THE SYNTHESIS OF 2,6-DICHLOROBENZYLIDENE AMINOGUANIDINE ACETATE [α-^{14}C]

Samuel F. Sisenwine and Cesario O. Tio
Wyeth Laboratories, Inc., Research Division, Radnor,
Pennsylvania, 19087, U.S.A.
Jenny Ahern
New England Nuclear Corp., Boston, Massachusetts, U.S.A.

Received on November 14, 1975
Revised on March 5, 1976

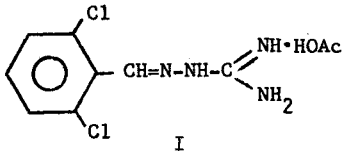
SUMMARY

2,6-Dichlorobenzylidene aminoguanidine acetate, a new antihypertensive agent, was labelled with ^{14}C at the benzal position for metabolic studies. The key reaction involved the reduction of the sterically hindered 2,6-dichlorobenzonitrile [cyano-^{14}C] with lithium aluminum hydride to 2,6-dichlorobenzaldehyde [carbonyl-^{14}C]. The labelled nitrile was prepared by a Sandmeyer reaction employing 2,6-dichloroaniline and K^{14}CN. Further reaction of the labelled aldehyde with aminoguanidine bicarbonate produced the desired radioactive drug.

Key Words: Guanabenz, 2,6-dichlorobenzylidene aminoguanidine acetate, 2,6-dichlorobenzonitrile

INTRODUCTION

The compound 2,6-dichlorobenzylidene aminoguanidine acetate (guanabenz, Wy-8678), I, has been found to be an active antihypertensive agent in animals and man (1-5). Little information, however, is available on its metabolic disposition in various species. Recently, in an investigation performed by DeMarchi *et al.* (6), metabolic data were obtained from rats given a radiolabelled drug in which ^{14}C was inserted in the aminoguanidine moiety.



I

It is reasonable to expect that a metabolic cleavage of the -CH=N- group can occur with the concomitant production of ^{14}C-labelled aminoguanidine. In fact, this cleavage has been observed in ongoing

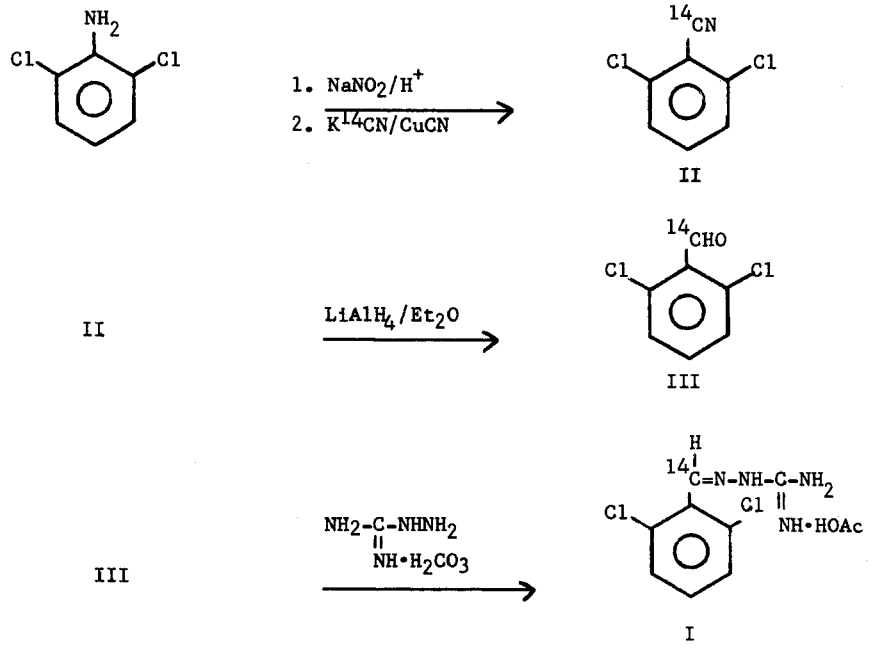
experiments (7). It was of interest, therefore, to synthesize a labelled compound with the radioactive label on the benzal carbon to investigate the fate of the 2,6-dichlorobenzylidene moiety. The present work describes the synthesis of 2,6-dichlorobenzylidene aminoguanidine acetate [α-^{14}C].

RESULTS

The synthesis of non-radioactive 2,6-dichlorobenzylidene aminoguanidine acetate is performed easily and in high yield by the reaction of aminoguanidine bicarbonate with commercially available 2,6-dichlorobenzaldehyde (8). Obtaining 2,6-dichlorobenzaldehyde [carbonyl-^{14}C], however, initially presented difficulties. The aldehyde had usually been produced by halogenation of 2,6-dichlorotoluene to yield 2,6-dichlorobenzalchloride and by subsequent hydrolysis of the product to yield the aldehyde. For a radioactive synthesis, this approach was considered impractical because of low yields and the high cost of the starting material, radiolabelled 2,6-dichlorotoluene.

