

SYNTHESIS OF 4-AMINO-5-CHLORO-N-[2-(DIETHYLAMINO)ETHYL]-2-  
[(BUTAN-2-ON-3-YL)OXY]-[CARBONYL-<sup>14</sup>C]BENZAMIDE HYDROCHLORIDE (<sup>14</sup>C-BATANOPRIDE)

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SUMMARY

The title compound (**8**) was synthesized by a 7-step sequence. 4-Amino-2-hydroxy-[carbonyl-<sup>14</sup>C]benzoic acid (**1**) was selectively methylated to provide the ether ester **2**, which was smoothly chlorinated in acetic acid to give **3**. The ester was hydrolyzed with aqueous potassium hydroxide to the amino acid **4**. This reacted readily, as a mixed anhydride, with diethylaminoethylamine, yielding [<sup>14</sup>C]-metoclopramide (**5**). Sodium ethanethiolate in dimethylformamide cleaved the methoxy group cleanly to the phenol (**6**); this material was not isolated but was condensed *in situ* with 3-chloro-2-butanone, yielding **7**. Formation of the salt with concentrated hydrochloride acid in acetone provided the title compound (**8**), having a radiochemical purity of 95.6% and a specific activity of 29.8 μCi/mg.

**Key Words:** Antiemetic, antinauseant, 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-[(butan-2-on-3-yl)oxy]-[carbonyl-<sup>14</sup>C]benzamide hydrochloride, batanopride.

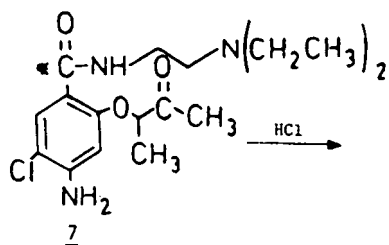
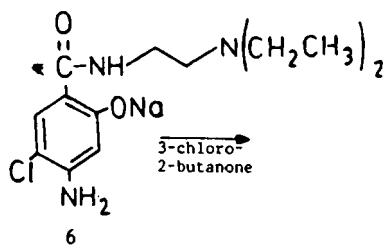
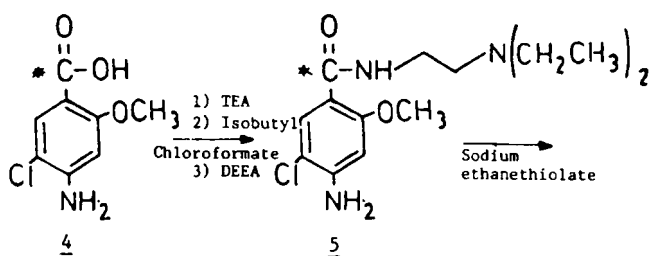
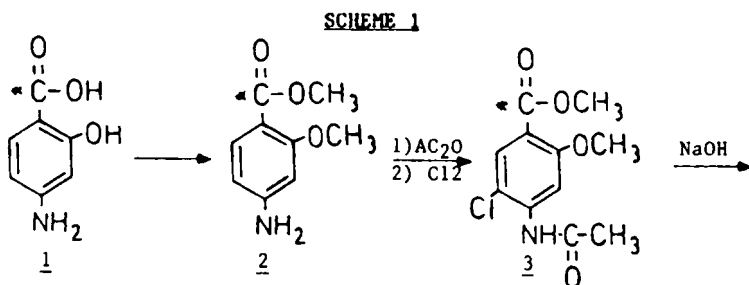
INTRODUCTION

During an extensive synthetic program in the antiemetic area, 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-(butan-2-on-3-yl)oxy]benzamide hydrochloride (batanopride) was prepared in our laboratories<sup>1</sup>. This compound was found to prevent the prolonged and severe nausea and emesis associated with the clinical administration of antineoplastic agents<sup>2</sup>.

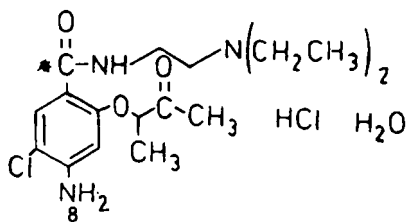
Thoroughly profiling the metabolic fate of this compound required preparation of <sup>14</sup>C-labelled material. Placement of the label was desired in the carbonyl group, since this position was considered unlikely to be lost through metabolic activity. The synthetic route is outlined in Scheme 1.

