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PREPARATION OF TWO ION-PAIR COMPLEXES OF 3-*dl*-α-TOCOPHERYLCARBONYL-1-HEXYL-PYRIDINIUM-[^{14}C]-LABELED CROMOLYN AND 3-*d*-α-[5-METHYL-^{3}H] TOCOPHERYLCARBONYL-1-HEXYLPYRIDINIUM-CROMOLYN

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SUMMARY

Ion-pair complexes of 3-*dl*-α-tocopherylcarbonyl-1-hexyl pyridinium-[^{14}C]-labeled cromolyn and 3-*d*-α-[5-methyl-^{3}H] tocopherylcarbonyl-1-hexylpyridinium-cromolyn have been prepared with radiochemical yields of 56.0 and 65.7 %, respectively.

Keywords: cromolyn, ion-pair complexes, tocopherol hexylnicotinate

INTRODUCTION

Cromolyn[1], or cromoglycic acid, due to its poor oral absorption, has been used as topical anti-allergy drug. If a molecule as polar as sodium cromolyn was effective topically, it was anticipated that even better results could be

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obtained using cromolyn conjugates that exhibited greater solubility in lipids[2,3]. Ion-pair formation may be responsible for the transdermal absorption of highly charged drugs such as alkylpyridinum salts conjugates[4,5].

RESULTS AND DISCUSSION

To evaluate the percutaneous penetration of cromolyn by autoradiography in rats, [^{14}C]-labeled cromolyn (5) and [^{3}H]-labeled tocopherol hexylnicotinate (11) were originally synthesized in five and four steps as illustrated in Schemes 1 and 2, respectively. The specific radioactivities and radiochemical purities were estimated to be 4.58 MBq (123.8 μCi)/mmol and 60.2 % for 5, and 3.53 MBq (95.5 μCi)/mmol and 99.5 % for 11 (Fig. 1). Finally, ion-pair complexes (6, 12) between tocopherol hexylnicotinate as a quaternary ammonium salt and cromolyn were prepared in overall radiochemical yields of 56.0 % for 6, and 65.7 % for 12, respectively. The proposed methods were for simple and faster preparations for the ion-pair complexes.

