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Synthesis of N-[4-(2-Dimethylaminoethoxy)benzyl-α-^{14}C]-3,4,5-trimethoxybenzamide hydrochloride and N-[4-(2-Methylaminoethoxy)benzyl-α-^{14}C]-3,4-diethoxybenzamide hydrochloride

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SUMMARY

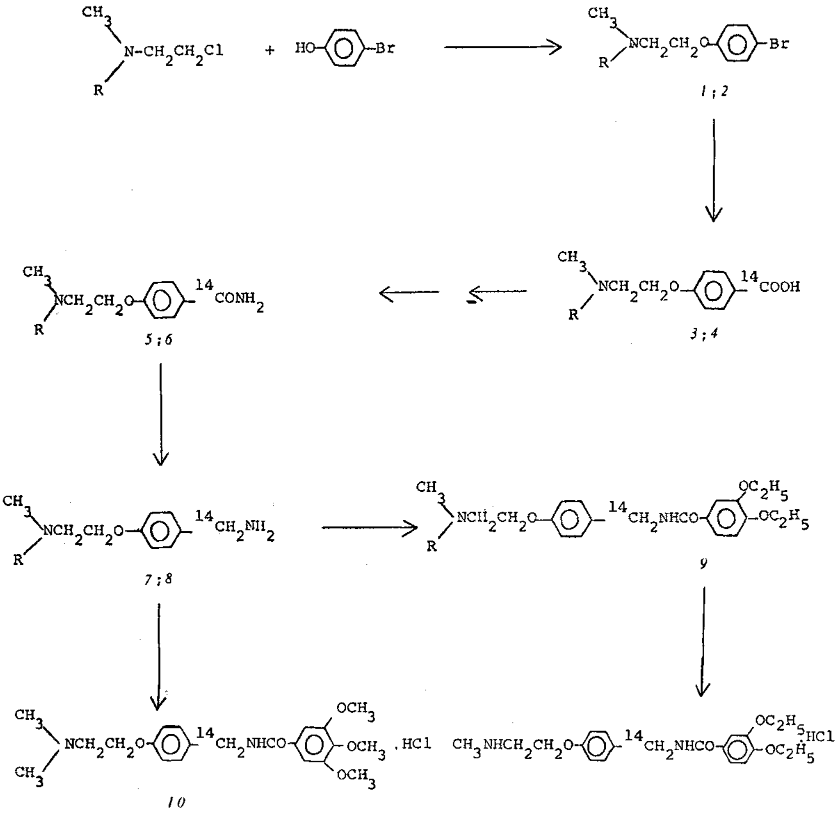
The anti-emetic compounds N-[4-(2-dimethylaminoethoxy)benzyl-α-^{14}C]-3,4,5-trimethoxybenzamide hydrochloride (10) and N-[4-(2-methylaminoethoxy)benzyl-α-^{14}C]-3,4-diethoxybenzamide hydrochloride (11) were prepared. The synthesis of 10 in four steps provided the purified material in 29 % yield from carbon dioxide. The same series of reactions was used to prepare N-[4-(2-benzylmethylaminoethoxy)benzyl-α-^{14}C]-3,4-diethoxybenzamide (9), which after an additional debenzylation step furnished 11 in 56 % yield based on carbon dioxide.

INTRODUCTION.

Metabolic studies required labelling of the anti-emetic compounds N-[4-(2-dimethylaminoethoxy)benzyl]-3,4,5-trimethoxybenzamide hydrochloride (1) (*10*) and N-[4-(2-methylaminoethoxy)benzyl]-3,4-diethoxybenzamide (2) (*11*). The alpha position of the benzylamine moiety was chosen as the site for incorporation of ^{14}C. Both the ease of chemical synthesis and the requirements of the metabolic studies justify this choice. The alkoxy benzoic acids, possible breakdown products, can be assayed by fluorometric methods accurately and with high sensitivity; therefore eliminating the necessity of labelling the benzoic acid fragment.

