitate thus obtained was dehydrogenated as described in Paragraph XV using 10% palladium on pumice (6 g). The crude product was recrystallized from ethanol-ether to give 1-(3,4-dimethoxyphenyl)-6,7-dimethoxyisoquinoline-4-^{14}C. Yield: 2.84 g (8.73 mmoles), 91.3% based on XVIII. Radiochemical yield: 0.42 mCi (0.15 mCi/g, 0.05 mCi/mmole).

N-(3,4-Dimethoxyphenylethyl)-3,4-dimethoxybenzamide-^{14}C (XX).

It was prepared as described in Paragraph VIII starting with homoveratrylamine (1.5 g, 8.28 mmoles), 3,4-dimethoxybenzoyl chloride-^{14}C (1.08 g, 5.38 mmoles, 0.48 mCi). The crude product was recrystallized

from ethyl acetate to give N-(3,4-dimethoxyphenylethyl)-3,4-dimethoxybenzamide-^{14}C. Yield: 1.71 g (4.95 mmoles), 91.7% based on the amount of VII used. Radiochemical yield: 0.44 mCi (0.26 mCi/g, 0.09 mCi/mmole).

1-(3,4-Dimethoxyphenyl)-6,7-dimethoxyisoquinoline-1-^{14}C (XXI).

It was prepared as described in Paragraph XIX starting with N-(3,4-dimethoxyphenylethyl)-3,4-dimethoxybenzamide-^{14}C (1.71 g, 4.95 mmoles, 0.44 mCi) and phosphorus oxychloride (4.5 ml) while the dehydrogenation was effected with 10% palladium on pumice catalyst (2 g). The crude product was recrystallized from ethanol-ether to give 1-(3,4-dimethoxyphenyl)-6,7-dimethoxyisoquinoline-1-^{14}C. Yield: 1.41 g (4.33 mmoles), 88.6% based on XX. Radiochemical yield: 0.39 mCi (0.28 mCi/g, 0.09 mCi/mmole).

N-(3,4-Dimethoxyphenylethyl)-3-methoxy-4-^{14}C-methoxybenzamide (XXII).

It was prepared as described in Paragraph XVIII starting with homoveratrylamine (1.63 g, 8.99 mmoles) and 3-methoxy-4-^{14}C-methoxybenzoyl chloride (1.26 g, 6.28 mmoles, 0.39 mCi). The crude product was recrystallized from ethyl acetate to give N-(3,4-dimethoxyphenylethyl)-3-methoxy-4-^{14}C methoxybenzamide. Yield: 1.93 g (5.59 mmoles), 87.2% based on XIII. Radiochemical yield: 0.34 mCi (0.18 mCi/g, 0.06 mCi/mmole).

1-(3-methoxy-4-^{14}C-methoxyphenyl)-6,7-dimethoxyisoquinoline (XXIII).

It was prepared as described in Paragraph XIX starting with N-(3,4-dimethoxyphenylethyl)-3-methoxy-4-^{14}C-methoxybenzamide (1.93 g, 5.59 mmoles, 0.34 mCi) and phosphorous oxychloride (4 ml). The crude product was dehydrogenated with 10% palladium on pumice (2 g) and the product was recrystallized from ethanol-ether to give 1-(3-methoxy-4-^{14}C-methoxyphenyl)-6,7-dimethoxyisoquinoline. Yield: 1.65 g (5.07 mmoles) 91.2% based on XXII. Radiochemical yield: 0.31 mCi (0.19 mCi/g, 0.06 mCi/mmole).

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