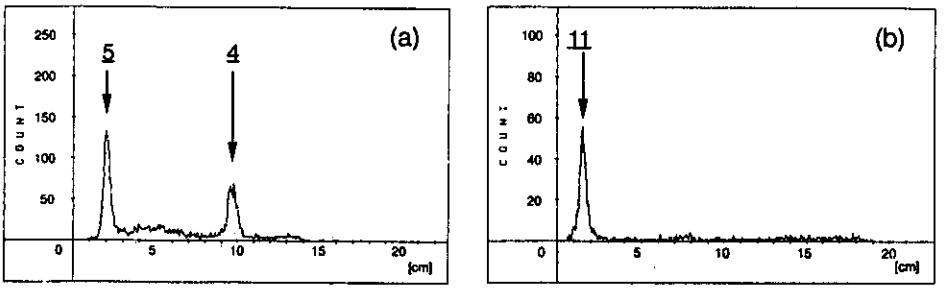
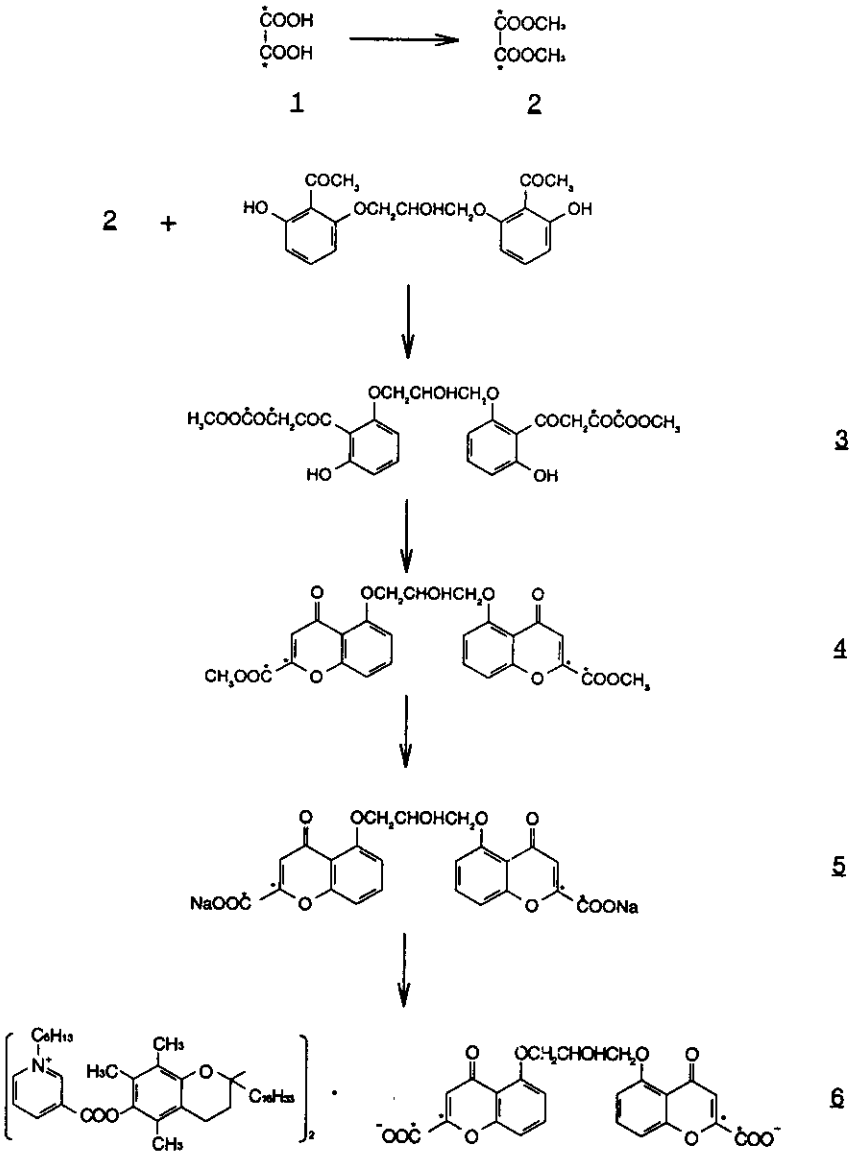
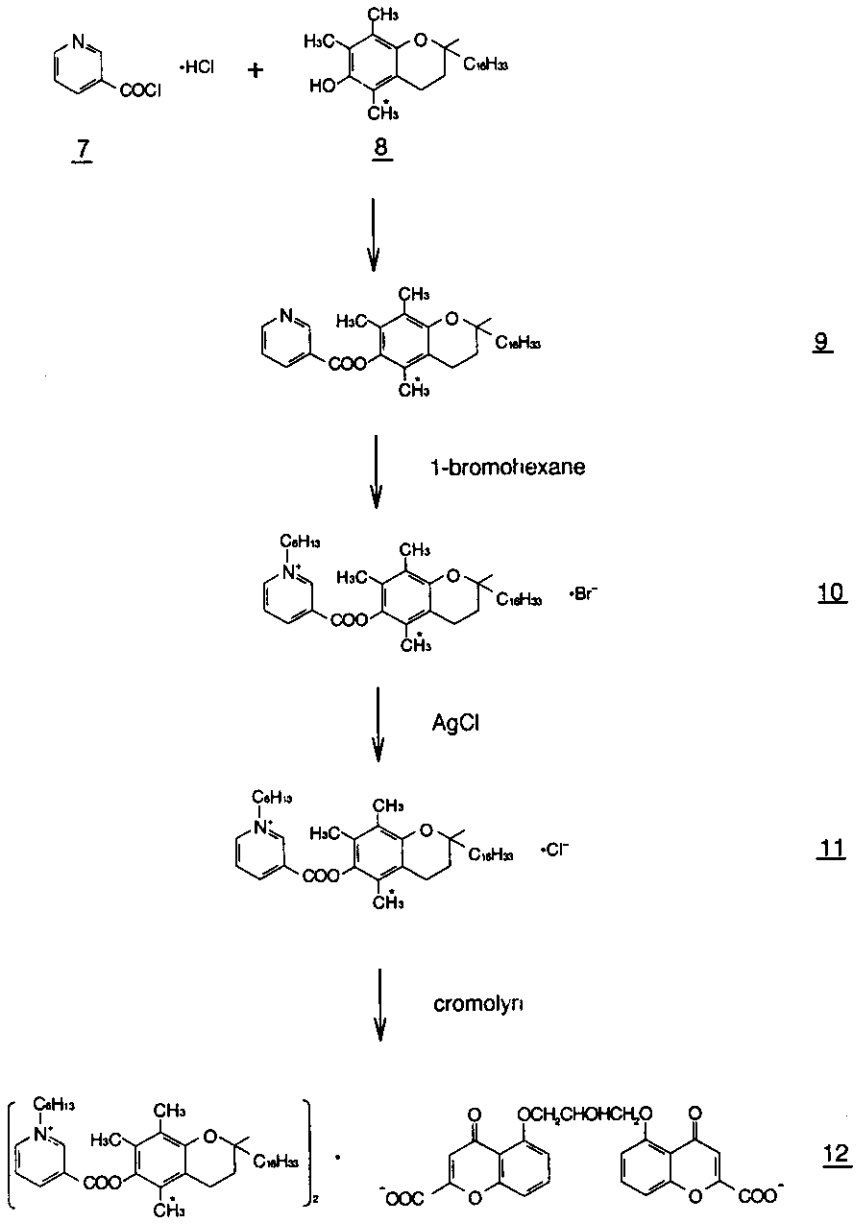


Figure 1. Radio TLC chromatograms of (a) the [^{14}C]-labeled cromolyn (5) and (b) the [^{3}H]-labeled tocopherol hexylnicotinate (11). The eluting solvent systems used were chloroform : methanol (1 : 1) and *n*-hexane : isopropyl ether (1 : 1) for 5 and 11, respectively.



