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FLUORINATED CHROMENES[1]: 2,2,2-TRIFLUOROETHOXY PRECOCENE ANALOGS AND THEIR CORRESPONDING 3,4-EPOXIDES

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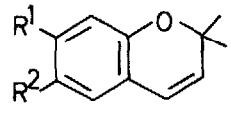
Summary: Preparation of potential insect antijuvenile hormone agents 2,2-dimethyl-7-(2,2,2-trifluoroethoxy)-2H-chromene (3a), 6-methoxy-2,2-dimethyl-7-(2,2,2-trifluoroethoxy)-2H-chromene (3b) and 7-methoxy-2,2-dimethyl-6-(2,2,2-trifluoroethoxy)-2H-chromene (3c) and the corresponding 3,4-epoxides 5a and 5b is reported.

The latest results reported in the literature on the mode of action of precocenes (1)[2,3], the naturally occurring insect antijuvenile hormones[4], strongly indicate the conversion of these compounds into the corresponding 3,4-epoxides via a bioactivation metabolism. These epoxides are selective cytotoxic agents which destroy the insect corpus allatum preventing juvenile hormone production by this gland. Although preparation of epoxides of both precocene I[5] and precocene II[3] has recently been accomplished, the high chemical unstability of these compounds render them unsuitable for biological assays.



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Precocene I : $R^1 = OCH_3$; $R^2 = H$
Precocene II: $R^1 = R^2 = OCH_3$

On the other hand, metabolic studies carried out in vitro with fat body homogenates of cabbage looper (Trichoplusia ni, Hübner) larvae[3], an insensitive insect to the action of precocenes, have also shown the importance of O-demethylation, particularly at C-6, as one of the primary detoxification pathways of precocene II.

Furthermore, among the precocene analogs so far synthesized, 7-ethoxy-6-methoxy-2,2-dimethyl-2H-chromene has exhibited a significant increase of precocenic activity on insect sensitive species relative to that displayed by the naturally occurring compounds[6].

Consequently, we anticipated that with the preparation of 6- or 7-(2,2,2-trifluoroethoxy) precocene analogs 3a-3c and the corresponding 3,4-epoxides 5a and 5b the following goals could be accomplished:
(i) prevent the metabolic cleavage of aromatic alkoxy groups at C-6 (3c);
(ii) modify the behaviour of the 3,4-double bond towards either metabolic deactivation before reaching the corpus allatum or activation at this gland (3a,3b);
(iii) enhance the stability of the 3,4-epoxides through the electron withdrawing influence of the fluorinated substituents at C-7 (5a,5b).

Reduction of the corresponding (2,2,2-trifluoroethoxy)-4-chromanones 2[7] (2-6 mmol) with 100% equivalent excess of LAH in dry ether (1h; r.t.) afforded the 4-chromanols which were dehydrated in situ with 6N HCl (1.5h; r.t.). After usual work-up of the crude reaction mixtures, pure chromenes 3[8] were isolated in good overall yields by bulb to bulb distillation (Table).

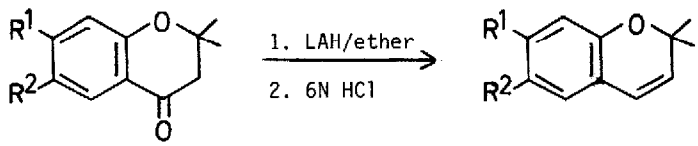

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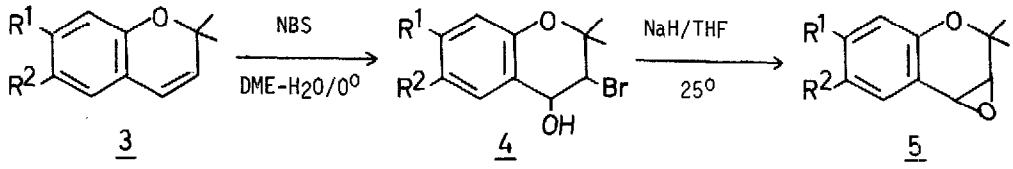
Table

	R^1	R^2	m.p. or b.p. (^{o}/torr)[a]	yield	^{1}H-NMR/60MHz (CCl_4) δ,ppm	^{19}F-NMR/56.4MHz[b] (CCl_4) δ,ppm
3a	CF_3CH_2O	H	36-8^o	84	4.25(q,2H,J=8Hz) 5.41(d,1H,J=10Hz) 6.19(d,1H,J=10Hz)	5.00(t,J=8Hz)
3b	CF_3CH_2O	CH_3O	128-32/0.25	80	4.20(q,2H,J=8Hz) 5.38(d,1H,J=10Hz) 6.13(d,1H,J=10Hz)	4.53(t,J=8Hz)
3c	CH_3O	CF_3CH_2O	125-9/0.2	93	4.31(q,2H,J=8Hz) 5.56(d,1H,J=10Hz) 6.20(d,1H,J=10Hz)	4.68(t,J=8Hz)

[a] m.p. determined on a Kofler hot stage apparatus are uncorrected; b.p. measured in bulb to bulb distillation.

