SYNTHESIS OF SOME 2,3-^{14}C-QUINOXALINE DERIVATIVES

Walfred S. Saari and William C. Lumma, Jr.
Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania 19486

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SUMMARY

6-Chloro-1H-quinoxalin-2-one-2,3-^{14}C was prepared by the novel condensation of 4-chloro-1,2-phenylenediamine with glyoxylic acid-^{14}C (U). The labelled quinoxalinone was transformed further into 2,6-dichloroquinoxaline-2,3-^{14}C and 6-chloro-2-(1'-piperazinyl)-quinoxaline-2,3-^{14}C.

Key Words: 6-Chloro-2-(1'-piperazinyl)-quinoxaline, 6-chloro-1H-quinoxalin-2-one, 2,6-dichloroquinoxaline, glyoxylic acid, quinoxaline.

INTRODUCTION

^{14}C-Labelled 6-chloro-2-(1'-piperazinyl)-quinoxaline, 6, a serotonin reuptake blocking agent (1), was desired for metabolism studies. Since no syntheses of ^{14}C-labelled quinoxaline derivatives could be found in the literature, several methods (2) for the preparation of this ring system were evaluated for their applicability to radiochemical synthesis. The selected procedure is outlined in Scheme I.

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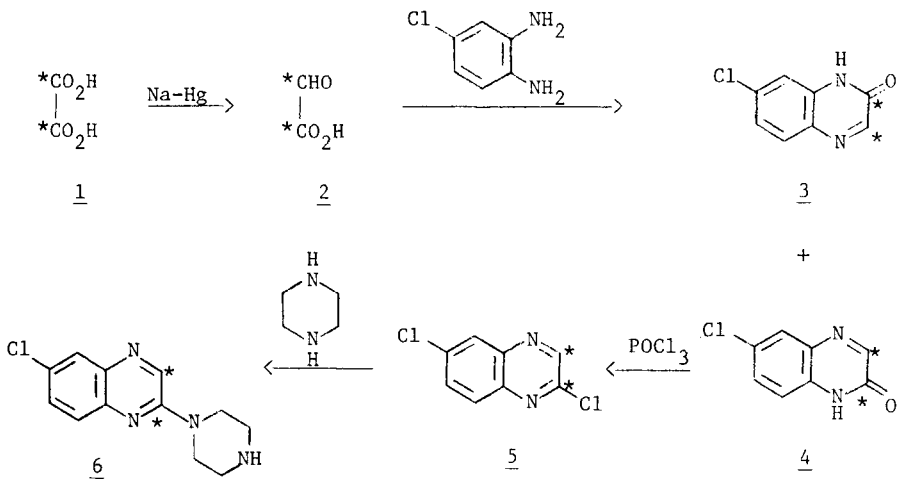

Scheme I. * = ^{14}C

Uniformly labelled oxalic acid, 1, (3) was reduced with 1.2% Na-amalgam by the method of Murray, Bills and Ronzio (4) to give an aqueous solution of glyoxylic acid, 2. After removing water by lyophilization, 2 was condensed with 4-chloro-1,2-phenylenediamine in MeOH to afford a mixture of the chloroquinoxalinones 3 and 4. The desired 6-chloro isomer 4 was obtained pure by recrystallization from methyl cellosolve.

Condensation of glyoxylic acid, in contrast to glyoxylic acid esters, with o-phenylenediamines does not appear to have been employed previously for the synthesis of quinoxalinones. Use of glyoxylic acid, rather than the commonly used esters, for the preparation of labelled quinoxalinones has the advantage of eliminating the additional steps required for synthesis of the labelled glyoxylic acid ester. Other synthetic applications of the glyoxylic acid condensation will be disclosed in a forthcoming publication.

To complete the synthesis of 6, purified 4 was converted to the dichloroquinoxaline 5 with $POCl_3$ followed by displacement of the activated 2-chloro substituent with piperazine. This method represents a convenient synthesis of

labelled 6 as well as other intermediates, e.g. 4 and 5, which could be useful for other radiochemical quinoxaline syntheses.

EXPERIMENTAL

Glyoxylic Acid-^{14}C (U), 2 (4). A solution of 353 mg (3.92 mmole), 28 mCi, of oxalic acid-^{14}C (U) (3) in 6.5 ml H_2O was diluted to 24 ml with distilled H_2O and cooled to 5° with an ice bath. While maintaining a temperature of 5-10° and a pH of 1.5-2 (pH meter) by periodic addition of 6 N HCl, a total of 60 g of 1.2% Na-Hg was added to the vigorously stirred oxalic acid solution over 1/2 hr. After addition of amalgam was complete and pH became stabilized, the mixture was warmed to 20° and the pH raised to 2.25 by addition of solid $NaHCO_3$. The aqueous solution was decanted from Hg and filtered with slight suction through a pad of diatomaceous earth which had been prewashed with distilled H_2O. Water washings were combined with the filtrate and lyophilized to give a white solid.

