POTENTIAL DRUGS LABELLED WITH ^{14}C. I. THE SYNTHESIS OF 3-BENZYLAMINO-5,6-DIHYDRO-8,9-DIMETHOXY--IMIDAZO[5,1-a]ISOQUINOLINE HYDROCHLORIDE

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SUMMARY

3-Benzylamino-8,9-dimethoxy-5,6-dihydro-imidazo-[5,1-a]isoquinoline hydrochloride was labelled with ^{14}C in two different positions: In one case the ^{14}C was built into the position 2 of the imidazole ring, in the other case into the position 3 of the isoquinoline ring. In the first case the mechanism of the halogen-cyano exchange reaction of 1-chloromethyl--5,6-dimethoxy-3,4-dihydro-isoquinoline was investigated by tracer experiments.

Key Words: antiarrhitmic, hypotensive, tracer experiments

DISCUSSION

In the course of investigations of isoquinoline derivatives as possible drugs against heart diseases, 3-benzylamino-8,9-dimethoxy-5,6-dihydro-imidazo[5,1-a]isoquinoline hydrochloride (1) proved to be an antiarrhitmic and hypotensive agent[1]. For further pharmacological investigation radioactive 1 was required. In the first case the ^{14}C atom was built into the position 2 of the imidazole ring (1a), but metabolic investigations showed the

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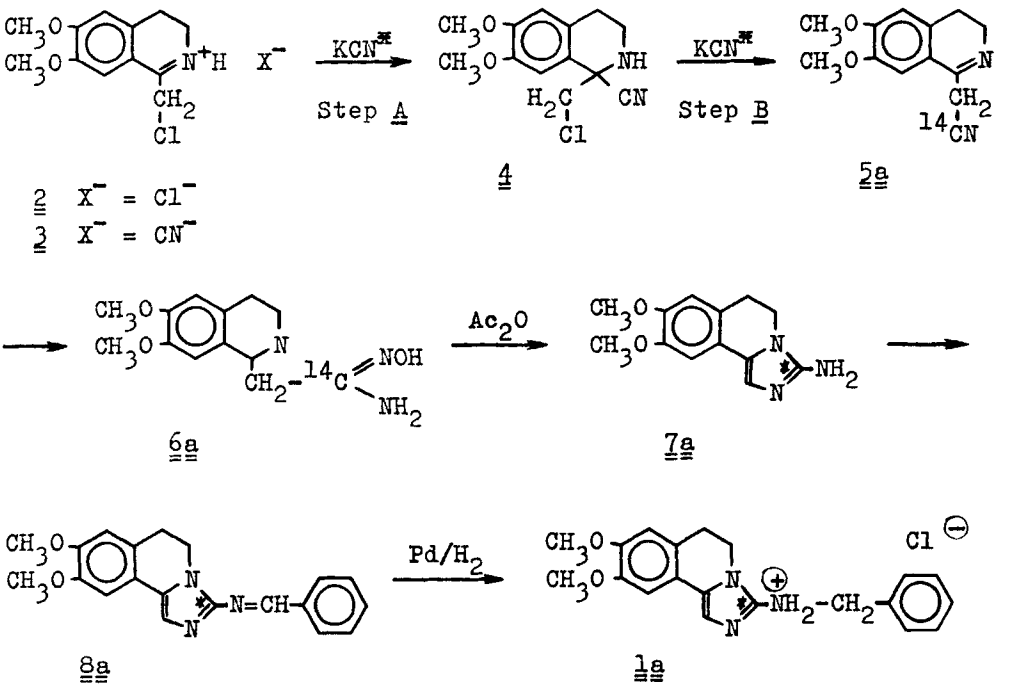
opening of the imidazole ring[2] therefore the labelled atom had to be built into the isoquinoline ring (1b).

Scheme 1.



The synthesis of 1a (see Scheme 1) started from 1-chloromethyl-5,6-dimethoxy-3,4-dihydro-isoquinoline hydrochloride (2). The reaction between 2 and KCN (step A) results in an adduct (4) which in the presence of KCN is transformed to 1-cyanomethyl-5,6-dimethoxy-3,4-dihydro-isoquinoline (5) by refluxing in ethanol[3] (step B). Investigations (see Table 1) showed that in the step B there is a nearly unlimited interchange between the cyanide ions and the cyano group of 4. The assumption of an equilibrium in aqueous medium between 4 and its ionic form (3) can explain our experimental data (similarly to diazocyanide and its ionic form, diazonium cyanide[4]).