[b] CF_3COOH used as external reference.

Epoxides 5a and 5b were prepared using the procedure developed for the synthesis of precocene II epoxide[3].



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(3a: R^1= CF_3CH_2O; R^2= H)

(3b: R^1= CF_3CH_2O; R^2= OCH_3)

Thus, dropwise addition of a soln. of NBS (0.356 g, 2 mmol) in DME (10 ml) to a stirred soln. of 3a (0.516 g, 2 mmol) in DME-H_2O (20:8 ml) at 0° resulted in the rapid attack of starting chromene[9]. After removal of DME in vacuo, the residue was extracted with ether and the joined organic fractions were washed with 2N HCl, $NaHCO_3$ saturated soln., brine and dried ($MgSO_4$) yielding the crude bromohydrin 4a { IR (CCl_4):$\bar{\nu}$, 3580 cm^{-1}. ^{1}H-NMR ($CDCl_3$):δ, 3.99 (d,1H,J=10Hz,>CHBr); 4.82(d,1H,J=10Hz,>CHOH) ppm. ^{19}F-NMR ($CDCl_3$,CF_3COOH ext. ref.): 4.98 ppm (t, J=8Hz)}. A soln. of crude 4a in THF (10 ml) was added dropwise under N_2 to a stirred suspension of NaH (3 mmol) in THF (20 ml) at 25°. A vigorous reaction took place which was completed after 30 min . The insoluble salts were filtered off and solvent removal under vacuo led to a residue which was carefully bulb to bulb distilled to afford 0.425 g (77% overall yield) of epoxide 5a[8] which crystallized on standing (m.p. 62-4°) { m/e 274 (M^+); IR (CCl_4):$\bar{\nu}$,1620, 1505 and 1165 cm^{-1}. ^{1}H-NMR (CCl_4) δ, 1.20 (s,3H); 1.48(s,3H); 3.17(d,1H,J=4Hz); 3.67(d,1H,J=4Hz); 4.22(q,2H,J=8Hz); 6.25-6.55(2H); 7.12 (d,1H,J=9Hz) ppm. ^{19}F-NMR(CCl_4,CF_3COOH ext. ref.): 5.00 ppm (t, J=8Hz)}.

In a similar manner, chromene 3b (3 mmol) gave bromohydrin 4b (m.p. 112-4°) { IR (CCl_4): $\bar{\nu}$, 3580 cm^{-1}. ^{1}H-NMR($CDCl_3$): δ, 4.06 (d,1H,J=10Hz, >CHBr); 4.82 (d,1H,J=10Hz,>CHOH)ppm. ^{19}F-NMR ($CDCl_3$, CF_3COOH ext. ref.): 4.95 ppm. (t,J=8Hz)}, which was dehydrobrominated to afford 5b[8] in 66% overall yield after bulb to bulb purification (155-60°/0.15 torr) { m/e 304 (M^+); IR (CCl_4): $\bar{\nu}$, 1620, 1505 and 1170 cm^{-1}. ^{1}H-NMR(CCl_4) δ, 1.18(s,3H); 1.47(s,3H); 3.24 (d,1H,J=4Hz); 3.63 (d,1H,J=4Hz); 3.75(s,3H); 4.27(q,2H,J=8Hz); 6.37(s,1H); 6.78 (s,1H) ppm. ^{19}F-NMR (CCl_4,CF_3COOH ext. ref.): 4.74 ppm (t,J=8Hz)}.

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References and notes

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7.- Obtained according to a general method for the preparation of aryl 2,2,2-trifluoroethyl ethers developed in this laboratory (F. Camps, J. Coll, A. Messeguer and M. A. Pericás, submitted for publication).

8.- All compounds gave satisfactory microanalyses.

9.- The course of the two step sequence was easily followed by GLC using a glass column packed with 3% OV-101 on silanized Chromosorb W.

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