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Synthesis of 3-(*o*-Chlorophenyl)-2-methyl-4 (3H)-quinazolinone-2 and 4-^{14}C

E. J. MERRILL
Warner-Lambert Research Institute Morris Plains, N. J., 07950.
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SUMMARY

The synthesis of 3-(o-chlorophenyl)-2-methyl-4[3H]-quinazolinone labeled with ^{14}C in both the 2 and 4 positions of the quinazolinone ring is described.

INTRODUCTION.

3-(*o*-Chlorophenyl)-2-methyl-4[3H]-quinazolinone * has been shown to possess sedative-hypnotic properties [1]. In order to more easily study the absorption, excretion, and distribution patterns of this drug in various biological species [2] and also investigate the metabolites [3], the drug was labeled with ^{14}C in both the 2 and 4 positions of the quinazolinone ring.

DISCUSSION.

Cyclizations to give 2,3-substituted 4[3H]-quinazolinones have been accomplished using a variety of conditions [5, 6], including refluxing toluene with a catalytic amount of phosphorous trichloride [4], and polyphosphoric acid [7, 8, 9]. The synthesis, which produced 3-(*o*-chlorophenyl)-2-methyl-4[3H]-quinazolinone-2-^{14}C (IV) is shown in Figure 1.

Acetic anhydride has been the preferred reagent for acylating anthranilic acid and its derivatives [4–9], although Starke [10] has recently reported using acetic acid.

The use of sodium acetate to incorporate the radioactive atom has several advantages. The radioactive sodium acetate was much easier to manipulate than either acetic anhydride or acetic acid and as a labeled precursor was about six times less expensive than acetic-^{14}C anhydride. The yield was

* The Trade name for this compound is mecloqualone.

unaffected for, in cold runs, the 3-(*o*-chlorophenyl-2-methyl-4[3H]-quinazolinone was obtained in yields of between 50-60 %. This procedure, however, gave a product with a yellow color which had no detectable effect on the purity of the product. The color was removed by either recrystallization from Skellysolve B* or by percolation through a column of Florisil **. Either of these procedures produced a colorless, pure product.

3-(*o*-Chlorophenyl)-2-methyl-4[3H]-quinazolinone-4-^{14}C (V) was synthesized as shown in Figure 2. This procedure gave a white product which, in cold runs, was obtained in yields of 60-70 %. However, the hot run gave a mixture of V and the uncyclized 2-acetamido-N-(*o*-chlorophenyl)benzamide (VI). This was identified by comparison with an authentic sample [11] by thin-layer chromatography (TLC). The uncyclized material exhibited an R_f of about 0.75 on silica gel GF plates when irrigated with triethyl amine and fluoresced strongly under UV light which is typical of anthranilic acid deriva-

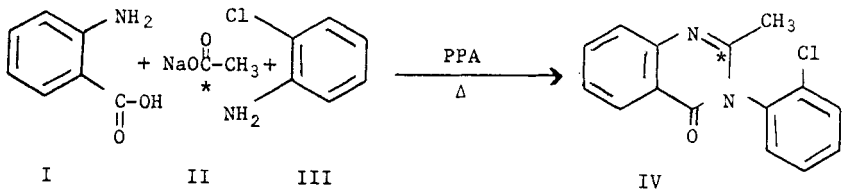

FIG. 1. Reaction sequence for 3-(*o*-chlorophenyl)-2-methyl-4[3H]-quinazolinone-2-^{14}C.

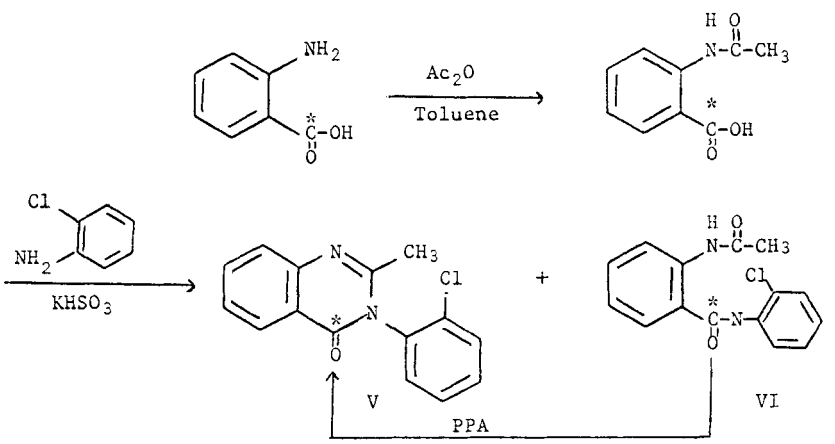

FIG. 2. Reaction sequence for 3-(*o*-chlorophenyl)-2-methyl-4[3H]-quinazolinone-4-^{14}C.

* Skellysolve B is principally *n*-hexane and is available from Skelly Oil Co., El Dorado, Kansas.

** Florisil (100-200 mesh) is a selective adsorbent prepared by the Floridin Co., and is available from Fischer Scientific Co., Fair Lawn, N. J.

tives. In order to complete the cylization, it was necessary to heat the mixture in polyphosphoric acid (PPA) as in the synthesis of IV.

