POTENTIAL DRUGS LABELLED WITH ^{14}C. II. SYNTHESIS OF 1-CYANO-3-IMINO-8,9-DIMETHOXY-3,4,5,6--TETRAHYDRO-THIAZOLO[4,3-a]ISOQUINOLINE HYDROCHLORIDE

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SUMMARY

The synthesis of 1-cyano-3-imino-8,9-dimethoxy--3,4,5,6-tetrahydro-thiazolo[4,3-a]isoquinoline hydrochloride labelled with ^{14}C in five different positions: in position 3 (1a), in the cyano group at position 1 (1b), in position 5 (1c), in position 10b (1d) and in the methoxy groups at position 8 and 9 (1e) was carried out.

INTRODUCTION

In a previous paper[1] the radiochemical synthesis of an imidazo-[5,1-a]isoquinoline derivative has been described. The experience gained there was applied to the synthesis of ^{14}C labelled 1-cyano-3-imino-8,9-dimethoxy-3,4,5,6-tetrahydro-thiazolo[4,3-a]isoquinoline hydrochloride (1) which is a potent coronary dilatator being capable of reducing ECG changes due to local myocardial ischemic area and increasing nutritional circulation in the ischemic area.[2]

Five labelled isomers of 1 were prepared in order to study its metabolism. The positions of the ^{14}C labeling are shown in Scheme 1.

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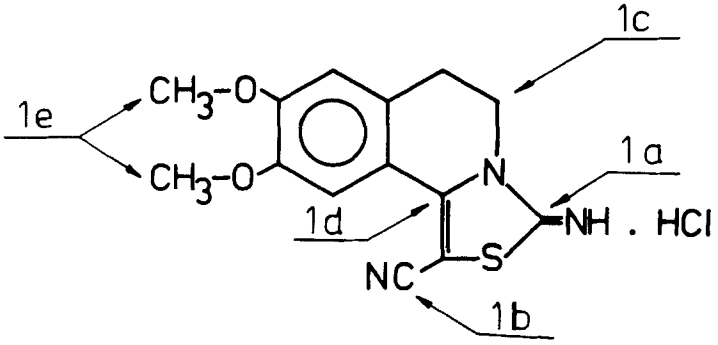
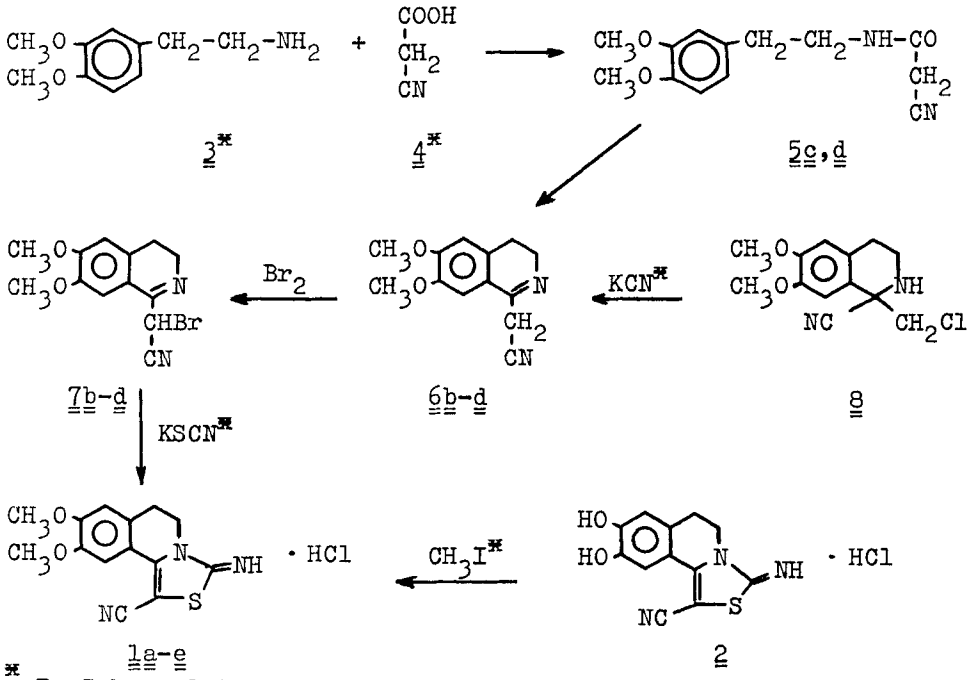
Scheme 1



SYNTHESIS

The conventional synthesis of 1 gives four possibilities to introduce the ^{14}C atom by using labelled starting materials: $KS^{14}CN$, $K^{14}CN$, homoveratrylamine-1-^{14}C and cyanoacetic-1-^{14}C acid,* respectively (see Scheme 2). The fifth labelled isomer was prepared by methylating 1-cyano-3-imino-8,9-dihydroxy-3,4,5,6--tetrahydro-thiazolo[4,3-a]isoquinoline (2) with methyl-^{14}C iodide.

