Tetrahedron Letters,Vol.26,No.38,pp 4677-4680,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

THE SYNTHESIS OF CYCLOPROPYL ANALOGUES OF PRECOCENE I

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Abstract A new, short synthesis of precocene I is described together with the syntheses of two cyclopropyl analogues. One of these compounds showed interesting biological activity against the bean aphid, Aphis fabae.

Precocenes I and II (1a and 1b) were first isolated from the common bedding plant Ageratum Houstonianum in 1976,[1] and were shown to interfere with the production of juvenile hormones 2(a)-(d) in certain insects. The metabolic fate of the precocenes has been extensively investigated,[2] and in addition a number of analogues have been prepared.[3] Most of the available evidence seems to suggest that the 3,4-double bond is oxidised within the corpora allata (the gland in which juvenile hormone is produced) of sensitive insects, to produce an epoxide (3a or 3b) which may then form covalent links with macromolecules within the organ. The enzymes involved are probably the same epoxidases which catalyse the last step in juvenile hormone production, and the precocenes may thus be lethal substrates for these enzymes. In those insects where the precocenes have little effect, this may be due to rapid hydrolysis of the epoxides yielding 3,4-diols (4a or 4b), which are biologically inactive.

We wished to prepare various analogues of the precocenes, in order to establish structure-activity relationships, and we record here our initial efforts. 7-Hydroxycoumarin (5) (R=H) was converted into its methyl ether (5) ($R=CH_3$) and was then treated with excess of methyl magnesium iodide to produce diol (6). This was not isolated or purified, but was immediately dehydrated to yield precocene I (1a). This provides a novel and inexpensive route to the compound, and typical experimental details are given below.

The cyclopropyl analogue (7) was prepared by addition of dichlorocarbene generated in a two phase system ($CHCl_3$, aqueous NaOH, benzyltriethylammonium chloride) m.pt. 90-92°, $\delta(CDCl_3)$ 1.7 and 1.25 (2s, 6H, CH_3),

2.1 (d, 1H, J 11Hz, 3-H), 3.81 (d, 1H, J 11Hz, 4-H), 3.75 (s, 3H, OCH_3), 6.36-7.27 (m, 3H, aromatic H); $C_{13}H_{14}{}^{35}Cl_2O_2$ requires M^+ 272.0368, found 272.0370].

The adduct (7) was reduced to yield the cyclopropyl analogue (8) (Sodium and t-BuOH in THF) [oil; $\delta(CDCl_3)$ 0.85 (m, 2H, cyclopropyl H), 1.2 and 1.5 (2s, 6H, CH_3), 1.5 (m, 1H, 3-H), 1.9 (m, 1H, 4-H), 3.75 (s, 3H, OCH_3), 6.2-7.3 (m, 3H, aromatic H); $C_{13}H_{16}O_2$ requires M^+ 204.115, found 204.118]. Various attempts to prepare the corresponding difluorocyclopropyl analogue using a variety of difluorocarbene precursors, failed to produce the desired compound.

Compounds (7) and (8) were tested for biological activity by ICI Plant Protection Ltd. Compound (7) produced a 90-100% kill when tested against the bean aphid, Aphis fabae (at 125 p.p.m.), but neither compound had other insecticidal, fungicidal, herbicidal or anti-JH activity.

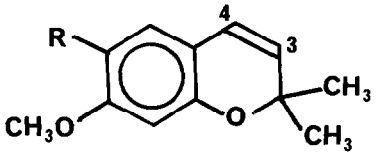
Experimental

7-Methoxycoumarin (5) (R=CH_3)

