Flavonoid Epoxides. Part 17.[1] Stereospecific Synthesis and Acid-catalysed Rearrangement of Aurone Epoxides

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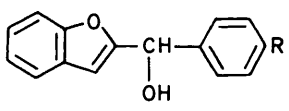
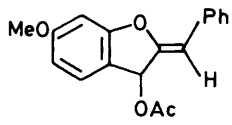
The configurations of 6-methoxyaurone epoxides were determined by direct epoxidation of the parent aurones (1) and (2) by *m*-chloroperbenzoic acid. *trans*-6-Methoxyaurone epoxide (3) was also synthesised indirectly through the intermediacy of the reduced ketone derivatives (4) and (5) of aurone (1) and aurone epoxide (3). *m*-Chloroperbenzoic acid was found to be complementary to alkaline hydrogen peroxide as an epoxidation agent for various aurones. Coumarins (10) were obtained on acid-catalysed rearrangement of aurone epoxides (8). The chlorohydrin derivative (11) of aurone epoxide (3), on treatment with alkali, gave the corresponding flavonol (12). Reduced aurone epoxide (5) gave aurone (1) on treatment with hydrochloric acid.

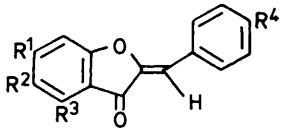
Both *trans*- (1) and *cis*-6-methoxyaurones (2) [2,†] on treatment



(6)
a ; R = H
b ; R = OMe



(9)



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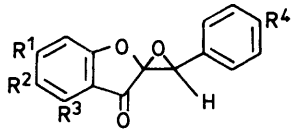
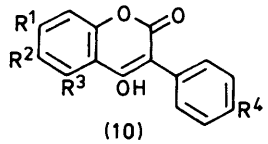
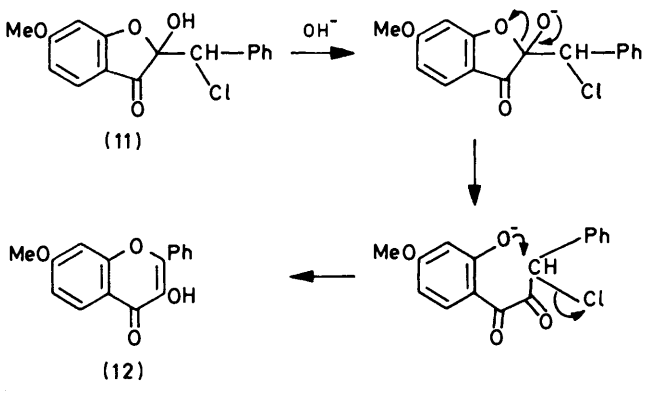


(8)



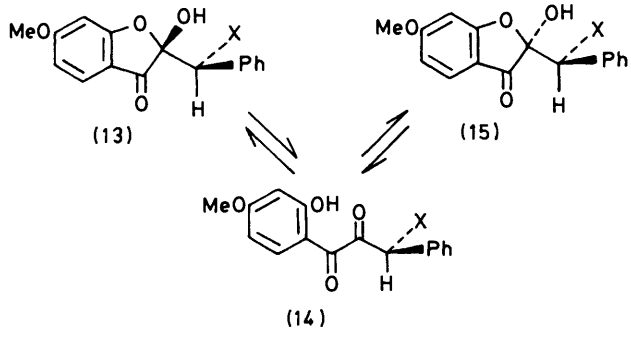
(10)

a ; $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
b ; $R^1 = R^3 = H$, $R^2 = Me$, $R^4 = OMe$
c ; $R^1 = R^3 = H$, $R^1 = R^4 = OMe$
d ; $R^2 = R^4 = H$, $R^1 = R^3 = OMe$
e ; $R^2 = R^3 = H$, $R^1 = OMe$, -naphthyl in place of $C_6H_5R^4$
f ; $R^2 = R^3 = R^4 = H$, $R^1 = OMe$



(11) (12)

Scheme 2.



