SYNTHESIS OF A NEW ANTICONVULSANT LABELLED WITH ^{14}C: 1,4-DIHYDRO-1-[4'-(ETHYLAMINOACETYL)-AMINOPHENYL]-3(2H)--ISOQUINOLINONE

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SUMMARY

1,4-Dihydro-1-[4'-(ethylaminoacetyl)-aminophenyl]--3(2H)-isoquinolinone was labelled with ^{14}C in two different positions: in one case in position 3 of the isoquinoline ring, in the other case in the carbonyl group of the ethylaminoacetyl moiety.

Key Words: Benzyloxycarbonyl-ethyl-glycine; 1,4-Dihydro-(4'-nitrophenyl)-3(2H)-isoquinolinone

INTRODUCTION

Some years ago a new method was published[1] for the synthesis of 1,4-dihydro-3(2H)-isoquinolinone derivatives, one of which, 1,4-dihydro-1-[4'-(ethylaminoacetyl)-aminophenyl]-3(2H)-isoquinolinone (1) possesses excellent anticonvulsive activity[2].

Two isotopic isomers of 1 (1a and 1b) were prepared for pharmacological investigation. In the case of 1a the ^{14}C atom was placed into the position 3 of the isoquinoline ring, in the case of 1b into the carbonyl group of the ethylaminoacetyl moiety.

The synthesis of 1a started from benzyl cyanide-1-^{14}C, which was allowed to react with 4-nitrobenzaldehyde in polyphosphoric

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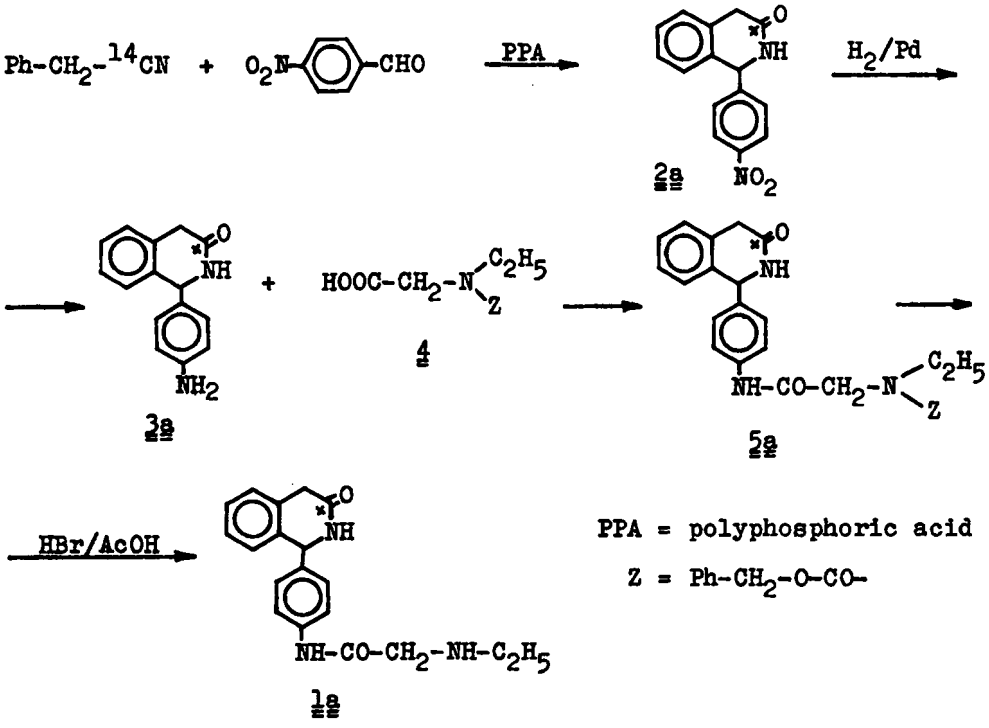
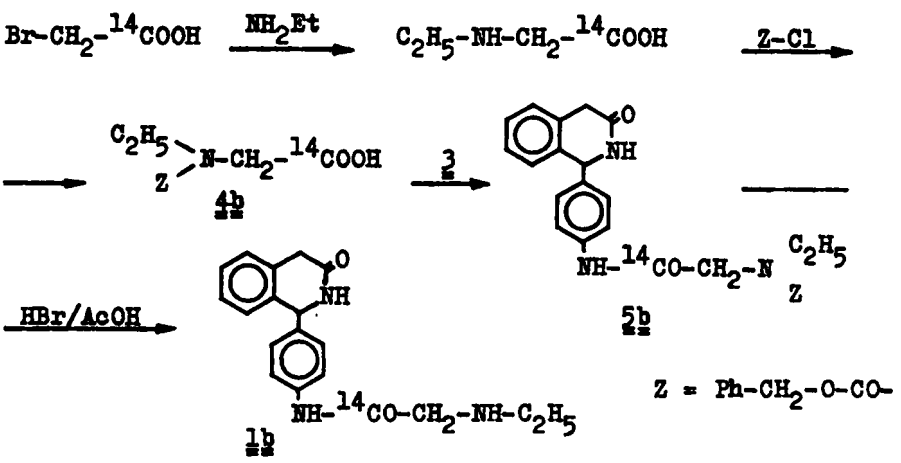
acid to give 1,4-dihydro-1-(4'-nitrophenyl)-3(2H)-isoquinolinone--3-^{14}C (2a). The nitro group of 2a was reduced by a Pd/charcoal catalyst to give 1,4-dihydro-(4'-aminophenyl)-3(2H)-isoquinolinone-3-^{14}C (3a), which was acylated with benzyloxycarbonyl-ethyl--glycine (4) by the mixed anhydride method to give 1,4-dihydro-1--[4'-(benzyloxycarbonyl-ethylamino-acetyl)-aminophenyl]-3(2H)--isoquinolinone-3-^{14}C (5a). Lastly the protecting group of 5a was removed by HBr in acetic acid.

