Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXXIV, No. 11

INVESTIGATIONS ON THE CHEMISTRY OF BERBANES 15[1]. SYNTHESIS OF THE *ALLO*-BERBANE SKELETON LABELLED WITH ^{14}C.

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Summary

[14-^{14}C]-*allo*-berbane-14-ol: (7,8-methylenedioxy-14α-hydroxy-[14-^{14}C]-*allo*-berbane, [14-^{14}C]**1**, spec. act.: 405 MBq/mM) was synthesized in nine reaction steps from K^{14}CN (overall radioactive yield: 2.8%).

Keywords: carbon-14, *allo*-berbane, α_2 adrenoceptor agent

Introduction

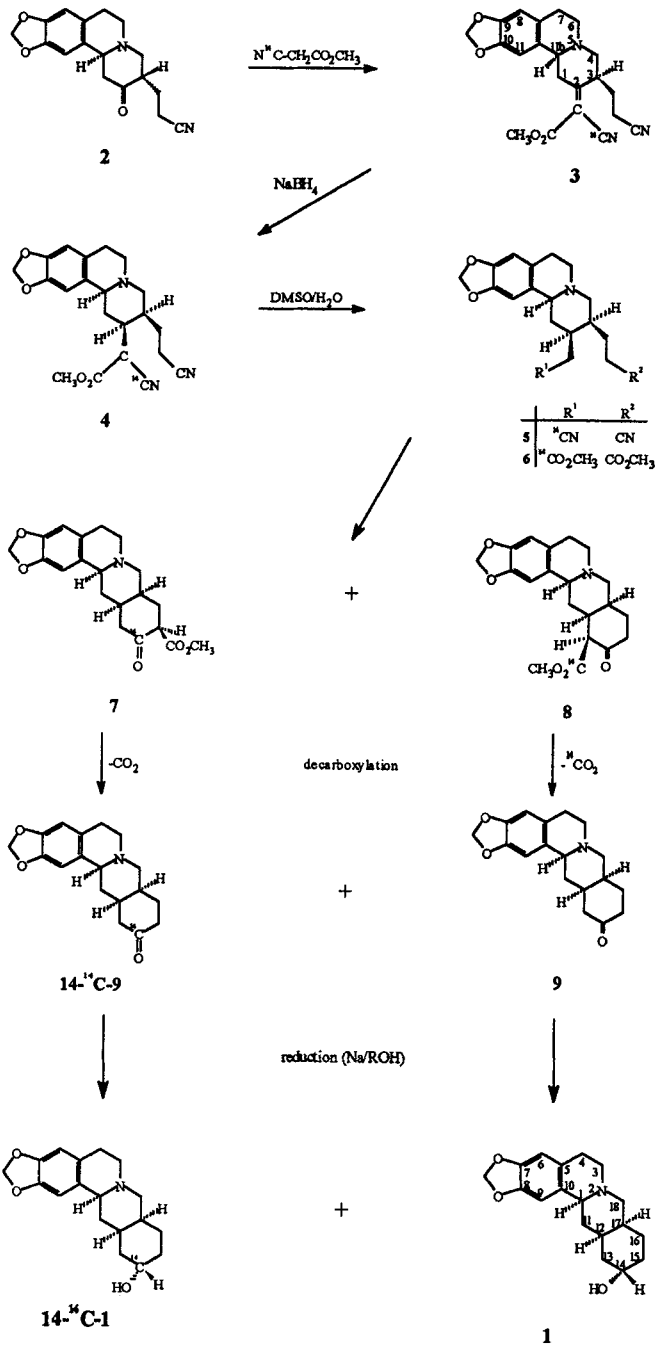
The alkaloid-like dibenzo[*a,g*]quinolizidine derivatives (berbanes) possess interesting biological activities[2-4]. Among them 14α-hydroxy-*allo*-berbane (**1**) emerged as an extremely selective α_2 adrenoreceptor blocking agent[3]. Studies on the biodegradations and metabolism of this compound required the synthesis of [^{14}C]-*allo*-berbane skeleton with high specific activity.

Results and Discussion

To accomplish the synthesis of the [^{14}C]-berbane skeleton utilization of the synthetic results of Szántay's group[1,5] were planned. Two possibilities seemed suitable for realizing our purpose; either performing the labelling at the future C-1 position in order to obtain [1-^{14}C]**1**, or introducing the radioactivity into the molecule at a later stage according to a novel stereoselective

CCC 0362–4803/94/111041–05

Received 16 May, 1994
Revised 26 June, 1994


N*C-CH2CO2CH3
2
3
NaBH4
DMSO/H2O
4
R1 R2
5 *CN CN
6 *CO2CH3 CO2CH3
7
+
8
-CO2
decarboxylation
-*CO2
14-*C-9
+
9
reduction (Na/ROH)
14-*C-1
+
1

approach[1], which results in ^{14}C labelling and formation of [14-^{14}C]**1**. Both possibilities were thoroughly investigated.

