SYNTHESES OF 2(1H)-QUINAZOLINONE-4-^{14}C DERIVATIVES.

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SUMMARY

1-Cyclopropylmethyl-6-methoxy-4-phenyl-2(1H)-quinazolinone (III) (SL-573) and 1-Cyclopropylmethyl-6-nitro-4-phenyl-2(1H)-quinazolinone (VI) (SL-522),each labelled with carbon -14 at C- 4 position were synthesized for use in metabolic studies. The syntheses were achieved by two types of reaction sequences shown in Figure 1 and 2. Overall radiochemical yields of SL-573-4-^{14}C and SL-522-4-^{14}C were 35% and 17% from carbon dioxide-^{14}C, and their specific activities were 5.52 mCi/mmole and 3.31 mCi/mmole, respectively.

INTRODUCTION.

In our investigations of pharmacologically active quinazolines it has been found that SL-573,[1] 1-cyclopropylmethyl-6-methoxy-4-phenyl-2(1H)-quinazolinone (III), has marked anti-inflammatory activities and also that SL-522,[2] 1-cyclopropylmethyl-6-nitro-4-phenyl-2(1H)-quinazolinone (VI), has anti-inflammatory and other pharmacological activities. The metabolic studies of these compounds in animals have, as a matter of course, become necessary in our research programs. There can be found many syntheses[3-8] of non-radioactive 2(1H)-quinazolinone derivatives, but to our knowledge none of radioactive ones have been reported so far. Only Dubnick *et al*[9] reported a synthesis of a 4(3H)-quinazolinone derivative, mecloqualone, labelled with carbon-14 at C-2 position. To meet the requirements of the metabolic studies** we synthesized for the first time ^{14}C-

labelled 2(1H)-quinazolinones, SL-573-4-^{14}C and SL-522-4-^{14}C, by different types of reaction sequences as described below.

DISCUSSION.

Synthesis of SL-573-4-^{14}C

The reaction sequence used is shown in Figure 1. The starting material, benzoic acid-(carboxyl-^{14}C), was prepared from barium carbonate-^{14}C by a standard method.[10] Although many kinds of procedures[11] are known for the preparation of benzaldehyde-(carbonyl-^{14}C), they are rather tedious and generally give comparatively low yields. We therefore successfully adapted a new method developed by Travnelis and Hergenrother[12] for non-radioactive preparation of arylaldehydes, which involved air oxidation of arylcarbinols in dimethyl sulfoxide. Thus reduction of benzoic acid-(carboxyl-^{14}C) with lithium aluminum hydride gave a quantitative yield of benzyl alcohol-α-^{14}C, which in turn was oxidized with bubbling air in dimethyl sulfoxide at 180° for about 6 hr to produce benzaldehyde-(carbonyl-^{14}C) in 91% overall yield from benzoic acid-(carboxyl-^{14}C).

In the series of reactions, the condensation of benzaldehyde-(carbonyl-^{14}C) with N-cyclopropylmethyl-N-(p-anisyl)urea[1] (I) gave us considerable difficulty in obtaining a good yield of the desired product (II). We tried a variety of Lewis acids as catalysts and searched for reaction conditions required for a maximum yield. As a result, we found that treatment of benzaldehyde-(carbonyl-^{14}C) in toluene with an excess of the urea (I) in the presence of methanesulfonic acid and removing water by azeotropic distillation afforded a maximum yield (59%) of dihydroquinazolinone-4-^{14}C (II). This method was similar to one described by Yamamoto et al,[1] except that the proportions of the reactants were varied considerably. The dihydroquinazolinone-4-^{14}C (II) was easily converted to SL-

** The results of the metabolic studies will be described elsewhere in the near future.

573-4-^{14}C (III) by means of a potassium permanganate oxidation in aqueous dioxane at room temperature. The overall yield of SL-573-4-^{14}C (III) from barium carbonate-^{14}C was 35% and it had a specific radioactivity of 5.52 mCi/mmole.