SCHEME 1



In the synthesis of 1b bromoacetic acid-1-^{14}C was reacted with ethylamine and the obtained crude ethylglycine-1-^{14}C was converted into benzyloxycarbonyl-ethylglycine-1-^{14}C (4b). It was reacted with 1,4-dihydro-1-(4'-aminophenyl)-3(2H)-isoquinolinone (3) to give 5b, the isotopic isomer of 5a. The protecting group in 5b was removed similarly to 5a to give 1b.

SCHEME 2



EXPERIMENTAL

Melting points are uncorrected. Thin layer chromatography was carried out on 5x20 cm plates using Kieselgel $PF_{254+366}$ (MERCK). The activity was measured by a Packard TRI-CARB liquid scintillation system.

Benzyl cyanide-1-^{14}C [*]

$K^{14}CN$ (0.1033 g, 1.5 mmoles, 47.4 mCi) and NaCN (0.3680 g, 7.5 mmoles) were stirred in abs. dimethylsulphoxide (4 ml) at 80°C for 1 h. After cooling, a solution of freshly distilled benzyl chloride (1.14 ml, 1.25 g, 10 mmoles) in dimethylsulphoxide (4 ml) was added. The mixture was stirred at room temperature for 5 hrs and left to stand overnight. Then NaCN (0.250 g, 5.0 mmoles) was added and the mixture was stirred at 50°C for 1 h. After cooling, water (80 ml) was added and the mixture was extracted with ether (5x20 ml), the collected extracts were washed with 25 % NaCl solution (20 ml), dried over $MgSO_4$ and the solvent was evaporated through a 20 cm Vigreaux column. 1.03 g (8.8 mmoles) of benzyl cyanide-1-^{14}C were obtained as a colourless oil. Yield: 88 %. Calculated activity: 41.7 mCi.

[*] Benzyl cyanide-1-^{14}C was synthetized by Roberts and Regan,[3] but their yield was poorer.

1,4-Dihydro-1-(4'-nitrophenyl)-3(2H)-isoquinolinone-3-^{14}C (2a)

Benzyl cyanide-1-^{14}C (1.03 g, 8.8 mmoles, 41.7 mCi) and polyphosphoric acid (4 ml) were stirred at 90-100°C for 1 h, then p-nitrobenzaldehyde (1.33 g, 8.8 mmole) was added in small portions within 1 h; the temperature of the heating bath was increased to 120°C during this period. After having completed the addition, stirring was continued at the same temperature for 4 hrs then the mixture was heated to 150-160°C for a short period, allowed to cool to 80°C, and poured into water (80 ml). The solution was made alkaline with conc. ammonia, and heated to the boiling point. The reddish-brown powder-like precipitate was filtered off from the hot solution, washed carefully with water and recrystallized from ethanol (60 ml) with Norite. 1.66 g (6.2 mmoles) of 2a were obtained. M.p.: 173-176°C. Yield: 70 %. Measured activity: 27.0 mCi. The material showed only one spot on a TLC plate (ethyl acetate : methanol = 9 : 1, R_f = 0.6).