Scheme 1. Synthesis of 3-*dl*-α-tocopherylcarbonyl-1-hexylpyridinium-[^{14}C]-labeled cromolyn



Scheme 2. Synthesis of 3-*d*-α-[5-methyl-^{3}H] tocopherylcarbonyl-1-hexylpyridinium-cromolyn

EXPERIMENTAL

Materials: [$^{14}C_2$]-Oxalic acid (37 MBq, 3.8 GBq/mmol) (1) and *d*-α-[5-methyl-^{3}H] tocopherol (185 MBq, 1.05 TBq/mmol) (8) were purchased from Amersham International plc (Buckinghamshire, UK). Cromoglycic acid sodium salt and *dl*-α-tocopheryl nicotinate were obtained from Sigma (St. Louis, MO). Nicotinic acid chloride hydrochloride (7) and 1-bromohexane were commercial samples from Tokyo Chemical Industry (Tokyo, Japan). Benzene was freshly distilled with sodium metal and pyridine. Other solvents were freshly distilled before use. All other reagents were of analytical reagent grade and purchased from Wako Chemical Industry (Osaka, Japan).

Synthesis of cromoglycic acid [2-^{14}C, carboxyl-^{14}C] disodium salts ([^{14}C]-labeled cromolyn) (5): [$^{14}C_2$]-Oxalic acid (1, 8.2 MBq/mmol) was dissolved in methanol (2.5 mL) and added to diazomethane ether solution at room temperature until the colour of the solution changed to yellow. The solvent was then evaporated off to give [$^{14}C_2$]-oxalic acid dimethyl ester (2). 2 and 1,3-bis(2-hydroxy-1,3-propandiyl)bis(oxy)-acetophenone (300 mg) were suspended in a solution of methanol (2.5 mL) and benzene (4 mL), added dropwise sodium methoxide (100 mg) in methanol (3.5 mL), and then refluxed at 60°C for 4h. The mixture was adjusted to pH 2 with 1 mol/L HCl and added to water (5 mL). The combined solution was extracted with chloroform (20 mL) which was twice evaporated to give 6,6'-(2-hydroxy-1,3-propandiyl)bis(oxy[α-(2-hydroxy)phenyl]bis[1,2-$^{14}C_2$]-2,4-dioxobutanoic acid methyl ester 3. A solution of 3 in methanol (5 mL) and HCl (0.1 mL) was heated at 50°C for 10 min, and 4 mol/L NaOH (0.2 mL) was added. After stirring at room temperature for 3h, the solution was purified by silica gel column chromatography (methanol : chloroform = 1 : 1) to give cromoglycic acid [2-^{14}C, carboxyl-^{14}C] di-sodium salts ([^{14}C]-labeled cromolyn) (5).

Preparation of the ion-pair complex (6) *between 3-dl-α-tocopherylcarbonyl-1-hexylpyridinium chloride (tocopherol hexylnicotinate) and [^{14}C]-labeled cromolyn*: tocopherol hexylnicotinate was dissolved in methanol and added to an aqueous solution of 5. The suspension was evaporated *in vacuo* to give 6, m. p. 239°C (dec). The radiochemical yield was 56.0 %.

Synthesis of 3-d-α-[5-methyl-^{3}H] tocopherylcarbonyl-1-hexylpyridinium chloride ([^{3}H]-labeled tocopherol hexylnicotinate) (11): *d*-α-[5-methyl-^{3}H]tocopherol (8, 53.8 MBq/mmol) was dissolved in a mixture of dried benzene (3 mL) and pyridine (3 mL). Nicotinic acid chloride hydrochloride (1 g) (7) was added to the solution and refluxed at 60°C for 2h. The solution was added dropwise to ice water and extracted with *n*-hexane. After evaporation, the residue was dissolved in methanol and purified by silica gel column chromatography (*n*-hexane : isopropyl ether = 1 : 1) to give 3-*d*-α-[5-methyl-^{3}H]tocopherylcarbonyl nicotinic acid 9. A solution of 9 and 1-bromohexane (5 g), dissolved in benzene (15 mL) was refluxed for 36 h. After cooling, the precipitate was removed by filtration and recrystallized from isopropyl ether to give 3-*d*-α-[5-methyl-^{3}H]tocopherylcarbonyl-1-hexylpyridinium bromide 10. A solution of 9 and AgCl (1.5 g) suspended in methanol (20 mL) was stirred in the dark at room temperature for 20h. After filtration of the precipitate using a membrane filter (0.45 μm, Millipore), the filtrate was evaporated to give 3-*d*-α-[5-methyl-^{3}H]tocopherylcarbonyl-1-hexylpyridinium chloride ([^{3}H]-labeled tocopherol hexylnicotinate) (11).

Preparation of the ion-pair complex (12) *between [^{3}H]-labeled tocopherol hexylnicotinate and cromolyn*: Cromolyn dissolved in water was added to a methanol solution of 11 and evaporated to give 12, m. p. 239°C (dec). The radiochemical yield was 65.7 %.

Analysis: The radiochemical purities of the final products were determined using an automatic TLC linear analyzer (Berthhold LB-2832, Wildbad, Germany) and silica gel plates (Merck, silica gel 60, normal phase, 5 x 20 cm).

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