A new and less expensive approach was attempted via a reduction of a ^{14}C-labelled nitrile to the ^{14}C-labelled aldehyde. 2,6-Dichloroaniline was easily converted to 2,6-dichlorobenzonitrile [cyano-^{14}C] (II) by the Sandmeyer reaction (9,10), as shown below. A Stephen reduction of the nitrile to produce the aldehyde could normally be the next step; however, steric hindrance has prevented this reduction (10). Lithium triethoxyaluminum hydride has also been reported to be a selective agent in the partial reduction of nitriles to aldehydes (11), but upon experimentation with unlabelled 2,6-dichlorobenzonitrile, it failed to produce the required product. Again, steric hindrance was believed to prevent reduction. The more potent reducing agent, $LiAlH_4$, which normally reduces aromatic nitriles to aromatic amines, was next employed, and a satisfactory yield of the product of partial reduction, 2,6-dichlorobenzaldehyde [carbonyl-^{14}C] (III) was obtained. Apparently, further reduction of the intermediate imino complex cannot proceed to the amine because of steric hindrance; however,

in this case, this property is used to good advantage. With the acquisition of the labelled aldehyde, conversion to the required drug (I) was easily accomplished. The overall radiochemical yield from $K^{14}CN$ was 12%. Metabolic studies using this drug are now in progress (7).



EXPERIMENTAL

I. 2,6-Dichlorobenzonitrile [cyano-^{14}C]

34.1 mM of $NaNO_2$ was added with stirring to 15.1 ml concentrated H_2SO_4 at 0°C. The mixture was warmed at ~55°C until a clear solution was obtained. The solution was cooled to room temperature and 30.0 mM of 2,6-dichloroaniline in 12 ml acetic acid was added dropwise with stirring. The above solution was stirred for one hour at room temperature and then carefully added in small portions to a stirred suspension of 14.96 mM of $K^{14}CN$, 15.0 mM of CuCN, and 373 mM Na_2CO_3 in 40 ml H_2O. The reaction mixture was stirred for one hour at room temperature and the product was isolated by steam distillation. The distillate was continuously extracted with ether, and the extract was taken to dryness on the flash evaporator. The 2,6-dichlorobenzonitrile [cyano-^{14}C] was recrystallized from petroleum ether (radiochemical

yield - 91%) and had a melting point of 147-148°C (uncorr.). TLC on silica gel plates in a heptane/ethyl acetate (9:1) system indicated > 99% radiochemical purity (R_f = 0.30).

II. 2,6-Dichlorobenzaldehyde [carbonyl-^{14}C]

16.3 mM of $LiAlH_4$ in 80 ml anhydrous ether was added dropwise to a chilled suspension of 13.65 mM of 2,6-dichlorobenzonitrile [cyano-^{14}C] in 100 ml anhydrous ether at 0°C, and the reaction mixture was then stirred for three hours at 0°C. Thirty ml 6N H_2SO_4 was added dropwise with rapid stirring, and the reaction mixture was stirred an additional 15 minutes at room temperature. The ether layer was separated and the aqueous layer was extracted two times with 150 ml ether. The combined ether extracts were washed twice with 50 ml water, dried over $CaSO_4$, and taken to dryness on the flash evaporator. The product was purified by TLC on 1000 μ silica gel plates in a heptane/ethyl acetate (9:1) solvent system and eluted from the plates with CH_2Cl_2. The 2,6-dichlorobenzaldehyde [carbonyl-^{14}C] was recrystallized from aqueous methanol (radiochemical yield - 19%) and had a melting point of 69°-70°C (uncorr.). TLC in a heptane/ethyl acetate (9:1) solvent system indicated >98% radiochemical purity (R_f - 0.47).

III. 2,6-Dichlorobenzylidene aminoguanidine acetate [α-^{14}C]

A solution of 2.58 mM of 2,6-dichlorobenzaldehyde [carbonyl-^{14}C] in 2 ml ethanol was added to a solution of 2.58 mM of aminoguanidine bicarbonate in 4 ml of H_2O and 250 μl acetic acid. An oil separated which gradually dissolved when the solution was heated on a steam bath. The solution was concentrated to approximately half its volume and the product crystallized during overnight refrigeration. TLC indicated that the product was ~96% radiochemically pure. 2,6-Dichlorobenzylidene aminoguanidine acetate [α-^{14}C] was purified by recrystallization from ethanol/diethyl ether (radiochemical yield - 69%) and had a melting point of 239-240°C (uncorr.). TLC on silica gel plates in a methanol/$CHCl_3$/NH_4OH (50:48.5:1.5) solvent system indicated >98.5% radiochemical purity (R_f - 0.60). One u.v. absorbing spot was observed which

corresponded to the standard.

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