Synthesis of Precocene 1 Epoxide (2,2-Dimethyl-3,4-epoxy-7-methoxy-2*H*-1-benzopyran)

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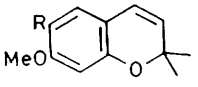
Summary The synthesis of the title compound, a possible reactive intermediate responsible for the biological activity of precocene 1, is described.

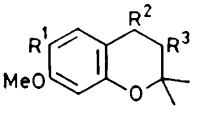
THE naturally occurring chromenes precocene 1 (**1**) and 2 (**2**)[1] when applied to the early larval instars of certain insect species cause them to moult precociously to prothetelic[2] adults. The compounds appear to act by terminating the production of juvenile hormones (JH) by selectively



(**1**) R=H
(**2**) R=OMe

destroying the *corpora allata* (c.a.), the glands where the JH are made.[3] The reports[4,5] that the diol (**4**) is a metabolite of (**2**) in some insect species coupled with the fact that carcinogenic polycyclic aromatic hydrocarbons and other toxins such as bromobenzene are activated biologically by epoxidation[6] suggested that the epoxides (**5**) and (**6**) might be the species responsible for the activity of (**1**) and (**2**) perhaps being produced by a lethal synthesis in the c.a. themselves.[7] We now describe the synthesis of (**5**) and find that its reactivity is in accord with this hypothesis.

The synthesis of (**5**) has been attempted previously[8] and the synthesis of (**6**) by the epoxidation of (**2**) with *m*-chloro peroxybenzoic acid (*m*-CPBA) has been claimed[4] but disputed subsequently.[9] Treatment of (**1**) with *m*-CPBA even under buffered conditions[10] gave only a mixture (1 : 1) of the *cis* and *trans* isomers of the ester† (**7**). Exposure of (**1**) to t-butyl hydroperoxide in the presence of $VO(acac)_2$ (acacH = pentane-2,4-dione) gave only recovered starting material but in the presence of $Mo(CO)_6$[11] the peroxide (**8**) was formed. Reaction of (**1**) with *N*-bromosuccinimide in aqueous tetrahydrofuran (THF) gave the bromohydrin (**9**).



(**3**) R^1=H, R^2=R^3=OH
(**4**) R^1=OMe, R^2=R^3=OH
(**5**) R^1=H, R^2R^3=O
(**6**) R^1=OMe, R^2R^3=O
(**7**) R^1=H, R^2=*m*-$ClC_6H_4CO_2$, R^3=OH
(**8**) R^1=H, R^2=Bu^tOO, R^3=OH
(**9**) R^1=H, R^2=OH, R^3=Br
(**10**) R^1=H, R^2=OMe, R^3=OH

This, on treatment with anhydrous K_2CO_3 in methanol,[12] gave (**10**). These results all suggest that a reactive epoxide is being formed which is trapped by any nucleophile present.[13] The bromohydrin (**9**) was treated therefore with

† All new compounds were characterised by the appropriate physical methods.

sodium hydride (4 equiv.) in THF (ambient temperature, 45 min). Filtration and evaporation gave the desired epoxide‡ (**5**) (88%) which could be purified only by crystallisation [hexane–ethyl acetate; m.p. 45—46 °C; ν_{max} (film) 1620, 1510, 1450, 1200, 1160, 1135, 1100, and 1035 cm^{-1}; δ (100 MHz, $CDCl_3$) 1·25 and 1·57 (6H, 2 s, 2,2-Me_2), 3·42 (1H, d, J 4·5 Hz, 3H), 3·74 (3H, s, OMe), 3·85 (1H, d, J 4·5 Hz, 4-H), 6·25—6·5 (2H, m, 6- and 8-H), and 7·15 (1H, d, J 8 Hz, 5-H)].

The compound does not survive chromatography on silica or alumina or g.l.c. under conditions[14] which permit the analysis of other sensitive epoxides. The epoxide ring is opened readily by nucleophiles, even water (pH 7·2, 20 °C, < 1 min) being sufficient to convert (**5**) into a mixture (1 : 1·7) of the *cis*- and *trans*-diols (**3**), respectively. This behaviour is reminiscent of that of the carcinogen *r*-7,*t*-8-dihydroxy-*t*-9,10-epoxy-7,8,9,10-tetrahydrobenzo-[*a*]pyrene[15] and related compounds and reinforces our hypothesis concerning the mode of action of (**1**) and (**2**).

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[1] W. S. Bowers, T. Ohta, J. S. Cleere, and P. A. Marsella, *Science*, 1976, **193**, 542.
[2] V. B. Wigglesworth, 'The Principles of Insect Physiology,' Methuen, London, 2nd edn., 1965, p. 73.
[3] G. E. Pratt and W. S. Bowers, *Nature*, 1977, **265**, 548; M. P. Pener, L. Orshan, and J. de Wilde, *ibid.*, 1978, **272**, 350; G. C. Unnithan, K. K. Nair, and W. S. Bowers, *J. Insect Physiol.*, 1977, **23**, 1081; H. Schooneveld, *Experientia*, 1979, **35**, 363.
[4] T. Ohta, R. J. Kuhr, and W. S. Bowers, *J. Agric. Food Chem.*, 1977, **25**, 478.
[5] M. E. Burt, R. J. Kuhr, and W. S. Bowers, *Pesticide Biochem. Physiol.*, 1978, **9**, 300.
[6] P. B. Hulbert, *Nature*, 1975, **256**, 146.
[7] G. T. Brooks, G. E. Pratt, and R. C. Jennings, *Nature*, in the press.
[8] J. D. Hepworth and R. Livingstone, *J. Chem. Soc.* (*C.*), 1966, 2013.
[9] B. J. Bergot, K. J. Judy, D. A. Schooley, and L. Tsai, *Pesticide Biochem. Physiol.*, submitted for publication.
[10] W. K. Anderson and T. Veysoglu, *J. Org. Chem.*, 1973, **38**, 2267; M. Imuta and H. Ziffer, *J. Org. Chem.*, 1979, **44**, 1351.
[11] K. B. Sharpless and R. C. Michaelson, *J. Amer. Chem. Soc.*, 1973, **95**, 6136.
[12] C. A. Henrick, F. Schaub, and J. B. Siddall, *J. Amer. Chem. Soc.*, 1972, **94**, 5374.
[13] H. S. Ryang and S. Y. Wang, *J. Org. Chem.*, 1979, **44**, 1191.
[14] A. F. Hamnett and G. E. Pratt, *J. Chromatogr.*, 1978, **158**, 387.
[15] S. K. Yang, D. W. McCourt, and H. V. Gelboin, *J. Amer. Chem. Soc.*, 1977, **99**, 5130.