SYNTHESIS OF TRITIUM LABELLED PRECOCENES

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SUMMARY

Regiospecific syntheses of tritium labelled precocene I (5a) and precocene II (5b), the antijuvenile hormones, have been accomplished. The syntheses involved condensations between 2-hydroxyacetophenones (1) with acetone-T to give cross condensation products 2 which on cyclodehydration furnished 2,2-dimethyl-4-chromanones-(2-gem dimethyl-T) (3). Reduction of 3 with lithium aluminium hydride gave chroman-4--ols (2-gem dimethyl-T) (4). Dehydration of 4 furnished 2,2-dimethylchromenes- (2-gem dimethyl-T) (5). Starting with appropriate acetophenones and acetone-T, precocene I (7-methoxy-2,2-dimethylchromene) and precocene II (6,7-dimethoxy-2,2-dimethylchromene) labelled with tritium in the 2-gem dimethyl positions, have been synthesised in high chemical as well as radiochemical yields.

Key Words: Synthesis, antijuvenile hormones, precocene I-T, precocene II-T, 7-methoxy-2,2-dimethyl-4-chromanone-T, 6,7-dimethoxy-2,2-dimethyl-4-chromanone-T.

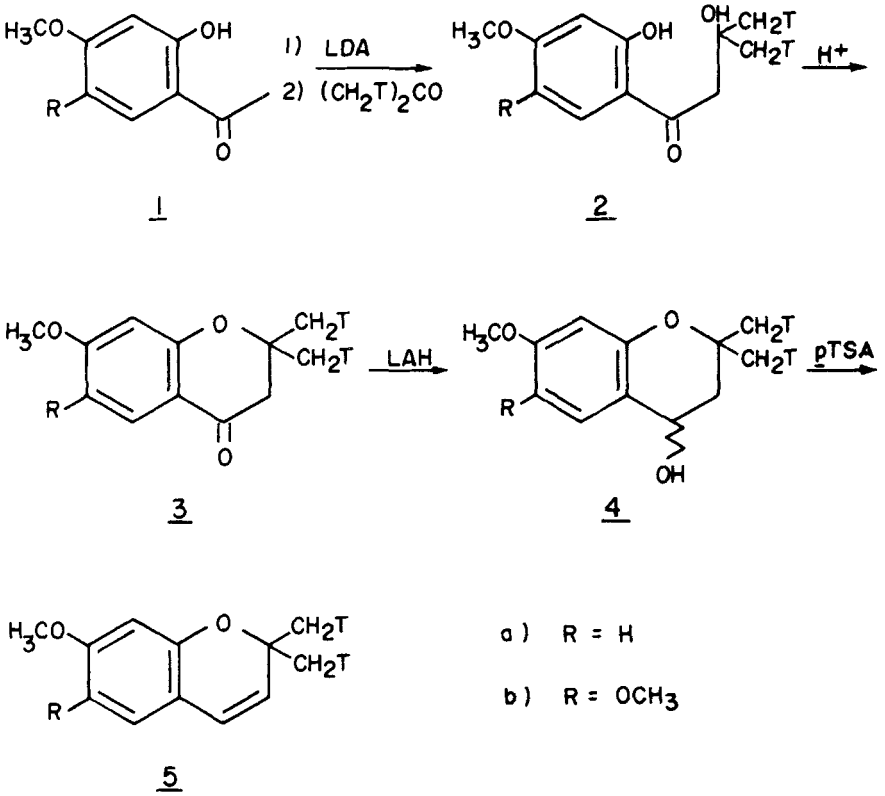
Precocene I (7-methoxy-2,2-dimethylchromene) and precocene II (6,7--dimethoxy-2,2-dimethylchromene), isolated from the plant Ageratum houstonianum are reported to have antijuvenile hormone activity[1]. The activity, however, is restricted to only a few insect species, probably due to different metabolic pathways involved. Further, some antifeedants also elicit such antijuvenile hormone-like responses[2]. In order to elucidate the mode of action of these compounds, radiolabelled precocene I (5a) and precocene II (5b) were required. The present communication deals with the synthesis of precocenes, labelled with tritium in the 2-gem dimethyl positions[3].

Synthesis of precocene II (5b) labelled with carbon-14 in the 2-gem dimethyl position by methylation of 6,7-dimethoxycoumarin with $[^{14}C]$-methyl magnesium iodide has been reported[4]. Syntheses of precocene I (5a) and precocene II (5b) labelled with tritium in 2-gem dimethyl positions via corresponding 4-chromanones (3a and 3b) are described here. The

0362-4803/81/121737-05$01.00

Received January 28, 1981
Revised March 23, 1981

procedure is essentially based on the general synthesis of 2,2-dialkyl-chromenes[5,6]. The high incorporation of the label and excellent chemical yield make this procedure equally suitable for the synthesis of 2,2-dialkyl-chromenes labelled with stable isotopes.