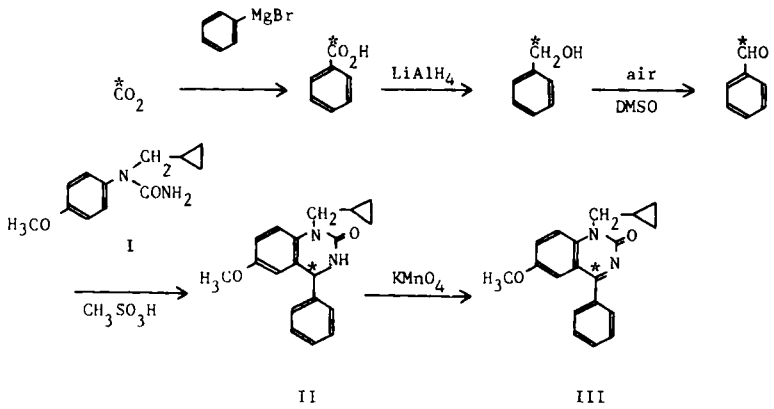

Figure 1. Reaction Sequence of Synthesis of SL-573-^{14}C

Synthesis of SL-522-4-^{14}C

Apparently, in the case of SL-522-4-^{14}C (VI), the Pictet-Spenglar type of reactions used for SL-573-4-^{14}C cannot be adapted for the formation of its quinazolinone ring because of the presence of a strong electron withdrawing nitro group on the phenyl ring. Accordingly we chose another procedure[6] outlined in Figure 2.

The starting material, 2-amino-5-nitrobenzophenone-(carbonyl-^{14}C) (IV), was prepared by the procedure[13] which we established previously for the synthesis of a benzodiazepinone-5-^{14}C derivative. The overall yield of IV was 53% from carbon dioxide-^{14}C through four steps of reactions. Condensation of IV with urethane was carried out by heating the mixture in the presence of anhydrous zinc chloride as a catalyst at 180-190° for several hours, giving 57% yield of quinazo-

linone-4-^{14}C (V) and 29% recovery of the starting material (IV).

Treatment of V in dimethylformamide with sodium hydride at room temperature followed by alkylation with cyclopropylmethyl bromide in the same solvent at 100° produced a mixture of two main products which were separated by column chromato-

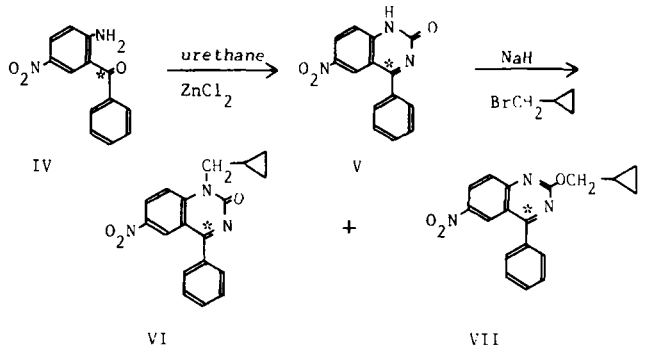

Figure 2. Reaction Sequence of Synthesis of SL-522-4-^{14}C

graphy on silica gel. One of these, which had a lower Rf-value and a melting point of 172-173°, showed a strong absorption of amide carbonyl at 1675 cm^{-1} in its ir spectrum and was identical in every respect with authentic SL-522. The yield of SL-522-4-^{14}C (VI) was 46% and the specific radioactivity was 3.31 mCi/mmole. The other compound (25% yield), mp. 142-144°, was found to be O-cyclopropylmethyl-quinazoline-^{14}C (VII) by comparison with the authentic sample.

EXPERIMENTAL

Benzoic acid-(carboxyl-^{14}C)

Benzoic acid-(carboxyl-^{14}C) was synthesized by a standerd method[10] of Grignard reaction with $^{14}CO_2$ and phenylmagnesium bromide; 0.95 g of benzoic acid-(carboxyl-^{14}C) (5.63 mCi/mmole) having a total activity of 44.3 mCi was prepared in a quantitative yield based on Ba$^{14}CO_3$.

Benzyl alcohol-α-^{14}C

To a solution of benzoic acid-(carboxyl-^{14}C) (0.95 g, 7.86 mmoles) in dry ether (50 ml) was added portionwise $LiAlH_4$ (0.65 g, 17 mmoles) at room temperature and the mixture was refluxed for 3.5 hr. After cooling, 5% HCl (50 ml) was added to the reaction mixture which was then extracted with ether. The extract was washed with 5% aqueous Na_2CO_3 solution and water, dried, and evaporated to give benzyl alcohol-α-^{14}C (0.82 g, 99%).

Benzaldehyde-(carbonyl-^{14}C)

A solution of benzyl alcohol-α-^{14}C (0.82 g, 7.78 mmoles) in dimethyl sulfoxide (15 ml) was heated at 180° with air passing through the solution for 6 hr. The mixture was diluted with water, extracted with ether, and the ether extract washed with water and dried. Evaporation of the solvent afforded benzaldehyde-(carbonyl-^{14}C) (0.74 g, 92%), which showed a carbonyl absorption at 1704 cm^{-1}. The product was pure enough to use without further purification.