* Active or inactive KCN was used according to Table 1 and 2.

Table 1.

	KCN in step A	KCN in step B	Measured activity	Calculated activity*
1.	active	active	5.90×10^5 dpm	-
2.	active	inactive	1.92×10^5 dpm	1.97×10^5 dpm
3.	inactive	active	3.72×10^5 dpm	3.94×10^5 dpm

* In calculating of activity one must take into consideration that both steps of the reaction were carried out with two moles of KCN. Detailed descriptions see in experimental.

In further investigations (see Table 2) to optimaze the radioactive yield of the reaction the molar ratio of KCN was varied in both steps. In this optimization we were assisted by recognizing that step B can be carried out also with KOH. Thus on using the molar ratio of reaction 5, inactive 4 in the presence of $K^{14}CN$ was converted into 1-cyano[^{14}C]methyl-5,6-dimethoxy-3,4-dihydro--isoquinoline (5a) with 63 % radiochemical yield

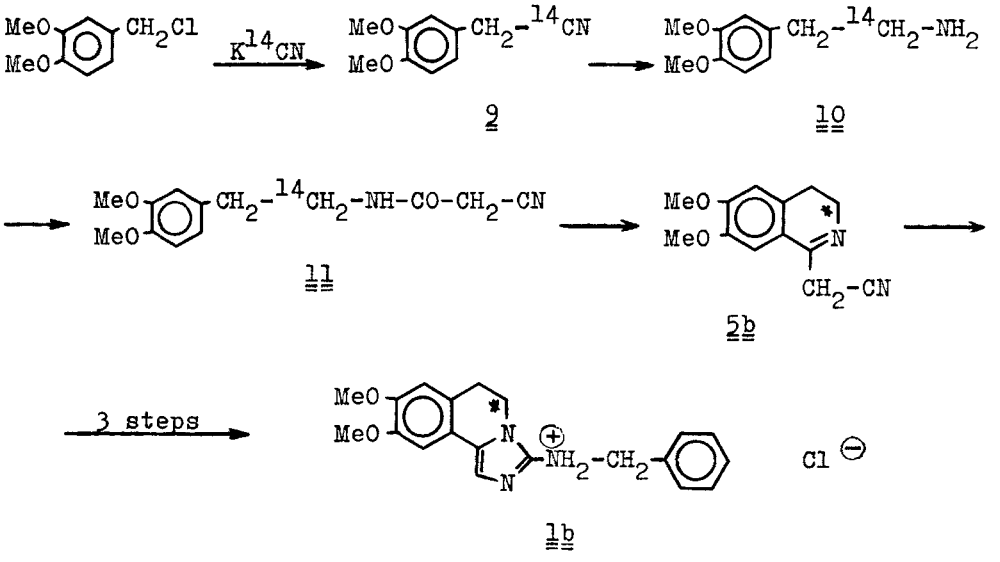
Table 2.

	Molar ratios of KCN in step A	Molar ratios of KCN in step B	Chemical yield	Radiochemical yield
1.	1.0*	1.0	-	-
2.	2.0	1.0	62 %	20.6 %
3.	1.0	2.0	70 %	23.3 %
4.	1.0	1.0	65 %	32.2 %
5.	1.0	0.2*	76 %	63.3 %
6.	1.0	0.0*	41 %	41.0 %
7.	1.0	0.04*	41 %	41.0 %

* 1 mole KOH was also added.

Then the cyano group of 5a was transformed into amidoxime (6a) and it gave with acetic anhydride - via a Beckmann rearrangement and followed by a ring closure - 3-amino-8,9-dimethoxy-5,6-dihydro--imidazo-2-^{14}C[5,1-a]isoquinoline (7a) which was converted into its benzyl derivative (1a) by the reduction of a Schiff base intermediate (8a). The radiochemical yield of 1a based on $K^{14}CN$ was 21.6 %.

Scheme 2.