The enolates of appropriate 2-hydroxyacetophenones (1), generated by lithium diisopropylamide, condensed with acetone-T to give cross condensation products 2. Acid catalysed cyclodehydration of 2 gave the 4-chromanones (3) in good yield with high retention of labels. Reduction of 3 to chroman-4-ols (4) was smoothly brought about by lithium aluminium

hydride. Dehydration of 4, using p-toluenesulfonic acid, gave precocenes (5). Precocenes (5) were purified by preparative thin layer chromatography to constant specific activities. The chemical identities of precocenes were firmly established by direct comparison with authentic samples[6].

EXPERIMENTAL

Radioactivity determinations were carried out with Beckman liquid scintillation spectrometer LS 100. TLC analysis was carried out using silica gel G (Acme Synthetic Chemicals, Bombay) containing F_{254} fluorescent indicator. The identities of labelled compounds were established by direct comparison with authentic samples[6]. Radiochemical homogeneity was established by TLC or recrystallisation to constant specific activities.

1-(2'-Hydroxy-4'-methoxyphenyl)-3-hydroxy-3-methyl-1-butanone-(3-methyl-T,4-T) (2a): To a solution of lithium diisopropylamide (5.0 mmol; prepared in situ from n-butyl lithium and diisopropylamine) in THF at -25°, 2-hydroxy-4-methoxyacetophenone (1a, 332 mg, 2 mmol) in THF (10 ml) was added[7]. After stirring for 1 hr, the temperature of the mixture was lowered to -40°, acetone-T[8] (150 mg, 2.5 mmol; 1.43 mCi/mmol) was added and the mixture stirred for another 2 hr. The reaction mixture was diluted with ether (50 ml) and acidified with dilute hydrochloric acid (5 ml). The organic layer was separated and the aqueous part was extracted with ether (3 x 20 ml). The combined extracts were washed neutral with brine and dried (sodium sulfate). Removal of solvents gave 2a which was purified by preparative TLC (chloroform:benzene, 6:4), Yield, 384 mg (86%); specific activity, 1.02 mCi/mmol. Compound 2a was chemically identical (TLC, IR, NMR) with an authentic sample[6]. Radiochemical purity was checked by TLC (chloroform:benzene; 6:4; Rf 0.25, blue spot in uv light, blue spot with alcoholic ferric chloride spray).

7-Methoxy-2,2-dimethyl-4-chromanone-(2-gem-dimethyl-T), (3a): Compound 2a (90 mg, 1.02 mCi/mmol) was heated under reflux with a mixture of methanol (20 ml) and concentrated hydrochloric acid (3 ml). After 2.5 hr, methanol was removed in vacuo and the residue poured into crushed ice (20 g). 3a crystallised out and was separated by filtration. A small quantity of 3a was recovered from the filtrate by extraction with ether. 3a was purified by repeated crystallisations from ether-petroleum ether (2:1) mixture to constant specific activity. Mp, 78°; yield, 70 mg (85%); specific activity 1.00 mCi/mmol. 3a was identical (mp, TLC, IR, NMR) with an authentic sample[6].

7-Methoxy-2,2-dimethylchroman-4-ol (2-gem-dimethyl-T) (4a):

Chromanone 3a (100 mg, 1.00 mCi/mmol) in dry ether was added to a stirred suspension of lithium aluminium hydride (200 mg) in dry ether (40 ml). The mixture was refluxed for 3.5 hr, cooled to 0° and the excess of the reagent destroyed using saturated sodium sulfate solution. After usual work up, 4a was obtained as a viscous liquid (100 mg, specific activity 1.0 mCi/mmol). 4a appeared as a crimson spot on TLC (chloroform, Rf 0.3, 25% aq. sulphuric acid spray, 100°, 1 min). It was identical (IR, NMR, TLC) with an authentic sample of 7-methoxy-2,2-dimethylchroman-4-ol[6]. The product was used as such for the next step.

7-Methoxy-2,2-dimethylchromene-(2-gem dimethyl-T) (Precocene I-T) (5a):

Compound 4a (100 mg, 1.0 mCi/mmol) was dissolved in dry benzene (10 ml) and a crystal of p-toluenesulfonic acid was added and heated to reflux. The progress of the reaction was monitored by TLC (benzene). The reaction was complete in 5 min. Precocene I (5a) was purified by preparative thin layer chromatography (benzene). Yield, 73 mg (79%); specific activity, 1.04 mCi/mmol. Precocene I-(T) was chemically identical to an authentic sample[6] in all respects. On TLC analysis (benzene:chloroform, 9:1; Rf 0.65, 25% aq.

sulfuric acid, 100°, 1 min) precocene I appeared as a crimson spot.

6,7-Dimethoxy-2,2-dimethylchromene-(2-gem dimethyl-T) (Precocene II-T) (5b):

5b was synthesised starting with 4,5-dimethoxy-2-hydroxyacetophenone (1b) and acetone-T (1.04 mCi/mmol) and following the above sequence of reactions. The yields and specific activities of the compounds are:

2b	74%	0.87 mCi/mmol	3b	81%	0.82 mCi/mmol
4b	100%	-	5b	72%	0.83 mCi/mmol

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7. All the glasswares was flame dried. THF was freshly distilled over LAH. Reactions were carried out in a dry argon atmosphere. Solution transfers were carried out by syringe via septum caps.

8. Prepared by the base (potassium hydroxide) catalysed exchange between tritiated water and acetone at 20° for 16 hr.