The procedures described in the Experimental demonstrated that the chemical and radiochemical purity was 99 + % for both IV and V.

EXPERIMENTAL.

3-(o-Chlorophenyl)-2-methyl-4[3H]-quinazolinone-2-^{14}C.

To a mechanically stirred suspension of 1.37 g (10 mmole) anthranilic acid in 7 g polyphosphoric acid was added 1.0 g (12 mmole) sodium acetate-1-^{14}C (6.5 mCi, specific activity = 0.62 mCi/mmole) [13]. The reaction mixture was immersed in an oil bath at 70° C, the temperature raised over one hour to 135° C and the heat source withdrawn. When the temperature reached 80° C, 1.04 ml (10.5 mmole) *o*-chloroaniline was added, and the temperature raised over 2 hours to 200° C and kept at this temperature for an additional 1/2 hour. The resulting syrup was poured into 30 ml H_2O and stirred mechanically. The suspension was neutralized with 20 % aqueous Na_2CO_3, 15 ml chloroform added, and left at room temperature overnight. The phases were separated and the aqueous phase extracted 4 × 15 ml chloroform. The organic phases were combined, dried with $MgSO_4$, and the solvent removed. The oily residue was dissolved in approximately 15 ml benzene and percolated through an 80 g Florisil column. Approximately 1,300 ml of eluate was collected. The solvent was removed and the residue recrystallized from hot Skellysolve B and gave 1.4 g (52 %) of the desired product, which melted 129-130° C. Alternatively, the product may be recrystallized from 70 % aqueous methanol. The specific activity was determined by liquid scintillation spectrometry [14] to be 0.62 mCi/mmole.

3-(o-Chlorophenyl)-2-methyl-4[3H]-quinazolinone-4-^{14}C.

To a magnetically stirred solution of 1.37 g (10 mmole) anthranilic acid-7-^{14}C (5.29 mCi, specific activity = 0.53 mCi/mmole) [15] in 25 ml toluene heated at 85-90° C was added 1.04 ml (11 mmole) acetic anhydride. The turbid reaction was stirred at this temperature for one hour, and then 1.25 ml (12 mmole) *o*-chloroaniline was added. After the clear solution had vigorously refluxed for one hour, 0.2 g potassium bisulfate was added and the reaction was refluxed with magnetic stirring overnight.

The reaction was cooled and 95 ml toluene added. The organic phase was washed with 3 × 15 ml of 1N aqueous NaOH with 3 × 15 of 1N aqueous hydrochloric acid and finally with 3 × 15 ml of water. The organic phase was dried with $MgSO_4$ and the solvent was removed. This residue, when subjected to thin-layer chromatography on Silica Gel GF with triethylamine, gave two radioactive spots, one spot corresponded to an authentic sample

of V at $R_f = 0.7$ while the other spot had an R_f value of 0.77, which corresponded to the uncyclized 2-acetamido-N-(*o*-chlorophenyl)benzamide. The cylization was completed in polyphosphoric acid by gradually increasing the temperature to 200° C over 2 hours and maintaining that temperature for an additional 30 minutes. The reaction was then poured into water, neutralized with Na_2CO_3 and the product was extracted with chloroform. After drying the organic phase with $MgSO_4$, the solvent was removed. The residue was recrystallized from 70 % aqueous methanol and then Skellysolve B to give 1.2 g (45 %) of the desired product, which melted at 129-130° C. The specific activity was determined by liquid scintillation spectrometry to be 0.54 mCi/mmole.

The IR's as mulls of both IV and V exhibited maxima at 1,690, 1,610, 1,590, 1,570, 1,470, 1,465, 1,380, 1,340, 1,280, 770, and 755 cm^{-1}. The UV of both compounds determined in ethanol exhibit maxima at 225, 265, 304, and 316 nm(mμ). The molecular extinction coefficient at 265 nm(mμ) was 9,350. A quantitative TLC on silica gel GF, when irrigated with triethyl amine, gave a single absorbing spot at an R_f of about 0.7, which contained all the radioactivity [12]. This TLC system was designed to separate the contaminants likely to be present in 3-(*o*-chlorophenyl)-2-methyl-4[3H]-quinazolinone.

The physical constants of IV and V were compared with a reference standard determined to be at least 99.5 % pure [16].

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10. STARKE, H. — *Ger. (East)*, 34,123 (Feb. 25, 1965).
11. An authentic sample was prepared by R. Novack and F. MacMillan of these laboratories.

12. The TLC plates were scanned on a Packard Model 7200 Radiochromatogram Scanner.
13. Purchased from Nuclear Research Chemicals, Inc.
14. The radioactivity was determined using a Packard Model 3310 Tri Carb Liquid Scintillation Spectrometer equipped with external standardization. A cocktail composed of 7.0 g PPO (2,5-diphenyloxazole), 0.3 g dimethyl POPOP [1,4-bis-2-(4-methyl-5-phenyloxazolyl)benzene] and 100 g naphthalene in 1 1 1,4-dioxane was used throughout. (See F. N. Hayes, Packard Technical Bulletin No. 1, (1963) p. 4).
15. Purchased from New England Nuclear Corp.
16. The reference standard was prepared and evaluated by M. Goodenough and A. D. Lewis of these laboratories.