1,4-Dihydro-1-(4'-aminophenyl)-3(2H)-isoquinolinone-3-^{14}C (3a)

In order to reduce the nitro group, 2a (1.66 g, 6.2 mmoles, 27.0 mCi) was dissolved in acetic acid (25 ml) and hydrogenated in the presence of Engelhardt's 10 % Pd/C catalyst (0.2 g). The catalyst had been prehydrogenated to shorten the non-desired induction period. At the end of the reduction step, the catalyst was filtered off, the acetic acid was evaporated in vacuo, the residual oily product was digested with water (50 ml), made alkaline with conc. ammonia, filtered off and the product was washed with water until neutral. 1.35 g of 3a (5.7 mmoles, 92 %) were obtained. M.p.: 208-213°C. Calculated activity: 24.8 mCi. The material showed only one spot on a TLC plate (ethyl acetate : methanol = 9 : 1, R_f = 0.5).

1,4-Dihydro-1-[4'-(benzyloxycarbonyl-ethylaminoacetyl)-aminophenyl]-3(2H)-isoquinolinone-3-^{14}C (5a)

A mixture of 4 (1.5 g, 6.3 mmoles) and triethylamine (0.85 ml, 0.62 g, 6.2 mmoles) in anhydrous dimethylformamide (10 ml) was cooled to -10°C and ethyl chloroformate (0.57 ml, 0.64 g, 5.9 mmoles) was added. A white precipitate was formed and the temperature of the mixture rose to -2°C. It was stirred at -5°C for 20 min., and the solution of 3a (1.35 g, 5.7 mmoles, 24.8 mCi) in dimethylformamide (10 ml) was added dropwise at the same temperature. Stirring was continued a 0-5°C for 3 hrs, the solution was allowed to stand at room temperature overnight, and poured into water (200 ml). The aqueous solution was extracted with chloroform (4x20 ml), the chloroform extract was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and the solvent was removed. An oily residue that slowly crystallized was obtained, this was digested with hot ethanol (10 ml) to give a white crystalline substance. After cooling, the crystals were separated by filtration and washed with cold ethanol (2 ml). 2.15 g (4.91 mmoles) of 5a were obtained. M.p.: 176-178°C[*]: Yield: 85 %. Calc. activity: 21.2 mCi. According to TLC the material contained traces of 3a (ethyl acetate : methanol = 9 : 1, R_f = 0.6).

1,4-Dihydro-1-[4'-(ethylaminoacetyl)-aminophenyl]-3(2H)-isoquinolinone-3-^{14}C (1a)

5a (2.15 g, 4.9 mmoles, 21.2 mCi) was dissolved in 4 N HBr in glacial acetic acid (15 ml) and allowed to react for 1 h. Anhydrous ether (60 ml) was added to the solution, the liquid layer was decanted and the residue was washed by repeated decantations with ether (2x20 ml). It was then dissolved in water (20 ml),

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[*] The inactive substance (5) was prepared as for 5a. After recrystallization from ethanol the melting point increased to 180-182°C. Anal.: Calcd. C 70.89 % H 5.95 % N 9.18 %
Found 71.09 % 5.82 % 9.06 %

precipitated by the addition of conc. ammonia, filtered off and recrystallized from ethanol (20 ml) to obtain 1a (0.98 g, 11.4 mCi). Yield: 62 %.

By adding 0.5 g of inactive 1 to the mother liquor a second fraction was obtained. Collecting the two fractions and recrystallizing them from ethanol (35 ml), 1.19 g of 1a were obtained. M.p.: 184-186°C. The material showed one spot on a TLC plate (solvent: methanol : water = 9 : 1, R_f = 0.3). Measured activity: 11.4 mCi. Radiochemical yield: 24 %.