Scheme 2



* In Scheme 2 they are marked with asterisks.

The synthesis of 1a was the simpliest and gave the best radiochemical yield (66 %) using $KS^{14}CN$ as starting material, however the easy degradation of the thiazole ring during the metabolism made this labelling unsuitable for pharmacokinetic investigation.

In the synthesis of 1b 1-(cyano-^{14}C)-methyl-6,7-dimethoxy-3,4-dihydro-isoquinoline (6b) was prepared by the reaction of 1-cyano-1-chloromethyl-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline (8) with $K^{14}CN$ as described earlier.[1] Then 6b was brominated and reacted with KSCN to give 1b in 24.7 % radiochemical yield.

The synthesis of 1c and 1d was carried out in a similar way using homoveratrylamine-1-^{14}C (at 1c) and cyanoacetic-1-^{14}C acid (at 1d). Both syntheses were tedious and gave moderate yields (6 % and 10.4 %, respectively), but the labelled analogues obtained in this way were essential for pharmacokinetic investigation.

EXPERIMENTAL

Melting points are uncorrected. TLC was carried out on 5x20 cm plates coated with Silica gel $PF_{254+366}$ (MERCK) and a Berthold TLC scanner was used for evaluation. Radioactivity was measured with a Packard Tri-Carb liquid scintillation spectrometer.

1-Cyano-3-imino-8,9-dimethoxy-3,4,5,6-tetrahydro-thiazolo[4,3-a] isoquinoline-3-^{14}C hydrochloride (1a)

A mixture of $K^{14}CN$* (79.2 mg, 33.8 mCi, 1.21 mmoles) and sulphur (39.1 mg, 1.22 mA) was refluxed in acetone (10 ml) for 5 hours. After evaporating the solvent the residue was dissolved in dry ethanol (15 ml) and 7 (1.305 g, 4.22 mmoles) was added and refluxed for 1 hour. Thereafter inactive KSCN (0.292 g, 3.0 mmoles) was added and refluxed for 1 additional hour. Then the mixture was evaporated to dryness, the residue was triturated with water (10 ml), filtered off and washed with water (5x5 ml). The 1.219 g of crude material obtained were recrystallized from dimethylformamide (DMF) (5 ml) and 0.991 g (3.46 mmoles) of base

* $K^{14}CN$ was prepared by the Bánfi's method.[3]

were obtained. M.p.: 231-4°C. By adding inactive base 1 (0.5 g) to the mother liquor a second crop was obtained (0.448 g). M.p.: 228-231°C. Both crops were dissolved in $CHCl_3$ (50 ml) and 20 % HCl in methanol (2 ml) was added. The precipitated crystals were filtered off and washed with $CHCl_3$ (3x5 ml) to yield 1a (1.1698 g, 3.61 mmoles). M.p.: 257-263°C (decomp.). A_{sp}: 19.5 mCi/g. A_t: 22.3 mCi. Radiochemical yield: 66 %. The material showed only one spot on TLC (benzene-methanol 9:1, R_f 0.4).

1-Cyano-^{14}C-3-imino-8,9-dimethoxy-3,4,5,6-tetrahydro-thiazolo [4,3-a]isoquinoline hydrochloride (1b)

The preparation of 1b starting from 6b* (630 mg, 2.74 mmoles, 20 mCi) was carried out as described for 1c to give 604 mg (68.3 %) of yellowish crystals (1.87 mmoles, 13.6 mCi). M.p.: 250-257°C, A_{sp}: 22.45 mCi/g.

1-Cyano-3-imino-8,9-dimethoxy-3,4,5,6-tetrahydro-thiazolo [4,3-a]isoquinoline-5-^{14}C hydrochloride (1c)

6c** (860 mg, 3.74 mmoles, 10.7 mCi) and $NaHCO_3$ (325 mg, 3.86 mmoles) were boiled in methanol (7.5 ml), then 4x0.05 ml of bromine (0.624 g, 3.9 mmoles) were added during a period of 20 minutes. Then 750 mg (7.7 mmoles) of KSCN in methanol (7.5 ml) were added under reflux and stirring. Thereafter the mixture was refluxed for 2 hours and kept overnight at room temperature. Then the precipitated crystals were separated by filtration and washed successively with water, ethanol and ether. The material obtained (842 mg) was recrystallized from DMF (10 ml) then from a mixture of ethanol-water-1 N HCl 17.5:14:3.5 (50 ml), yielding 479 mg of 1c as white crystals. M.p.: 252-255°C (decomp.). A_{sp}: 8.58 mCi/g, A_t: 4.04 mCi. Radiochemical yield: 6.6 %. The material proved to be identical with 1 by TLC.