(13) (14) (15)

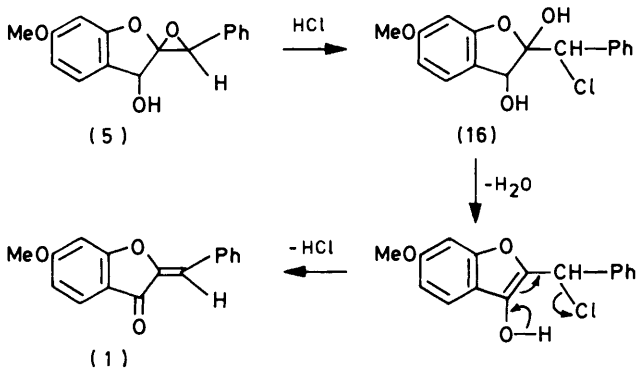
Scheme 3.

boron trifluoride–diethyl ether or of concentrated sulphuric acid into the corresponding 4-hydroxy-3-arylcoumarins was reported earlier.[10] In the present work, aurone epoxides (8d) and (8e) were also found to rearrange on reaction with boron trifluoride–diethyl ether to give coumarins (10d) and (10e), respectively, in near quantitative yields. In addition coumarins (10a), (10b), and (10c) were obtained from the crude products of peracid epoxidation of aurones (7a), (7b), and (7c), respectively. The yields of epoxides obtained in these latter epoxidation reactions were estimated from the amounts of coumarins obtained.

Early in the work reported here, an attempt was made to form isomeric chlorohydrin derivatives of 6-methoxyaurone epoxide as a possible approach to the synthesis of the isomeric *cis*-6-methoxyaurone. With certain epoxides the stereochemistry of epoxide ring opening by hydrochloric acid can be controlled by the choice of solvent.[6] For example, *trans*-3-benzylidenechromanone epoxides, on treatment with hydrogen chloride in ethanol, yielded the corresponding *erythro*-chlorohydrins, whereas with hydrogen chloride in benzene the *threo*-chlorohydrins were obtained.[11] The *erythro*-chlorohydrins on cyclisation with base gave the original *trans*-epoxides, while the *threo*-chlorohydrins under the same conditions gave the corresponding *cis*-isomers.

In the present work, however, only one chlorohydrin was isolated from the reaction of epoxide (3) with hydrochloric acid in ether, ethanol, or benzene. In each of these reactions the solvent was saturated with dry hydrochloric acid before the addition of the epoxide. When hydrogen chloride was added to a solution of epoxide (3) in diethyl ether to saturation point the product was 4-hydroxy-7-methoxy-3-phenylcoumarin (10f). This compound was previously obtained by the rearrangement of the same epoxide by means of boron trifluoride–diethyl ether or of sulphuric acid.[10] That the chlorohydrin (11) (Scheme 2) had the α-hydroxy-β-chloro rather than the α-chloro-β-hydroxy structure was shown when it did not liberate iodine from an acidified potassium iodide solution as would be expected from an α-halogenoketone,[12] and by the n.m.r. evidence of ring-chain tautomerism it exhibited (see below). Instead of the regeneration of epoxide (3) by ring closure of chlorohydrin (11) by base a rearrangement occurred with the formation of 7-methoxyflavonol (12) in high yield. The suggested mechanism for this reaction is outlined in Scheme 2.

The n.m.r. spectrum of chlorohydrin (11), freshly prepared in deuteriochloroform, showed methoxy and methine signals at δ 3.92 and 5.19, respectively. When the spectrum was taken again after 60 h it showed two methoxy (δ 38.4 and 3.92) and two methine (δ 5.19 and 5.36) signals of approximately equal intensity in each case. The solvolysis products of aurone epoxide (3) give similar n.m.r. results and are attributed to equilibration, through an intermediate α-diketone (14), between the *erythro*- (13) and *threo*- (15) derivatives in each case (Scheme 3).[13] Only a trace of the open-chain diketone tautomer (14) could be detected in some cases. The compounds, including chlorohydrin (11) and (13; X = Cl), crystallised in one isomeric form only. It is possible that *erythro*- and *threo*-isomers of chlorohydrin (11) were initially formed on reaction



Scheme 4.

of epoxide (3) with hydrochloric acid in ethanol or in benzene solutions, respectively, but that on crystallisation of the products, equilibration occurred in solution and subsequently crystals of only one isomeric form were produced.