In the second case the synthesis of 1b was longer (see Scheme 2). Homoveratronitrile-1-^{14}C (9) was prepared from veratryl chloride and K^{14}CN using [6]crown-18 as phase transfer catalyst[5]. Then 9 was reduced to homoveratrylamine-1-^{14}C (10) by Egli's method[6] and coupled with cyanoacetic acid in the presence of dicyclohexylcarbodiimide to N-homoveratryl-cyanoacetamide (11). This was cyclized by Bischler-Napieralski's method to 1-cyano-methyl-5,6-dimethoxy-3,4-dihydro-isoquinoline-3-^{14}C (5b). Then 5b was converted into 1b in the same way as 5a. The application of slight modifications came as a consequence of the smaller amounts of the material. The total radiochemical yield was 5.3 %.

EXPERIMENTAL

Melting points are uncorrected. Thin layer chromatography was carried out on 5 x 20 cm plates using Kieselgel $PF_{254+366}$ (MERCK). The radioactivity was measured by a Packard TRI-CARB liquid scintillation system.

General method for tracer experiments:

To 2 (1.38 g, 5 mmoles) in water (13.5 ml) KCN* (0.65 g, 10 mmoles) was added in water (3.5 ml). The mixture containing precipitates was stirred for one hour, then filtered off, and the cake was washed with water. The solid (4) without drying was dissolved in ethanol (9 ml) and another portion of KCN (0.65 g, 10 mmoles) in water (3.5 ml) was added to the solution. It was kept under reflux for 30 minutes and then for 24 hours in refrigerator. The crystals (5) were separated from ethanol by filtration, washed with ethanol and dried. Pale yellow needles were obtained with a melting point at 169-170°C. After recrystallization from 50 % ethanol (30 ml) 0.865 g (3.76 mmoles, 75 %) of almost colourless 5 were obtained. M.p. 172-173°C.

To find out the optimum of the incorporated radioactivity in some experiments the molar ratios in both steps were varied according to Table 2.

1-Cyano[^{14}C]methyl-6,7-dimethoxy-3,4-dihydro-isoquinoline (5a)

Inactive 4 was prepared from 2 (2.76 g, 10 mmoles) as described at tracer experiments. Then it was refluxed with 0.132 g (2 mmoles, 73 mCi) of $K^{14}CN$** in a mixture of ethanol (36 ml) and 1N KOH (10 ml) for 30 minutes. After standing overnight in refrigerator the precipitated 5a was filtered off, washed with ethanol and dried to yield 1.79 g (7.8 mmoles) of pale yellow needles m.p. 170-173°C. In the filtrate inactive 5 (0.46 g, 2 mmoles) was dissolved and crystallized by standing overnight. The total amount of the obtained product was 2.42 g (10.5 mmoles). Recrystallization from 50 % ethanol (50 ml) gave 2.004 g (8.7 mmoles) colourless crystals. M.p. 173-174°C. Total activity: 41.2 mCi. Molar activity was 4.74 mCi/mmoles, close to the calculated one (5.22 mCi/mmoles).

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* Active or inactive KCN was used according to Table 1 and 2.

** $K^{14}CN$ was prepared by Bánfi's method[7]

(6,7-dimethoxy-3,4-dihydro-1-isoquinolinyl)-acetamidoxime-1-^{14}C (6a)

5a (2.004 g, 8.7 mmoles, 41.2 mCi) was dissolved in ethanol (50 ml) and a solution of hydroxylamine hydrochloride (1.21 g, 17.4 mmoles) and $NaHCO_3$ (1.78 g, 1.2 mmoles) in water (3.5 ml) was added. It was refluxed for 22 hours, the ethanol was evaporated and the residue was suspended with water (10 ml), filtered off and washed with water. 1.84 g (7.0 mmoles) of 6a were obtained as a reddish powder. M.p. 133-140°C. Yield 80 %.

3-Amino-8,9-dimethoxy-5,6-dihydro-imidazo[5,1-a]isoquinoline--2-^{14}C (7a)

6a (1.84 g, 7.0 mmoles, 33.2 mCi) was suspended in water (15 ml) and acetic anhydride (0.8 ml, 0.865 g, 8.5 mmoles) was added dropwise, then the mixture was stirred for 15 minutes at room temperature and for 3 hours at 70-80°C. Then the hot solution was filtered, cooled and the pH was made alkaline (pH 10) with 40 % NaOH. It was kept in refrigerator overnight, filtered off and washed with water. 1.447 g (5.9 mmoles) of 7a was obtained as pale brownish crystals. M.p. 214-222°C. Yield 84.3 %.