The alpha position of the benzylamine moiety can be labelled in several ways. One method involves a Willgerodt reaction on the substituted acetophenone followed by a Hoffman reaction (3). Others utilize reduction of a cyano or carboxamide group of which the amide gave superior yields and a more easily purified product.

The starting bromides *1* and *2* were prepared from p-bromophenol and 2-dimethylaminoethyl chloride and 2-benzylmethylaminoethyl chloride, respectively. The 4-(2-dimethylaminoethoxy)-1-bromobenzene was converted to the Grignard reagent with magnesium in refluxing tetrahydrofuran. Carbonation of the Grignard reagent at −25° C furnished the acid *4* in 91 % yield. The amide *6* was prepared via the acid chloride and shown by T.L.C. analysis to be 95 % radiochemically pure. Without further purification, the amide was reduced with lithium aluminum hydride and the resulting amine *8* was treated with 3,4,5-trimethoxybenzoyl chloride. The N-[4-(2-dimethylaminoethoxy)-benzyl]-3,4,5-trimethoxybenzamide (*10*) was isolated as the hydrochloride in 29 % overall yield based on carbon dioxide.



R = CH_3 for *2* *4* *6* *8*
R = $C_6H_5CH_2$ for *1* *3* *5* *7* *9*

In order to prepare N-[4-(2-methylaminoethoxy)benzyl]-3,4-diethoxybenzamide (*11*) the same sequence of reactions was used except that all intermediates were purified to assure the success of the synthesis. The Grignard reagent of the starting bromide (*1*) was carbonated in tetrahydrofuran at -20° C and the acid *3* was isolated in 84 % yield. The acid was converted to the amide *5*, via the acid chloride, reduced to the amine *7*, and acylated with 3,4-diethoxybenzoyl chloride in 98 %, 96 %, and 91 %, yields, respectively. A final catalytic debenzylation of *9* furnished the final product *11* which was isolated as the hydrochloride.

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EXPERIMENTAL (4).

4-(2-Benzylmethylaminoethoxy)bromobenzene (1). — To a slurry of 8.16 g (0.12 mole) of freshly prepared sodium ethoxide in 200 ml of chlorobenzene was added 17.3 g (0.10 mole) of p-bromophenol. The mixture was heated to reflux for 2 hrs. During the heating period approximately 25 ml of solvent was distilled. To the refluxing slurry a solution of 27.5 g (0.15 mole) of 2-benzylmethylaminoethyl chloride in 250 ml of chlorobenzene was added dropwise over one hour. The reaction mixture was refluxed for 18 hrs. After cooling to room temperature, the solution was filtered and the filtrate evaporated. Distillation furnished 28.7 g (90 %) of *1*; b. p. 155-175° C (0.025 mm).
Anal. Calcd for $C_{16}H_{18}BrNO$: C, 60.01; H, 5.66; N, 4.38;
Found : C, 60.14; H, 5.66; N, 4.71.

4-(2-Dimethylaminoethoxy)bromobenzene (2) (5, 6, 7). — This compound was prepared by a method similar to the one indicated above from 4-bromophenol and 2-dimethylaminoethyl chloride. It was isolated as the hydrochloride, m. p. 156-157° C from methanol-ether.
Anal. Calcd for $C_{10}H_{14}NOBr.HCl$: C, 42.80; H, 5.38;
Found : C, 42.50; H, 5.40.