Benzyloxycarbonyl-ethyl-glycine-1-^{14}C (4)

Chloroacetic acid (9.5 g, 0.1 moles) was dissolved in 30 % aqueous ethylamine (100 ml) and refluxed for 20 hrs. The solution was evaporated to dryness in vacuo, the residual thick oil was mixed with 1 N sodium hydroxide (100 ml) and water (30 ml). The water was evaporated, then again water (100 ml) was added and this was evaporated again. The residue was dissolved in water (100 ml), the pH of the solution was set to 10 with 2 N NaOH, cooled below 5°C and benzyloxycarbonyl chloride (25 ml) was added dropwise under stirring to the solution, at such a rate that the temperature should not increase above 5-10°C. Meanwhile the pH was maintained at 10 by the addition of 2 N NaOH. After completion of the addition of the reagent, the solution was stirred further at 5°C for 2 hrs, then extracted with dichloromethane (2x30 ml) in order to remove benzyloxycarbonyl chloride. The pH was set to 1 with hydrochloric acid under cooling with ice, the solution was extracted with dichloromethane (3x30 ml), the extract washed with water, dried over $MgSO_4$ and the solvent was removed in vacuo. 13.5 g (57 %) of 4 was obtained as a yellowish oil. The material showed only one spot on a TLC plate (solvent: 90 ml of ethyl acetate and 10 ml of 20:6:11 mixture of pyridine, acetic acid and water). The spot was detected in UV light after thorough drying. The dicyclohexylamine salt of 4 was prepared as follows:

4 (1 g) was dissolved in anhydrous ether (5 ml) and a solution of dicyclohexylamine (1.5 ml) in ether (5 ml) was added. The white crystalline substance was separated by filtration and recrystallized from benzene. M.p.: 149-150°C.

Anal.:	Calcd.	C 68.87 %	H 9.16 %	N 6.69 %
	Found	68.78 %	9.08 %	6.81 %

Bromoacetic acid-1-^{14}C

Bromoacetic acid-1-^{14}C was prepared as described earlier[4] from sodium acetate-1-^{14}C (0.8305 g, 10.1 mmoles, 52.0 mCi) with 75 % yield. Calculated activity: 38.8 mCi.

Benzyloxycarbonyl-ethyl-glycine-^{14}C (4b).

Bromoacetic acid-^{14}C (1.0 g, 7.5 mmoles, 38.8 mCi) was dissolved in water (10 ml) and ethylamine (7.5 ml) was added dropwise. The solution was refluxed for 5 hrs and kept at room temperature overnight, then evaporated to dryness in vacuo. The residue was dissolved in 1 N NaOH (10 ml), water was evaporated again and the procedure was repeated with another portion of water (10 ml). The residue was dissolved in water (20 ml) cooled to 5°C and benzyloxycarbonyl chloride (1.8 ml) was added. The mixture was stirred at 5-10°C for 2 hrs while maintaining the pH between 9 and 10 by the addition of 2 N NaOH. Finally, the solution was stirred at 15-20°C for 1 h, extracted with methylene chloride (2x15 ml) to remove benzyloxycarbonylchloride, the solution was cooled to 5°C, the pH of the solution was set to 1 and then it was extracted with methylene chloride (5x15 ml). The extract was dried over $MgSO_4$ and the solvent was removed in vacuo to obtain 4b (1.18 g, 66 %) as a colourless oil. Calculated activity: 26.0 mCi. By TLC the material was identical with 4.

1,4-Dihydro-1-[4'-(benzyloxycarbonyl-ethylamino-acetyl-1-^{14}C)--aminophenyl]-3(2H)-isoquinolinone (5b)

5b was prepared from 4b in the same way as described for 5a 1.72 g (69 %) of 5b were obtained from 1.18 g (5 mmoles, 26.0 mCi)

of 4b, ethylchloroformate (0.58 ml, 0.65 g, 6.0 mmoles) and 3 (1.15 g, 5 mmoles). M.p.: 178-180°C. Calculated activity: 18.9 mCi. The material showed only one spot on a TLC plate (solvent was the same as for 5a).

1,4-Dihydro-1-[4'-(ethylaminoacetyl-1-^{14}C)-aminophenyl]-3(2H)--isoquinolinone (1b)

The protecting group was removed as described for 1a. The reaction was carried out in 4 N HBr in acetic acid (10 ml), then the material was recrystallized from ethanol (2x20 ml). 0.612 g (50 %) of 1b were obtained. M.p.: 182-184°C. Measured activity: 8.8 mCi. According to TLC the material contained traces of 5b. By adding inactive 1 (0.5 g) to the concentrated mother liquor, 0.673 g (4.48 mCi) of 1b were obtained with lower specific activity. Radiochemical yield: 26 %.

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