1-Cyclopropylmethyl-6-methoxy-4-phenyl-3,4-dihydro-2(1H)-quinazolinone-4-^{14}C (II)

A mixture of benzaldehyde-(carbonyl-^{14}C) (0.77 g, 7.0 mmoles), N-cyclopropylmethyl-N-(p-anisyl)urea[1] (I) (1.85 g, 8.4 mmoles) and three drops of methanesulfocic acid in anhydrous toluene (80 ml) was heated to 110° with gradual azeotropic-distillation of produced water for 10 hr during which time toluene was added to maintain the volume of the mixture about 40 ml. The mixture was then poured into 5% Na_2CO_3 aqueous solution and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated to dryness to give an oily residue. Chromatography of the residue on silica gel gave 1-cyclopropylmethyl-6-methoxy-4-phenyl-3,4-dihydro-2(1H)-quinazolinone-4-^{14}C (II) (1.28 g, 59%), mp. and mixed mp. 132-135°, identical in every respect with authentic sample.

1-Cyclopropylmethyl-6-methoxy-4-phenyl-2(1H)-quinazolinone-4-^{14}C (SL-573-4-^{14}C) (III)

To a solution of 1-cyclopropylmethyl-6-methoxy-4-phenyl-3,4-dihydro-2(1H)-quinazolinone-4-^{14}C (II) (1.28 g, 4.15 mmoles) in dioxane (20 ml) was added a solution of $KMnO_4$ (0.70 g, 4.4 mmoles) in water (7 ml). The mixture was stirred at room temperature for 7 hr. After an addition of formic acid (1 ml), the mixture was filtered, and the precipitate was washed with acetone. The combined filtrate was concentrated under reduced pressure to give a residue which was taken up in ethyl acetate. The solution was washed with water, dried, and evaporated to afford an oily residue. The residue was chromatographed over silica gel, eluted with chloroform, and evaporation of the main fractions gave a crude product. Dilution of the product with the authentic carrier (0.20 g) followed by recrystallization from benzene-ether-n-hexane gave 1-cyclopropylmethyl-6-methoxy-4-phenyl-2(1H)-quinazolinone-4-^{14}C (III) (0.85 g, 15.4 mCi, 5.52 mCi/mmole, 68%), mp. and mixed mp. 116-117°, identical in all respects with authentic SL-573.

6-Nitro-4-phenyl-2(1H)-quinazolinone-4-^{14}C (V)

A mixture of 2-amino-5-nitrobenzophenone-(carbonyl-^{14}C)[13] (IV) (1.5 g, 6.2 mmoles, 30.8 mCi, 4.97 mCi/mmole), urethane (3.5 g, 39 mmoles) and $ZnCl_2$ (0.2 g, 1.5 mmoles) was heated to 180-190° for 5 hr. The solidified mixture was triturated with water (30 ml) and ethyl acetate (10 ml). The solid collected by filtration was dried at room temperature *in vacuo* overnight to give 6-nitro-4-phenyl-2(1H)-quinazolinone-^{14}C (V) (1.11 g, 67%), mp. 244-247°(dec.). This material showed an amide carbonyl band at 1660 cm^{-1} in its ir spectrum and was used for the following reaction without further purification. From the filtrate, 2-amino-5-nitrobenzophenone-(carbonyl-^{14}C) (IV) (0.43 g, 29%) was recovered.

1-Cyclopropylmethyl-6-nitro-4-phenyl-2(1H)-quinazolinone-4-^{14}C (VI) (SL-522-4-^{14}C)

To a suspension of NaH (50% mineral oil coating, 0.31 g, 6.5 mmoles) in dimethylformamide (20 ml) was added 6-nitro-4-phenyl-2(1H)-quinazolinone-4-^{14}C

(V) (1.11 g, 4.1 mmoles), and the mixture was stirred at room temperature for 1.5 hr and at 50-60° for 0.5 hr. After cooling, cyclopropylmethyl bromide (1.0 g, 7.4 mmoles) was added to the mixture, and it was heated with stirring at 100° for 4.5 hr. The mixture was poured into ice-water, extracted with ethyl acetate, and the extract was washed with water, dried, and evaporated. The residue, which showed two major spots on tlc, was diluted with authentic unlabelled SL-522 (0.3 g) and chromatographed on silica gel. From the first fraction eluted with chloroform was obtained a crystalline product which was recrystallized from isopropyl alcohol to yield 2-cyclopropylmethyloxy-6-nitro-4-phenylquinazoline-4-^{14}C (VII) (0.33 g, 5.11 mCi, 4.97 mCi/mmole, 25%), mp. and mixed mp. 142-144°. The second fraction, after evaporation of chloroform, gave a crystalline material which was recrystallized from isopropyl alcohol to afford 1-cyclopropylmethyl-6-nitro-4-phenyl-2(1H)-quinazolinone-4-^{14}C (VI) (0.92 g, 9.47 mCi, 3.31 mCi/mmole, 46%), mp. and mixed mp. 172-173°. This material was identical in every respect with authentic SL-522.

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