3-Benzylideneamino-8,9-dimethoxy-5,6-dihydro-imidazo[5,1-a] isoquinoline-2-^{14}C (8a)

7a (1.35 g, 5.5 mmoles, 26.0 mCi) and freshly distilled benzaldehyde (0.7 ml, 0.69 g, 6.5 mmoles) and n-butanol (2 ml) were stirred at 120-125°C for 45 minutes, then it was kept in refrigerator for 3 hours. The product filtered off, washed with cold ethanol (3x1 ml) and 1.41 g (4.25 mmoles) of 8a were obtained as pale yellow crystals. M.p. 176-180°C. Yield: 77 %.

3-Benzylamino-8,9-dimethoxy-5,6-imidazo[5,1-a]isoquinoline-2-^{14}C--hydrochloride (1a)

8a (1.41 g, 20.1 mCi) was hydrogenated in ethanol (15 ml) with a palladium-charcoal catalyst. 77 ml (3.5 mmoles) of hydrogen

were absorbed. The catalyst was filtered off, the solution was acidified by HCl in ethanol. It was kept in refrigerator overnight and the precipitated white crystals were filtered off and washed with cold ethanol. After recrystallization from ethanol (25 ml) 1.15 g (3.11 mmoles) of 1a were obtained, m.p. 234-242°C. Yield 73 %. Total activity 14.7 mCi, specific activity 4.74 mCi/mmole. The material showed only one spot by TLC (benzene-EtOH--conc. NH_4OH 86:30:4) and proved to be identical to the authentic product in all respects except radioactivity.

Homoveratronitrile-1-^{14}C (9)

Homoveratryl chloride (1.40 g, 7.5 mmoles) was dissolved in acetonitrile (15 ml) and [6]Crown-18 (0.135 g) and $K^{14}CN$ (0.120 g, 1.8 mmoles, 70.3 mCi) and inactive KCN (0.375 g, 5.7 mmoles) were added and the mixture was stirred for 24 hours at room temperatures. Then KCl was filtered off, washed with acetonitrile (2x2 ml) and the filtrate was evaporated in vacuo. The residue (1.337 g, more than 100 %) a light brown oil, solidified slowly. It showed only one spot (R_f 0.4) by TLC (benzene-ethyl acetate 8:2).

Homoveratrylamine-1-^{14}C (10)

9 (7.5 mmoles) was dissolved in methanol (25 ml) and Raney Ni (about 1 g) was added. To the well-stirred mixture $NaBH_4$ (2.0 g) in 8 N NaOH (10 ml) was added dropwise in a 90 minutes period at room temperature. The stirring was continued for 30 minutes (till the gas evolution stopped), Raney Ni was separated by filtration and washed with methanol (3x10 ml), the filtrate was evaporated by a rotating evaporator. The thick residue was diluted with water (30 ml) and extracted with chloroform (3x20 ml). The collected extracts were washed with water (20 ml) and dried over $MgSO_4$. The solvent was evaporated and 10 (852 mg, 4.72 mmoles) was obtained as a pale yellow oil in 68 % yield. The material contained about 5 % of unreacted 9 by TLC (butanol-acetic acid-water 4:4:1;

R_f (10) = 0.3, R_f (9) = 0.6), and it was chemically identical with authentic inactive material.

N-Homoveratryl-(1-^{14}C)-cyanoacetamide (11)

10 (852 mg, 4.72 mmoles, 47.8 mCi) cyanoacetic acid (440 mg, 5 mmoles) and dicyclohexyl-carbodiimide (1.13 g, 6.0 mmoles) were refluxed in dry benzene (25 ml) under stirring for 1 hour. Then the hot mixture was filtered from dicyclohexyl-urea and washed with hot benzene (10 ml). It was cooled to 5°C and left to stand overnight; the precipitated white crystals were separated by filtration and washed with benzene (2 ml) and petroleum ether (3x5 ml); 920 mg of 11 were obtained. M.p. 125-127°C. Specific activity: 41.39 mCi/g, total activity: 38.57 mCi. A second crop (307 mg) was obtained by evaporating the solvent of the mother liquor and the residue was purified on a Kieselgel column (eluent $CHCl_3$). The overall yield was nearly quantitative (1.159 g, 99 %). Both crops showed only one spot on a TLC plate (ethyl acetate; R_f = 0.45).