In attempts to prepare the chlorohydrin derivative (16) of epoxide (5) by its reaction with hydrogen chloride in diethyl ether or in ethanol, 6-methoxyaurone (1) only was obtained. A possible pathway for this reaction is outlined in Scheme 4.

Experimental

Reduction of Aurone (1).—Sodium borohydride (0.4 g) was added slowly to a solution of aurone (1) (1 g) in methanol (100 ml) at room temperature and kept at this temperature for 2 h. The mixture was diluted with water and the precipitate was collected and crystallised from benzene–light petroleum to give white crystals of (Z)-2-*benzylidene*-6-*methoxy*-2,3-*dihydrobenzo*[b]*furan*-3-*ol* (4) (0.85 g), m.p. 128—129 °C (Found: C, 75.7; H, 5.5. $C_{16}H_{14}O_3$ requires C, 75.6; H, 5.5%); $\nu_{max.}$ 3 333 (OH) and 1 678 cm^{-1} (olefin); δ ($CDCl_3$) 7.86—7.63 (2 H, m, 2′ and 6′-H), 7.52—7.20 (4 H, m, 3-′, 4′-, 5′-, and 4-H), 6.73—6.50 (2 H, m, 5- and 7-H), 5.97 (1 H, br s, α-H), 5.67 (1 H, br d, *J* 9 Hz, 3-H; br s on addition of D_2O), 3.80 (3 H, s, OMe), and 2.40 (1 H, br d, *J* 9 Hz, OH; D_2O exch.).

Reduction of Aurones (2) *and* (7b).—Aurone (2) was similarly reduced to give colourless needles of (*Z*)-2-benzylidene-6-methoxy-2,3-dihydrobenzo[*b*]furan-3-ol (60%), m.p. 118—119 °C (Found: C, 75.3; H, 5.8. $C_{16}H_{14}O_3$ requires C, 75.57; H, 5.55%); $\nu_{max.}$ 3 367 cm^{-1}.

Aurone (7b) [14] was similarly reduced, but in dioxan–methanol (2 : 1) at 50 °C for 2 h, to give (*Z*)-2-(4-methoxybenzylidine)-5-methyl-2,3-dihydrobenzo[*b*]furan-3-ol (70%), m.p. 104—106 °C (Found: C, 76.4; H, 6.15. $C_{17}H_{16}O_3$ requires C, 76.10; H, 6.01%), $\nu_{max.}$ 3 330 cm^{-1}.

Epoxidation of Benzofuran-3-ol (4).—*m*-Chloroperbenzoic acid (1 g) in methylene dichloride (25 ml) was added to a well-stirred solution of benzofuran-3-ol (4) (1 g) in methylene dichloride (25 ml) at 0 °C during 20 min, and the mixture was stirred at this temperature for a further 20 min. It was then washed successively with 10% aqueous sodium sulphite, 10% aqueous sodium hydrogen carbonate, saturated aqueous sodium chloride, and water. The solid obtained on removal of the solvent from the dried methylene dichloride solution was washed with a small quantity of dry diethyl ether and then dissolved in acetone. Dropwise addition of water precipitated small white needles of (*Z*)-2-benzylidene-6-methoxy-2,3-dihydrobenzo[*b*]furan-3-ol epoxide (5) * (0.41 g), m.p. 115—116 °C (Found: C, 71.65; H, 5.4. $C_{16}H_{14}O_3$ requires C, 71.11; H, 5.19%), $\nu_{max.}$ 3 200 cm^{-1} (OH).

Reaction of Other Peracids with Benzofuran-3-ol (4).—(*a*) *Peracetic acid.* Benzofuran-3-ol (4) (3 g) was added to a solution of sodium acetate (0.05 g) and peracetic acid (15% in acetic acid; 3 ml) in chloroform and kept at room temperature overnight. The mixture was diluted with diethyl ether, washed with water and then with aqueous sodium thiosulphate. The oil obtained on removal of the dried solvent was dissolved in light petroleum (b.p. 60—80 °C) and left to evaporate slowly for one week. The solid which separated recrystallised from n-hexane in colourless needles (1.4 g) of 3-acetoxy-2-benzylidene-6-methoxy-2,3-dihydrobenzo[*b*]furan (9), m.p. 75—76 °C alone or when mixed with an authentic sample (see below).