In the previously described pathway[5] reaction of β-(3,4-methylenedioxyphenyl)ethylamine HCl with sodium formate gave N-formylamine, the Bischler-Napieralski cyclization of which with $POCl_3$ could be performed in >80% yield. Introduction of ^{14}C labelling to position 1, actually, could have been accomplished by the use of sodium ^{14}C-formate. Further steps (**2** →→**6**, including a Wittig-Horner type phosphonate condensation, a catalytic hydrogenation and finally a methanolysis), however, would have involved low stereoselectivity. Hence a low overall yield and significant loss of activity from the labelled dihydroisoquinoline made this radio synthesis extremely expensive.

Therefore our attention turned onto an alternative method, in which the labelling is performed in a later stage of the synthesis. Though this novel stereoselective pathway, outlined above is *a priori* not favourable for radio synthetic purposes, as in the decarboxylation step from the mixture of **7** and **8** about the half of the radioactivity is necessarily lost (from **8**, $^{14}CO_2$ is eliminated and thus unlabelled **9** is formed), the high stereoselectivity and the good yields supported this choice. Elaborating the selective demethoxycarbonylation of *allo* cyanoester **4**, as well as the favourable regioselectivity of the Dieckmann condensation of **6** (**7**:**8** ~ 60:40) played an important role in obtaining [14-^{14}C]**1** in sufficient radiochemical yield.

Experimental section

Characterization of all intermediates as well as of the end product were done by comparing their mp, tlc, ir and ^{1}H-nmr behaviour with that of unlabelled samples synthesized and published[1] recently.

Methyl [^{14}C-cyano]acetate[6]

To a solution of potassium [^{14}C]-cyanide (0.3 g; 4.5 mM; 7.4 GBq), prepared[7] from barium [^{14}C]-carbonate, in 0.3N sodium hydroxide (1.5 mL) 2M sodium chloroacetate solution (2.5 mL; 5 mM) was added. The solution was heated at 80-90 °C for 30 min, then evaporated to dryness. To the residue methanol containing 20 % cc. HCl (5 mL) and diethylether (20 mL) was added under a nitrogen stream bubbling through a sodium hydroxide trap. The reaction mixture was dried on $MgSO_4$ then filtered. The ether solution of [^{14}C]-cyanoacetic acid was esterified with diazomethane in ether at 0 °C. The solvent was distilled off at atmospheric pressure and the residue was used in the next reaction without further purification. Yield: 0.38 g; 77 %; 5.85 GBq).

Methyl α-[^{14}C-cyano]-9,10-methylenedioxy-3β-cyanoethyl-1,3,4,6,7,11bα-hexahydro-2H-benzo-[*a*]quinolizin-2-ylideneacetate (3)

Cyano ketone **2** (1.14 g; 3.8 mM), ammonium acetate (0.38 g) and AcOH (0.4 mL) were admixed to the solution of ^{14}C-labelled methyl cyanoacetate (0.38 g; 3.8 mM) in dry benzene (6 mL). The stirred mixture was refluxed for 1 h by immersing it into an oil bath at 100 °C, then unlabelled methyl cyanoacetate (0.4 mL) was added and the reflux was continued for another 1.5 h. Addition of unlabelled cyanoacetate (0.3 mL) before further heating (1 h) was repeated. To the cooled mixture methylene chloride (20 mL) and water (8mL) was admixed, the pH of the latter was adjusted to 8-9 with cc. ammonium hydroxide while shaking the whole mixture. The organic layer was separated, washed with water and sat. NaCl solution, dried with $MgSO_4$ and evaporated. The residue was recrystallized (MeOH) to furnish yellow crystals (0.95 g; 66 %) of **3**. Mp: 160-162 °C, radioactivity: 3.04 GBq (52 %).