1-Cyanomethyl-6,7-dimethoxy-3,4-dihydro-isoquinoline-3-^{14}C (5b)

11 (1.159 g) was dissolved in $CHCl_3$ (6 ml) and freshly distilled $POCl_3$ (2 ml) was added during 10 minutes. Then the mixture was refluxed for 2 hours. The solution became dark. The solvent was evaporated and the residue was refluxed in 15 ml of dilute HCl (1:10) for 10 minutes. Then the pH was made alkaline with solid Na_2CO_3 and after cooling the product was extracted with $CHCl_3$ (3x20 ml), the collected extracts were washed with water, dried over $MgSO_4$ and the solvent was evaporated. A dark powder (1.03 g) was obtained which was purified by column chromatography (Kieselgel, eluent $CHCl_3$). 448 mg of 5b was obtained as yellow crystals. Yield 42 %, total activity: 19.9 mCi. The material contained contamination in traces by TLC (ethyl acetate; R_f = 0.55).

6,7-Dimethoxy-3,4-dihydro-1-isoquinolinyl-3-^{14}C-acetamidoxime (6b)

The reaction was carried out as described for 6a; 6b (306 mg, 1.16 mmoles, 11.9 mCi) was prepared from 448 mg (1.94 mmoles, 19.9 mCi) of 5b in 60 % yield. The material was chemically identical with authentic inactive material by TLC ($CHCl_3$-methanol 1:1; R_f = 0.4).

3-Amino-8,9-dimethoxy-5,6-dihydro-imidazo[5,1-a]isoquinoline-5-^{14}C (7b)

131 mg of 7b was obtained from 306 mg (1.16 mmoles, 11.9 mCi) of 6b as described at 7a. M.p. 210-220°C. A second crop was obtained by the extraction of the filtrate with $CHCl_3$ and it was purified by column chromatography (solvent: $CHCl_3$-methanol 9:1). The total yield was 171 mg (0.69 mmoles, 7.16 mCi, 60 %) of 7b. Both materials showed only one spot on a TLC plate ($CHCl_3$-ethanol 1:1; R_f = 0.4).

3-Benzilideneamino-8,9-dimethoxy-5,6-dihydro-imidazo[5,1-a]isoquinoline-5-^{14}C (8b)

9 (171 mg, 0.7 mmoles, 7.16 mCi) was dissolved in butanol (5 ml) and freshly distilled benzaldehyde (1 ml) was added. The mixture was heated to 105°C during 15 minutes, then it was stirred at 100-110°C for 45 minutes. After cooling the butanol was evaporated in vacuo at 80°C (oil pump) and the residue (a dark brown oil) was purified by column chromatography (solvent $CHCl_3$); 192 mg (0.57 mmoles, 83 %, 5.98 mCi) of 8b were obtained as yellow powder. M.p. 176-180°C. The material showed one spot by TLC (chloroform-methanol 9:1; R_f = 0.5).

3-Benzylamino-8,9-dimethoxy-5,6-dihydro[5,1-a]isoquinoline-5-^{14}C hydrochloride (1b)

9 (192 mg, 0.57 mmoles, 5.98 mCi) was hydrogenated in 20 ml of ethanol with a Palladium-charcoal catalyst at 60°C. The reaction was very rapid, it finished in 5 minutes. Then the catalyst was filtered off and the solvent was evaporated. A colourless oil

(168 mg) was obtained. It was dissolved in 2 ml of 20 % ethanol--HCl and 30 ml of abs. ether was added. The precipitated white crystals were separated by filtration and washed with ether. 133 mg (0.36 mmoles, 63 %, 3.76 mCi) of 1b were obtained with 28.37 mCi/g specific activity. M.p. 210-220°C. The material showed only one spot by TLC (ethyl acetate R_f = 0.5) and it was chemically identical with authentic inactive 1. Radiochemical yield: 5.3 %.

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