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* 6b was prepared as described previously.[1]

** The preparation of 6c was described earlier.[1]

1-Cyano-3-imino-8,9-dimethoxy-3,4,5,6-tetrahydro-thiazolo [4,3-a]isoquinoline-10b-^{14}C hydrochloride (1d)

Bromoacetic-1-^{14}C acid was prepared from 781 mg (9.5 mmoles, 143 mCi) of sodium acetate-1-^{14}C in the usual way.[5] It was transformed into cyanoacetic-1-^{14}C acid by the modification of the method of Gal and Shulgin.[4] The solid bromoacetic-1-^{14}C acid was then dissolved in water (5 ml) and the pH of the solution was adjusted to 7.5-8 with solid sodium carbonate. KCN (670 mg, 10 mmoles) was dissolved in water (5 ml) and added dropwise to the solution of sodium bromoacetate-1-^{14}C keeping the temperature below 30°C. The mixture was heated slowly to 100°C and kept there for an hour. After cooling it was acidified with conc. HCl (1.2 ml) and extracted with ether for 24 hours. The organic layer was dried, evaporated to dryness in a rotary vacuum evaporator and kept in a dessicator. The pure product (670 mg, 118 mCi) was obtained as white crystals. The yield was 83 % based on sodium acetate.

The preparation of 6d was similar to that reported[1] with the exeption of the molar ratios: to 670 mg (7.9 mmoles, 118 mCi) of cyanoacetic-1-^{14}C acid was added 1.9 g (10.5 mmoles) of homoveratrylamine in the mixture of 10 ml of dry benzene and 5 ml of dry ether. The ring closure was carried out in $POCl_3$ (3 ml) to yield the isoquinoline compound (6d). The final product was obtained from 976 mg (32.4 mCi) of 6d by the method described at 1c. The crude base (807 mg, 21 mCi) was dissolved in the hot mixture of ethanol-water-1N hydrochloric acid (16.7 ml, 13.4 ml, 3.4 ml, respectively), chilled, filtered off and washed with ethanol--water. On adding 434 mg of inactive salt to the mother liquor, further 475 mg of active salt were obtained. The collected salts were recrystallized from the mixture of ethanol:water (1:1) and had a melting point of 261-263°C.

The yield was 1.079 g (3.3 mmoles, 13.7 mCi) of 1d. The final product was checked by TLC (chloroform:methanol 15:1) and proved to be pure enough for pharmacological experiments. The total radiochemical yield was 10.4 %.

1-Cyano-3-imino-8,9-dimethoxy-$^{14}C_2$-3,4,5,6-tetrahydro-thiazolo [4,3-a]isoquinoline hydrochloride (1e)

Methyl iodide-^{14}C prepared[6] from 310 mg (90 mCi) of $Ba^{14}CO_3$ with a total yield of 65 % was distilled into ethanol (2 ml). A solution of 2 (1.32 g, 4.0 mmoles) in warm 50 % ethanol (40 ml) was added dropwise to the methyl-^{14}C iodide solution. When the addition was completed the mixture was refluxed under a dry ice condenser for 1 hour. Then 570 mg (4.0 mmoles) of radioactive methyl iodide obtained in the course of "inactive carrier distillation", was added and refluxed for an additional hour. Further 1.14 g (8 mmoles) of inactive methyl iodide was added dropwise into the mixture which was then refluxed for 2 hours and left to stand in refrigerator for 4 days. The product was filtered off, washed with 50 % ethanol; 688 mg (2.39 mmoles) of crude base were obtained. By adding 745 mg of inactive base to the mother liquor and recrystallizing, further 695 mg of labelled base were obtained. The combined crops were treated with the hot mixture of ethanol (34.5 ml), 1 N HCl (6.9 ml) and water (27.6 ml), cleared with charcoal, left to stand overnight, filtered off and dried. Adding 648 mg of inactive 1 to the mother liquor, additional salt was obtained. The total weight of the hydrochlorides was 1.921 g (6.0 mmoles). The twofold recrystallization from 50 % ethanol yielded 1.509 g (4.65 mmoles, 8.74 mCi) of pure 1e which showed only one spot by TLC (benzene-ethanol-water 43:15:2). M.p.: 240-6°C. Specific activity: 5.82 mCi/g.

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