DISCUSSION

4-Amino-2-hydroxy-[carbonyl-<sup>14</sup>C]benzoic acid (**1**), purchased from Amersham Corporation, was converted to the ether ester **2** as had been previously described<sup>3</sup>. Careful control of the reaction temperature and prompt isolation of the product was required to avoid contamination by N-methylated compounds. These byproducts not only lowered the yield but made purification more difficult.



\* position of radiolabel



Chlorination of the acetamide of **2** (formed *in situ*) proceeded smoothly, as did alkaline hydrolysis of **3** to the amino acid **4**. The amino acid was converted to the diethylaminoethyl amide **5** via a mixed anhydride; the low reactivity of the 4-amino group made its protection unnecessary. The yield of **5** exceeded that calculated and was probably due to some silica since purification was achieved by chromatography using 30% methanol in dichloromethane. This did not affect results since large excesses of reagents were used in subsequent reactions.

It was found that, with appropriate protection from moisture and oxygen, sodium ethanethiolate could be stored as a stock solution in dimethylformamide for several weeks. This reagent readily displaced substituted phenoxide from **5** providing the sodium salt of the phenol **6**. Because of the small quantity available the phenol was not isolated but reacted *in situ*. Despite use of excess 3-chloro-2-butanone, unreacted phenol was still present. Separation of **6** and **7** was achieved by chromatography. Use of silica gel presaturated with ammonia was necessary to prevent cleavage of the ether linkage. Treatment of the free base **7** in acetone with concentrated hydrochloric acid provided the desired product **8**, the hydrochloride hydrate. The radiochemical purity of **8** was 95.6% and the specific activity, 29.8  $\mu\text{Ci}/\text{mg}$ .

#### EXPERIMENTAL

NMR spectra were obtained on a Bruker 360 MHz instrument. Chemical shifts were referenced internally to the solvent. Radioactivity was measured by a Beckmann LS9000 liquid scintillator. Radiochemical purity was determined by HPLC.

**High Performance Liquid Chromatography (HPLC)**-Instrumentation: Hewlett Packard model 1084 or model 1081 liquid chromatograph with autosampler, UV detector, and HP1084 microprocessor. Method: Column, Bondapack C<sub>18</sub>, 3.9 mm ID x 30 cm (Waters); mobile phase,  $5 \times 10^{-3}$  M sodium 1-octane sulfonate in acetonitrile:water 3:7 adjusted to pH 2.7 with glacial acetic acid; flow rate, 1.5 ml/min; detector, 280 nm.

**Thin Layer Chromatography (TLC)**-Plates: Silica gel, 250  $\mu$  GHLF (Analtech). Method: Mobile phase, as indicated; visualization, 254 nm UV. All products gave TLC zones identical to those of authentic, unlabelled reference compounds.

**Flash Chromatography**-Column, 41 mm or 18 mm ID, as indicated. Method: Stationary phase, 32-63  $\mu$  silica gel (ICN); packing depth, 15 cm; mobile phase, as indicated; pressure, 5-7 psig; flow rate, maximum (eluent level drop of at least 5 cm/min above column bed.)

**Methyl 4-acetamido-5-chloro-2-methoxy-[carbonyl-<sup>14</sup>C]benzoate**. (3) Methyl 4-amino-2-methoxy-[carbonyl-<sup>14</sup>C]benzoate (**2**) was prepared as previously described<sup>3</sup> from 4-amino-2-hydroxy-[carbonyl-<sup>14</sup>C]benzoic acid (Amersham Corporation, diluted with non-radiolabelled **1** to a specific activity of 12.8 mCi/mmol).

To a magnetically stirred suspension of methyl 4-amino-2-methoxy-[carbonyl-<sup>14</sup>C]benzoate (126.3 mg, 0.697 mmole) (**2**) in glacial acetic acid (4 ml) was added via syringe acetic anhydride (75.6  $\mu$ l, 81.7 mg, 0.80 mmole). After a few minutes a solution was obtained. The reaction mixture was then stirred and heated in a

bath at 40-50° for 20 minutes.