6-Chloro-1H-quinoxalin-2-one-2,3-^{14}C, 4. A mixture of the crude lyophilized glyoxylic acid-^{14}C (U) and 503 mg (3.53 mmole) of recrystallized (H_2O) 4-chloro-1,2-phenylenediamine in 25 ml MeOH was stirred at room temperature for 4 hr. After concentrating under reduced pressure at 35-40°, the residue was washed with four 10 ml portions of H_2O and 2 ml 2-propanol and dried at 40° under reduced pressure to give 285 mg of a mixture of the chloroquinoxalinones 3 and 4. The labelled chloroquinoxalinone mixture was combined with 100 mg cold pure 6-chloro-1H-quinoxalin-2-one (1) and crystallized twice from 12-25 ml methyl cellosolve to give 211 mg of pure 4, mp 306-9° dec., soften at 301°, homogeneous upon tlc (R_f = 0.3, silica gel, 2% MeOH-$CHCl_3$). The labelled product was identical, mp and tlc, with an authentic cold sample.

2,6-Dichloroquinoxaline-2,3-^{14}C, 5. A solution of 211 mg (1.17 mmole) of 6-chloro-1H-quinoxalin-2-one-2,3-^{14}C in 3 ml $POCl_3$ containing 3 drops of DMF was stirred at reflux for 4 hr and allowed to cool to room temperature overnight. The reaction mixture was concentrated under reduced pressure (120° oil bath), 2

ml of toluene was added and the solution reconcentrated. After adding 2 ml more of toluene and reconcentrating, the residue was extracted with four 5 ml portions of hot n-butyl chloride which were filtered through a pad of diatomaceous earth, prewashed with hot n-butyl chloride, and combined. Removal of solvent under reduced pressure at 35° gave 207 mg of 2,6-dichloroquinoxaline-2,3-^{14}C, homogeneous upon tlc (R_f = 0.8, silica gel, $CHCl_3$).

6-Chloro-2-(1'-piperazinyl)-quinoxaline-2,3-^{14}C Hydrochloride, 6. A mixture of 204 mg (1.03 mmole) of 2,6-dichloroquinoxaline-2,3-^{14}C, 700 mg (8.13 mmole), anhydrous piperazine and 12 ml n-butanol was stirred at reflux for 10 hr. After concentrating under reduced pressure (steam bath), 15 ml saturated aqueous Na_2CO_3 solution was added and the product extracted into four 10 ml portions of $CHCl_3$. The $CHCl_3$ extracts were washed with 10 ml saturated Na_2CO_3 solution, combined, dried ($MgSO_4$), filtered and concentrated under a N_2 stream at 40°. This crude product was purified by chromatography on a 2000 µm preparative silica gel plate eluted with 10% MeOH-$CHCl_3$. After drying at room temperature, the band at R_f 0.2-0.4 was removed and extracted continuously with MeOH for 10 hr (Soxhlet) until the extracts were no longer yellow. The MeOH extract was concentrated under reduced pressure at 40-45° and the residue dissolved in 3 ml $CHCl_3$ which was filtered through a pad of diatomaceous earth, prewashed with $CHCl_3$. The $CHCl_3$ filtrate was concentrated in a N_2 stream at 45° and the residue converted to the HCl salt. In this way 273 mg (81.7% from 4) of product was obtained which upon tlc, silica gel, 5% MeOH-$CHCl_3$ saturated with NH_4OH, was identical with an authentic sample of 6-chloro-2-(1'-piperazinyl)-quinoxaline hydrochloride and appeared to be homogeneous but proved to have a radiochemical purity of 97.2%. Two recrystallizations from 5-10 ml of 90% EtOH-10% H_2O gave 116 mg (34.7% from 4) of pure 6, specific activity 15.3 µCi/mg with a radiochemical purity >99% determined by tlc, silica gel, R_f = 0.18 in 12% MeOH-$CHCl_3$ saturated with NH_4OH and R_f = 0.36 in n-butanol (65)-HOAc (10)-H_2O (25); λ max in MeOH containing 1% HCl, nm (A%), 370 (267), 250 (909), 210 (1075), λ min, nm (A%), 305 (87), 223 (251).

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