4-(2-Benzylmethylaminoethoxy)benzoic-^{14}C-acid (3). — A mixture of 243 mg (10 mmole) of magnesium, 5 ml of tetrahydrofuran, a crystal of iodine and a few drops of the bromide *1* was heated to reflux. The mixture was treated dropwise while stirring with a solution of 3.20 g (10 mmole) of *1* in 10 ml of tetrahydrofuran. After addition was complete, the reaction was heated at reflux for 45 min. The flask containing the Grignard reagent was attached to a vacuum line and frozen in liquid nitrogen. The flask was evacuated to 0.001 mm and 5 mmole (30 mci) of carbon dioxide-^{14}C was vacuum transferred into the flask. The reaction mixture was warmed to -20° C and stirred for 20 min at which time, the carbon dioxide absorption was complete. The reaction mixture was treated with 5 ml of water and stirred until all the solids dissolved. The resulting solution was brought to pH 1 with concentrated hydrochloric acid and then washed with ether. The ether was extracted twice with 1N hydrochloric acid and all aqueous solutions were combined. The pH was adjusted to 12 with 50 % aqueous sodium hydroxide and filtered. The filtrate was washed with ether and the pH brought to 6.2 (8). The solution was concentrated to approximately 100 ml and continuously extracted with ether for 3 days. Evaporation of the ether furnished 1.66 g of crude 4-(2-benzylmethylaminoethoxy)benzoic-^{14}C-acid. Radiochemical assay showed the yield to be 83 % and the purity to be 95 %. A non-labelled sample of *3* obtained in the manner described and purified by recrystallization from methanol-ether melted at 105-107° C.

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.55; H, 6.72; N, 4.91;
Found : C, 71.79; H, 6.97; N, 4.79.

4-(2-Dimethylaminoethoxy)benzoic-^{14}C-acid (4). — The Grignard reagent of 4-(2-dimethylaminoethoxy)bromobenzene (*2*) was prepared in the manner indicated above. Carbon dioxide (5 mmole, 24 mCi) was reacted with 7.5 mmole of this Grignard reagent in tetrahydrofuran at $-80°$ C for 15 min followed by 15 min at $-25°$ C. Isolation of the acid was achieved by continuous extraction with ether at pH 6.6 (9). The ether extract was evaporated to dryness and the residue extracted with boiling ethanol. Evaporation of the ethanol furnished 1.84 g (10) of a tan-white solid. A non-labelled sample of 4-(2-dimethylaminoethoxy)benzoic acid was prepared and isolated as the hydrochloride from water-acetone, m. p. 263-265° C (dec).

Anal. Calcd for $C_{11}H_{15}NO_3.HCl$: C, 53.76; H, 6.57;
Found : C, 53.62; H, 6.58.

4-(2-Benzylmethylaminoethoxy)benz-^{14}C-amide (5). — The crude acid (*3*) 1.66 g, was refluxed with thionyl chloride (11) for 3 hrs. The thionyl chloride was evaporated in vacuum and the last traces removed by evaporating with three 25 ml portions of benzene. The acid chloride was treated with 20 ml of anhydrous ammonia. The ammonia was allowed to evaporated and the residue partitioned between 10 ml of 2N sodium hydroxide and 30 ml of chloroform. The layers were separated and the aqueous layer extracted twice with chloroform. The combined chloroform extract was washed with water, dried over magnesium sulfate, treated with charcoal and evaporated to dryness. The residue was recrystallized from ethyl acetate-ether-petroleum ether (1 : 1 : 2). The yield based on the acid *3* was 98 %; m. p. 82-83° C. A non-labelled sample of the amide *5* prepared as above was found to melt at 78-81° C.

Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.79; H, 7.10; N, 9.85;
Found : C, 71.69; H, 7.32; N, 9.74.

4-(2-Dimethylaminoethoxy)benz-^{14}C-amide (6). — The total amount of crude 4-(2-dimethylaminoethoxy)benzoic acid (*4*) was converted to the amide as indicated above. After evaporation of the ammonia, the solid residue was distributed between 2N sodium hydroxide and ether-ethyl acetate (1 : 1) and the aqueous phase re-extracted twice more with the same solvent mixture followed by two extractions with ethyl acetate. All organic phases were combined, washed twice with water, dried over anhydrous magnesium sulfate and evaporated to dryness. Yield : 901 mg of a yellow solid.

T.L.C. analyse for radiopurity on a silica gel plate using methanol-chloroform-ethyl acetate-NH_4OH (30 : 30 : 30 : 1) showed the compound to be about 95 % radiochemically pure. It was used in the next step without further purification.