The reaction mixture was cooled to 20° and a 0.70 M solution of chlorine(g) (1.25 ml, 0.87 mmole) in glacial acetic acid was added, keeping the pipet tip beneath the surface of the stirred liquid. There was a slight exotherm (22°); the reaction mixture was stirred at ambient temperature for 20 minutes.

The solution was then poured into 10 times its volume of water (50 ml). A solid slowly separated. After 1 hour the mixture was filtered to give the title compound (62.4 mg) as a light yellow solid. TLC (dichloromethane:methanol 99:1) showed a single zone of *R<sub>f</sub>* 0.4.

The combined mother liquor and washings were extracted with three portions of dichloromethane and the extracts were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (column, 41 mm ID; mobile phase dichloromethane:methanol 98:2). Fractions rich in product were combined, evaporated, and purified on the same column (mobile phase dichloromethane:methanol 99:1). Evaporation of appropriate fractions gave additional pure product (62.6 mg). The total yield was 125 mg (70%).

4-Amino-5-chloro-2-methoxy-[carbonyl-<sup>14</sup>C]benzoic acid. (4)

A mixture of methyl 4-amino-5-chloro-2-methoxy-[carbonyl-<sup>14</sup>C]benzoate (125 mg, 0.485 mmole) (3), 95% ethanol (2.5 ml), water (3.4 ml) and 40% (w/w) aqueous sodium hydroxide solution (0.34 ml, 4.85 mmoles) was stirred and heated under reflux for 2 hours.

The clear yellow solution was diluted with water (15 ml). Slowly and with good mixing 1.4 N hydrochloric acid (3.46 ml, 4.88 mmoles) was added, giving an approximate pH of 2. The solid which separated was filtered, washed well with water and dried. The title compound (82.3 mg, 80% yield) was obtained as a grayish solid which showed a single zone of *R<sub>f</sub>* 0.7 on TLC (dichloromethane:methanol 9:1).

4-Amino-5-chloro-2-methoxy-N-[2-(diethylamino)ethyl]-[carbonyl-<sup>14</sup>C]-benzamide. (5)  
([<sup>14</sup>C-metoclopramide]).

To a stirred solution of 4-amino-5-chloro-2-methoxy-[carbonyl-<sup>14</sup>C]benzoic acid (82.3 mg, 0.408 mmole) in dry tetrahydrofuran (7 ml) was added, dropwise by syringe through a rubber septum, triethylamine (63 µl, 45.5 mg, 0.449 mmole). A slight exotherm occurred; the reaction mixture was stirred for 15 minutes at ambient temperature.

The reaction mixture was cooled in an ice-water bath and isobutyl chloroformate (58 µl, 61.3 mg, 0.449 mmole) was added dropwise by syringe to the stirred suspension. There was a slight exotherm and some additional solid separated; stirring with cooling was continued for 1 hour. N,N-Diethylethylenediamine (57 µl, 47.4 mg, 0.408 mmole) was then added slowly dropwise by syringe. The mixture was stirred with cooling for 1 hour and then at ambient temperature for 18 hours.

TLC (dichloromethane:methanol 7:3) showed product (*R<sub>f</sub>* 0.2) and a small amount

of starting acid (Rf 0.8). The mixture was filtered and the solids washed with tetrahydrofuran. The combined filtrate and washings were evaporated to give a solid.

The crude material was purified by flash chromatography (column ID 18 mm, mobile phase dichloromethane:methanol 7:3) and appropriate fractions were evaporated to give pure product. Less pure fractions were combined, evaporated, and purified to give additional pure material. The title compound was obtained as 143.6 mg (calculated, 122.3 mg) of colorless solid, which upon TLC gave a single zone of Rf 0.2.

