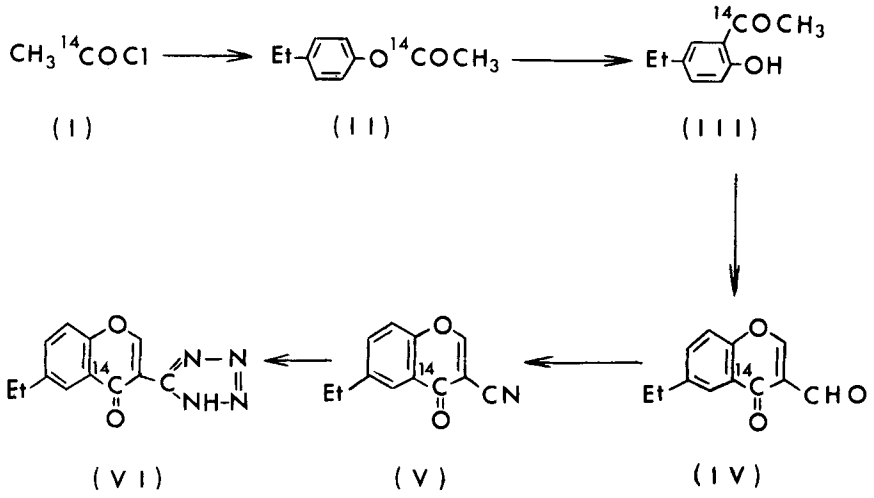
SYNTHESIS OF 6-ETHYL-3-(1H-TETRAZOL-5-YL)[4-^{14}C]CHROMONE (AA-344-^{14}C)

Much attention is devoted to the orally active antiallergic agents possessing a mode of action similar to that of disodium cromoglycate.[1,2] 6-Ethyl-3-(1H-tetrazol-5-yl)chromone (AA-344) was found to have antiallergic activity in the rat passive cutaneous anaphylaxis (PCA) test and to show the activity when administered orally in rats.[3]



This paper deals with the synthesis of 6-ethyl-3-(1H-tetrazol-5-yl)[4-^{14}C]-chromone (VI) for the study of metabolic fate in animals. By the ordinary acylation method, p-[1-^{14}C]acetoxyethylbenzene (II) was obtained from the reaction of p-ethylphenol with [1-^{14}C]acetyl chloride (I). 5-Ethyl-2-hydroxy-[carbonyl-^{14}C]acetophenone (III) was prepared from II by the Fries rearrangement and then reacted with dimethylformamide in the presence of $POCl_3$

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to afford 6-ethyl-3-formyl-[4-^{14}C]chromone (IV).[4] IV was converted to 6-ethyl-3-cyano-[4-^{14}C]chromone (V) in one step by treating with hydroxylamine hydrochloride according to the method described for the preparation of nitrile derivative from aliphatic aldehydes.[5] The reaction of V with sodium azide in the presence of $AlCl_3$ in the manner described for the synthesis of tetrazole[6] gave VI in 22.8 % radiochemical yield based on I.

EXPERIMENTAL

Material

[1-^{14}C]Acetyl chloride (50 mCi, 1.25 mmol) purchased from New England Nuclear, Mass.,U.S.A., was diluted with 9.75 mmol of radioinactive acetyl chloride.

p-[1-^{14}C]Acetoxyethylbenzene (II)

After a mixture of 1345 mg (11 mmol) of p-ethylphenol, 50 mCi (11 mmol) of diluted [1-^{14}C]acetyl chloride (I) and 1 ml of pyridine was refluxed for 1 h, the insoluble material was removed by filtration and washed with ether. The combined organic layer was washed with 15 ml of water containing 0.5 g of ammonium acetate, followed by 15 ml of water and then dried over anhydrous Na_2SO_4. Evaporation of the dried solution in vacuo left 1628 mg (90 % crude yield based on I) of II which appeared as the pale yellow liquid.

5-Ethyl-2-hydroxy-[carbonyl-^{14}C]acetophenone (III)

A mixture of 1628 mg of II and 4 g of anhydrous $AlCl_3$ (analytical grade, Wako Pure Chemicals) was heated at 140° for 1.5 h and then added to ice-water with stirring. The resulting mixture was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous Na_2SO_4 and evaporated in vacuo to give 1548 mg (95 % crude yield based on II) of the red liquid as III. III was used in next process without purification.

6-Ethyl-3-formyl-[4-^{14}C]chromone (IV)

To a solution of 1548 mg of crude III in 10 ml of dimethylformamide, 3.6 ml of $POCl_3$ was added dropwise with stirring and cooling. The mixture was stirred for 5 h without heating and then poured into 200 ml of ice-water. The precipitate was filtered off, washed with water then dried and dissolved in ethyl acetate. To the solution was added a small amount of ether-n-hexane mixture (1:1,v/v) and then 1387 mg (73 % yield based on III) of crude product was crystallized. TLC, Rf. 0.49, Kieselgel 60F-254 (Merck)/$CHCl_3$.

6-Ethyl-3-cyano-[4-^{14}C]chromone (V)

A mixture of 1387 mg of crude IV, 482 mg of hydroxylamine hydrochloride, 11 ml of ethanol and 135 ul of conc.HCl was refluxed for 9.5 h with stirring and allowed to stand in a refrigerator over-night. The crude product was filtered off, washed with n-hexane and dried in vacuo. Recrystallization from ethanol gave 854 mg of V (62 % yield based on IV). TLC, Rf. 0.41, Kieselgel 60F-254 (Merck)/$CHCl_3$.

6-Ethyl-3-(1H-tetrazol-5-yl)[4-^{14}C]chromone (VI)

A mixture of 854 mg of V, 2447 mg of anhydrous $AlCl_3$, 1765 mg of NaN_3 and 21 ml of anhydrous tetrahydrofuran was refluxed at 75-85° for 14 h. Under the nitrogen stream, 30 ml of dil. HCl was added to the mixture and stirring for 15 min. After the addition of 50 ml of water, the resulting mixture was concentrated to 1/2 of its volume. The insoluble product was filtered off, washed with water, dried in vacuo and recrystallized from ethanol. The product was recrystallized from EtOH-CCl_4 mixture (1:2,v/v) to give 614 mg (59 % yield based on V) of VI, mp. 221° and Rf-values on the three radiochromatography-systems, identical with that of authentic AA-344. The radiochemical yield and the specific activity of VI were 22.8 % based on I and 4.5 mCi/mmol respectively. The radiochemical purity was shown to be 99 % based on both the reverse isotope dilution and the radiochromatographic methods. The radiochromatography of VI was carried out in the following three systems:
TLC, Rf. 0.52, Kieselgel 60F-254 (Merck)/$CHCl_3$-MeOH-HCOOH (10:1:0.1, v/v).

TLC, Rf. 0.70, silicagel F-254/366 (Woelm)/$CHCl_3$-MeOH-HCOOH (15:1:0.2, v/v).

TLC, Rf. 0.40, silicagel F-254/366 (Woelm)/$CHCl_3$-acetone-HCOOH (15:1:0.2, v/v).

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N.Hayashi, K.Shirozaki and A.Nohara

Central Research Division,
Takeda Chemical Industries, Ltd.,
17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka
532, Japan.