A non-labelled sample, recrystallized from ethyl acetate-ether-petroleum ether, melted at 142-144° C.

Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.41; H, 7.74;
Found : C, 63.28; H, 7.95.

4-(2-Benzylmethylaminoethoxy)benzyl-^{14}C-amine (7). — A solution of 1.15 g (4.05 mmole) of the amide *5* in 35 ml of tetrahydrofuran was added dropwise to a slurry of 1.04 g of lithium aluminum hydride in 45 ml of tetrahydrofuran. After addition was complete the mixture was refluxed for 21 hrs, cooled to 0° C and then 1.2 ml of 15 % aqueous sodium hydroxide was added. The mixture was stirred, 10 ml of water added and then it was allowed to stand at room temperature for 45 min. The mixture was filtered and the solid was washed with tetrahydrofuran and chloroform. The filtrate was concentrated to approximately 10 ml, diluted with 10 ml of water and extracted three times with chloroform. The combined extract was dried over magnesium sulfate, concentrated and vacuum distilled to give 1.06 g (96 %) of the amine *7*. Radiochemical purity by T.L.C. analysis was 98 %. A non-labelled sample of *7* was prepared as above and distilled for analysis : b. p. 165-175° C (0.05 mm).

Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.50; H, 8.22; N, 10.37;
Found : C, 75.04; H, 8.08; N, 10.13.

4-(2-Dimethylaminoethoxy)benzyl-^{14}C-amine (8) (2, 12). — To a stirred suspension of 823 mg of lithium aluminum hydride in 50 ml of dry tetrahydrofuran was added a solution of 901 mg of 4-(2-dimethylaminoethoxy)-benz-^{14}C-amide in 40 ml dry tetrahydrofuran over a period of 1 hr. The mixture was stirred at room temperature for 1 hr and then refluxed for 24 hrs. The dark gray mixture was cooled with ice and worked up by slowly adding 15 ml of a saturated aqueous ammonium chloride solution. After stirring of 1 hr at room temperature the solution was decanted from the pasty residue. The latter was washed with tetrahydrofuran and distributed between 2N sodium hydroxide and ethyl acetate. The aqueous phase was re-extracted three times with ethyl acetate and the extract was washed with water. All organic phases were combined, dried over anhydrous magnesium sulfate and evaporated, yielding 1.027 g of an oily substance.

T.L.C. analyses for radiopurity on a silica gel plate using methanol-chloroform-ethyl acetate-NH_4OH (30 : 30 : 30 : 1) showed the compound to be about 95 % radiochemically pure. It was used in the next step without further purification.

N-[4-(2-Benzylmethylaminoethoxy)benzyl-α-^{14}C]3,4-diethoxybenzamide (9). — A mixture of 1.06 g of *7*, 10 ml of water and 10 ml of methylene chloride was cooled to 0° C. The mixture was stirred and 10 ml of 0.4 N sodium hydroxide and a solution of 910 mg of 3,4-diethoxybenzoyl chloride in 10 ml of methylene chloride were added simultaneously. The temperature was maintained at 0-5° C during the addition, held at that temperature for 4 hrs and then raised to 10° C for 1 hr. The layers were separated and the aqueous layer was extracted three times with methylene chloride. The combined methylene chloride extract was dried over magnesium sulfate then evaporated to dryness. The residue was crystallized from toluene-petroleum ether to furnish 1.64 g (21.2 mCi, 91 %) of *9*, m. p. 107.5-108° C (lit. 109-111° C).