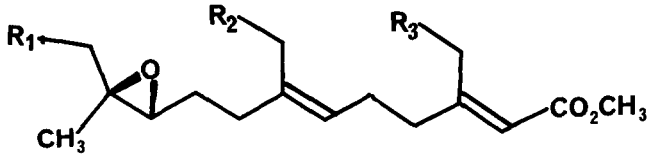
7-Hydroxycoumarin (12g; 74mM) and anhydrous potassium carbonate (47g) were stirred for 4 hours in refluxing acetone (500 ml) containing iodomethane (24 ml; ca. 55 g; ca. 4-fold excess). The reaction mixture was then cooled, filtered, and concentrated to yield a pinkish solid which was recrystallised from toluene. Yield: 9.36 g; 72%; m.p. 119-20°C; $\delta_{(CDCl_3)}$ 3.9 (s,3H, OCH_3); 6.25 (d, 1H, J 9 Hz, 3-H); 6.8-7.5 (m, 3H, aromatic H); 7.65 (d, 1H, J 9 Hz, 4-H).

7-Methoxy-2,2-dimethyl chromene (Precocene I) (1a)

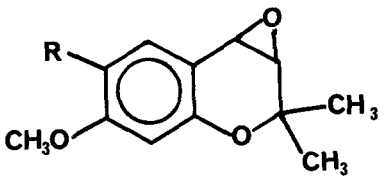
To magnesium turnings (1.2g, ca. 50 mM) in anhydrous diethyl ether (20 ml) was added a solution of iodomethane (3 ml, 6.8g, 48 mM) in diethyl ether (10 ml), and the mixture was stirred for 30 minutes at 25°, and refluxed for 10 minutes to complete formation of methyl-magnesium iodide. A solution of 7-methoxycoumarin (3.52g, 20 mM) in THF (30 ml) was then added dropwise with stirring to the Grignard reagent at room temperature. After one hour, the reaction mixture was refluxed for 2½ hours, and then poured into a saturated solution of ammonium chloride (100 ml). This was then extracted with ethyl acetate (3 x 50 ml), and the combined organic extract was washed with water (2 x 25 ml), then dried, and concentrated to yield a dark-brown oil. This was dissolved in benzene (100 ml) and the mixture refluxed in a Dean and Stark apparatus to effect dehydration. When this was judged to be completed (TLC analysis - silica gel with ethyl acetate: petrol 1:1 R_F of 1a = 0.69), the solution was concentrated and the product purified by column chromatography (silica gel with ethyl acetate:petrol 1:2) to yield 2.47g of 1a (64% yield) as a colourless oil.
$\delta(CDCl_3)$ 1.4 (s, 6H, CH_3) 3.70 (s, 3H, OCH_3), 5.42 (d, 1H, J10Hz,3-H), 6.25 (d, 1H, J10Hz,4-H), 6.2-7.5 (m, 3H, aromatic H).



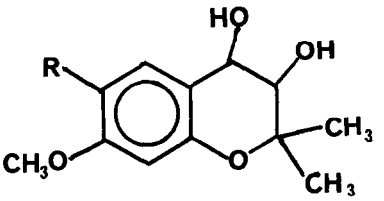
1a R=H
1b R=OCH_3



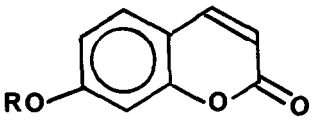
2(a-d) JH_o $R_1=R_2=R_3=CH_3$; JH_1 $R_1=R_2=CH_3$, $R_3=H$;
JH_2 $R_1=CH_3$, $R_2=R_3=H$; JH_3 $R_1=R_2=R_3=H$



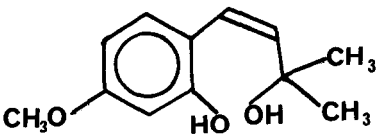
3a,b



4a,b



5 R=H or CH_3



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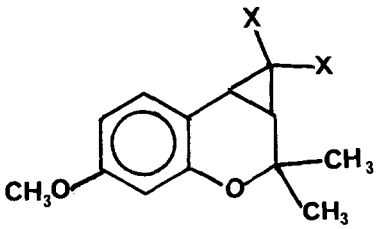

7 X=Cl
8 X=H

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ACKNOWLEDGEMENT

P.D.K. thanks the S.E.R.C. for a postgraduate studentship.

(Received in UK 18 July 1985)