Methyl 9,10-methylenedioxy-3β-cyanoethyl-1,3,4,6,7,11bα-hexahydro-2H-benzo[*a*]quinolizin-2β-ylacetonitrile-^{14}C (5)

Unsaturated nitrile ester **3** (0.95 g; 2.5 mM) was dissolved in a mixture of methanol (25 mL) and methylene chloride (25 mL) and cooled to 0-5 °C in ice-water bath, $NaBH_4$ (40 mg; ~ 0.9 mM) was added to the mixture in small portions. The progress of the reduction was checked by tlc (Kieselgel 60 F_{254}, eluent: benzene - methanol 10 : 1). The solvent was at the end of the procedure evaporated under reduced pressure (rotadest), the residue dissolved in CH_2Cl_2 (25 mL) and the inorganics has been extracted with water. The organic layer was dried, evaporated and the oil obtained recrystallized in diethyl ether. To the mother liquor unlabelled *allo* cyanoacetate (unlabelled **4**, 0.3 g) was admixed, and the recrystallization procedure was repeated. The pale yellow crystals of the *allo* nitrile ester **5** (mp: 144-146 °C) were unified, dissolved in DMSO (15 mL) and stirred at 170 °C under argon atmosphere. Progress of demethoxycarbonylation could be followed by tlc (as above). When the reaction was complete, the mixture was poured onto water (50 mL), and the dinitrile **5** was extracted with CH_2Cl_2. The organic phase was successively washed with water (8-10 times 10 mL) to get rid off the DMSO, dried ($MgSO_4$) and evaporated. The residue was recrystallized in methanol to give colourless crystals of *allo* dinitrile **5** (0.80 g).

Methyl 9,10-methylenedioxy-3β-methoxycarbonylethyl-1,3,4,6,7,11bα-hexahydro-2H-benzo-[*a*]quinolizin-2β-ylacetate-^{14}C (6)

Dinitrile **5** (0.8 g; 2.5 mM; 0.85 GBq) was esterified in a mixture of methanol (25 mL) and cc. H_2SO_4 (3 mL) by refluxing for 20 h. The progress of the procedure was checked by tlc (as above). After completion of the methanolysis the mixture was poured onto ice (~ 100 g), its pH was adjusted with 25 % NH_4OH to 8-9 and extracted with CH_2Cl_2. The organic phase was then dried and evaporated, and the residue treated with ether-hexane to obtain colourless crystals of **6** (0.56 g; 58 %). Radiochemical yield: 1.30 GBq (0.909 GBq/mM).

7,8-Methylenedioxy-14-oxo-[14-^{14}C]-*allo*-berbane (9)

Diester **6** (0.56 g; 1.45 mM) was dissolved in dry benzene (3 mL), potassium *tert*-butoxide (0.3 g) was added and the mixture was refluxed for 40 min. AcOH (0.15 mL) was added to the cooled solution before evaporation to dryness. The crude mixture of ketoesters **7** and **8** was decarboxylated without separation and purification. The residue, obtained after the evaporation, was dissolved in 10 % aqueous HCl (15 mL) and refluxed for 5 h. The solution was cooled and then treated with 20 % aqueous NaOH (pH 9). The precipitate was filtered off, washed with water and recrystallized in methanol to give colourless crystals of berbanone **9** (0.22 g; 50 % combined yield from **6**). Radiochemical yield: 0.4 GBq (0.54 GBq/mM).

7,8-Methylenedioxy-14α-hydroxy-[14-^{14}C]-*allo*-berbane.HCl (14-^{14}C-1)

Pieces of sodium metal (0.6 g; 26 mM) were dispersed in hot xylene (15 mL) by shaking vigorously and subsequently cooled back to room temperature, then *allo*-berbanone **9** (0.22 g; 0.74 mM) was admixed. To the stirred dispersion dry ethanol (5 mL) was dropped in small portions (in about 2 h). Progress of the reduction was checked by tlc (Kieselgel 60 F_{254}, eluent: benzene-methanol = 14:3). After an additional hour stirring the mixture was treated with AcOH (1.4 mL), evaporated onto Silicagel 60 (63-200 μm) (2 g), and chromatographed on a silicagel column (20 g). By-products and starting material were eluted with benzene - methanol 10:1 mixture, the target molecule (**1**) with benzene - methanol 1:1. The pure fractions were collected, the *quasi* pure fractions were diluted with unlabelled product (0.04 g) and purified repeatedly by column chromatography. All the fractions containing pure [14-^{14}C]**1** (and **1**) were pooled, acidified with 2N HCl in methanol to pH 2, evaporated and recrystallized in methanol - ether to produce [14-^{14}C]-labelled *allo*-berbanol hydrochloride (**14-^{14}C-1**.HCl) (0.170 g, 204 MBq). Mp: 241-245 °C. The radiochemical purity proved to be higher than 98% (determined by tlc method: DC-Alufolien Kieselgel 60 F_{254}, eluent: benzene - methanol = 14-3, R_f**1** = 0.25).

References and Notes

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