4-Amino-5-chloro-N-[2-diethylamino)ethyl]-2-[(butan-2-on-3-yl)-oxy]-[carbonyl-<sup>14</sup>C]benzamide hydrochloride. (8)

A. Sodium ethanethiolate solution.

A stirred suspension of 60% sodium hydride/mineral oil (2.0 g, 50.1 mmole) in dry dimethylformamide (40 ml) was cooled in an ice-water bath and a solution of ethanethiol (3.71 ml, 3.13 g, 50.1 mmole) in dry dimethylformamide (9 ml), was added slowly dropwise, keeping the temperature below 10°. Vigorous bubbling occurred. After addition was complete, the reaction mixture was stirred with cooling for 10 minutes and then at ambient temperature for 15 minutes. Gas evolution had ceased giving a clear, greenish solution. The volume of solution was 54.7 ml, calculated to be 0.92 M in sodium ethanethiolate.

B. 4-Amino-5-chloro-2-hydroxy-N-[2-diethylamino)ethyl]-[carbonyl-<sup>14</sup>C]benzamide. (6)

To a magnetically stirred solution of 4-amino-5-chloro-2-methoxy-N[2-diethylamino)ethyl]-carbonyl-<sup>14</sup>C]benzamide (143.5 mg, 0.479 mmole) (5) in dry dimethylformamide (2 ml) was added by syringe through a rubber septum, 0.92 M ethanethiolate solution (2.45 ml, 2.24 mmoles) in dimethylformamide. The reaction mixture was stirred and heated in an oil bath at 100-105° for 2 hours. Heating was then discontinued, and the reaction mixture allowed to cool for 4.5 hours. TLC(dichloromethane:methanol:conc. NH<sub>4</sub>OH 90:9.7:0.3) indicated the reaction to be complete. The title compound showed a single zone of Rf 0.4. A freshly developed TLC plate showed 6 to have a characteristic bright blue fluorescence at 254 nm, which had faded after 24 hours. The starting material 5 showed a zone of Rf 0.6 in this system.

C. 4-Amino-5-chloro-N-[2-(diethylamino)ethyl]-2-(butan-2-on-3-yl)oxy]-[carbonyl-<sup>14</sup>C]benzamide. (7)

To the stirred reaction mixture from step B was added by syringe, at 40°, 3-chloro-2-butanone (0.23 ml, 241 mg, 2.24 mmoles). A solid separated immediately. The reaction mixture was then stirred for 10 hours at 105-110° and then stored at ambient temperature for 10 hours. TLC (same as B) showed product (Rf 0.64) with some unchanged 6.

The reaction mixture was evaporated to give a paste. This was purified by flash chromatography (column, 18 mm; mobile phase, dichloromethane:methanol:conc. NH<sub>4</sub>OH 90:9.7:0.3). Before placing the crude material on the column, mobile phase

was run through until ammonia appeared in the eluate. Appropriate fractions were combined and evaporated to give 60.7 mg of the title compound (36% yield from 5) as a dark resin.

D. 4-Amino-5-chloro-N-[2-(diethylamino)ethyl]-2-[butan-2-on-3-yl]oxy]-[carbonyl-<sup>14</sup>C]benzamide hydrochloride. (8)

To the purified base (7) from step C (60.7 mg, 0.17 mmole), was added a solution of concentrated hydrochloric acid in acetone, (291  $\mu$ l, 0.171 mmole) containing 50  $\mu$ l of concentrated hydrochloric acid solution/ml acetone solution. The mixture was agitated thoroughly. An oil separated, which crystallized upon seeding with authentic (8) (non-radiolabelled).

The mixture was allowed to crystallize for 2 hours. The solvent was evaporated in a stream of nitrogen and the residue was dried under vacuum to give the title compound (60.2 mg, 90% yield) as a brownish crystalline solid. The compound had a radiochemical purity of 95.6% and a specific activity of 29.8  $\mu$ Ci/mg. TLC (dichloromethane:methanol:conc.  $\text{NH}_4\text{OH}$  90:9.7:0.3),  $R_f$  0.5. The product had the same retention time upon HPLC (11 min.) as an authentic sample; nmr spectrum was consistent with structure and identical to reference. Radiochemical purity was determined by High Pressure Liquid Chromatography as described in the experimental section.

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