N[4-(2-Methylaminoethoxy)-benzyl-α-^{14}C]-3,4-diethoxybenzamide hydrochloride (11). — A solution of 1.64 g (3.55 mmole) of *9* in 18 ml of acetic acid-ethanol (3 : 1) and 600 mg of 10 % palladium on charcoal was stirred under a hydrogen atmosphere until the theoretical amount of hydrogen (3.55 mmole) was taken up. The uptake of hydrogen was complete in 30 min. The mixture was filtered and the catalyst washed with methylene chloride. The solvent was evaporated in vacuum and the residue converted to the hydrochloride *11* with a slight excess of methanolic hydrogen chloride. The methanol was evaporated and the hydrochloride was recrystallized from acetonitrile-acetone (1 : 1) to furnish 1.17 g (16.85 mCi at 5.93 mCi/mmole) of *11* : yield 80 % from *9*, 56 % from carbon dioxide-^{14}C; m. p. 172-173° C (lit. m. p. 171-173° C) (13).

N[4-(2-Dimethylaminoethoxy)benzyl-α-^{14}C]-3,4,5-trimethoxybenzamide hydrochloride (10). — To 1.26 g of crude 4-(2-dimethylaminoethoxy)benzyl-^{14}C-amine (*8*) in 50 ml of acetonitrile was added at room temperature with stirring, a solution of 1.10 g (4.76 mmole) 3,4,5-trimethoxybenzoyl chloride in 50 ml of acetonitrile over a period of 30 min. After complete addition, the reaction mixture was refluxed for 8 hr. The resulting yellow solution was then evaporated to dryness, the residue quenched in ice-water and adjusted to pH 13 with 5 N sodium hydroxide. The aqueous phase was extracted three times with ether-ethyl acetate (1 : 1) and three times with ethyl acetate, carefully readjusting the aqueous layer to pH 13 after every extraction by adding sodium hydroxide. All organic extracts were washed twice with water, dried over anhydrous magnesium sulfate and concentrated to dryness to yield 1.057 g (2.72 mmole) of an oily substance, from which 753 mg of crystalline material could be obtained by recrystallization from ether-petroleum ether. After dissolving the free base in a minimum of methanol, a calculated amount of methanolic hydrogen chloride (6.2 N) was added and the solvent was removed *in vacuo*. 560 mg (1.32 mmole) of crystalline *10*, m. p. 179-183° C, was obtained from acetonitrile-ether. From the mother liquors, after two recrystallizations from above solvent mixture, another 44 mg (0.106 mmole) of product was isolated. The compound was shown to be 98 % radiochemically pure by T.L.C. analysis on a silica gel plate using chloroform-ethylacetate-methanol-NH_4OH (30 : 30 : 30 : 1) as a developing system. Yield : 604 mg (1.42 mmole 28.4 % based on carbon dioxide-^{14}C); 6.22 mCi at 4.37 mCi/mmole.

The combined mother liquors were again treated with methanolic hydrogen chloride. To this solution, after filtering from some insoluble by-product, there was added 425 mg (1 mmole) of "pure", inactive *10* and the whole was recrystallized from acetonitrile-ether two times to yield 373 mg pure (demonstrated by above T.L.C.-system) product, containing 0.205 mCi. This corresponds to 0.047 mmole of undiluted product.

The total yield therefore amounted to 1.473 mmole, or 29.4 % based on carbon dioxide-^{14}C.

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4. Melting points are uncorrected. Infrared spectra were recorded on a Beckmann IR 5 or a Beckmann IR 9. All radiochemical impurities were established by T.L.C. on silica gel G_f. Chromatograms were scanned on a Packard Model 7200 Radiochromatogram Scanner. Radiochemical assays were made on either a Nuclear-Chicago Mark I or a Packard Model 3375 liquid scintillation counter.
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8. The isoelectric point of *3* was found to be at pH 6.20 by potentiometric titration.
9. The isoelectric point of 4-(2-dimethylaminoethoxy)benzoic acid was found to be at pH 6.56.
10. Assay of chemical purity of *4* by ultraviolet absorption shows the isolated 1.84 g to represent a yield of 91 %.
11. The thionyl chloride was purified according to L. F. FIESER and M. FIESER "Reagents for Organic Synthesis", p. 1158, John Wiley and Sons, Inc., New York, 1967.
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