(*b*) *Monoperphthalic acid.* Benzofuran-4-ol (4) (2.5 g) in diethyl ether (50 ml) was added to a solution of monoperphthalic acid (2 g) in ether (50 ml) and the mixture was kept at room temperature for 48 h. The solution was washed successively with water, sodium hydrogen carbonate, and water. The solid obtained on removal of the solvent from the dried solution crystallised from methanol in pale yellow plates of 6-methoxyaurone (1), m.p. and mixed m.p. 148—149 °C.

Preparation of Benzofuranyl Acetate (9).—A mixture of benzofuran-3-ol (4) (1 g), acetic anhydride (4 ml), and acetic acid (4 ml) was heated on a steam-bath for 3 min and then poured, with vigorous stirring, onto crushed ice (10 g). The solid which separated crystallised from n-hexane in colourless needles of 3-*acetoxy*-2-*benzylidene*-6-*methoxy*-2,3-*dihydrobenzo*[b]*furan* (9) (0.9 g, 77%), m.p. 75—76 °C (Found: C, 72.6; H, 5.3. $C_{18}H_{16}O_4$ requires C, 72.98; H, 5.4%), $\nu_{max.}$ (Nujol) 1 730 cm^{-1}. When the acetylation was carried out with acetic anhydride in pyridine at room temperature for 17 h a 17% yield of acetate (9) was obtained.

Oxidation of Benzofuranol Epoxide (5).—Epoxide (5) (0.1 g) was added to a freshly prepared suspension of manganese dioxide (1 g) in dry diethyl ether (10 ml). The mixture, which was warmed during the addition, was stirred at room temperature for 4 h and then filtered. The solid obtained on removal of the solvent crystallised from chloroform–ligroin to give colourless needles of (*Z*)-2-benzylidene-6-methoxybenzo[*b*]-furan-3(2*H*)-one epoxide (3) (0.06 g), m.p. 104 °C alone or when mixed with an authentic sample.† [1]

Epoxidation of trans-*Aurone* (1).—A mixture of *trans*-aurone [2a] (1) (1 g), *m*-chloroperbenzoic acid (1 g), and dry benzene (100 ml) was heated under reflux for 1 h. The cooled solution was washed successively with sodium thiosulphate (5%), sodium hydrogen carbonate (5%), and water, and was then dried (Drierite). Removal of the solvent yielded a pale yellow solid which crystallised from chloroform–ligroin in pale yellow plates of the starting *trans*-aurone (1) (0.4 g, 40%), m.p. and mixed m.p. 146—147 °C.

The mother-liquor, on standing at 0 °C, deposited a pale yellow crystalline compound. Recrystallisation from chloroform–ligroin afforded colourless plates of (*Z*)-2-benzylidene-6-methoxybenzo[*b*]furan-3(2*H*)-one epoxide (3) (0.4 g, 38%), m.p. and mixed m.p. 109 °C.†

* Systematic name: 3-hydroxy-6-methoxy-3′-phenylspiro[benzo-[*b*]furan-2(3*H*),2′-oxiran].

† This compound crystallises in two modifications; m.p. 103 °C and m.p. 110 °C.[1]

Epoxidation of cis-*Aurone* (2).—*cis*-Aurone [2a] (2) (1 g) was similarly epoxidised. Crystallisation of the product from light petroleum (b.p. 80—100 °C) afforded yellow needles of starting *cis*-aurone (0.3 g, 30%), m.p. and mixed m.p. 136—137 °C.

The mother-liquor, on standing, deposited colourless needles which, on recrystallisation from light petroleum (b.p. 40—60 °C) containing a trace of acetone, afforded colourless fluffy needles of (E)-2-*benzylidene*-6-*methoxybenzo*[b]*furan*-3(2H)-*one epoxide* (0.4 g, 39%), m.p. 120—121 °C, $\nu_{max.}$ (KBr) 1 718 cm^{-1}; δ 7.54 (1 H, d, *J* 8 Hz, 4-H), 7.44 (5 H, m, Ph), 4.75 (1 H, s, α-H), and 3.92 (3 H, s, OMe). Since the microanalytical figures deviated from the normal standards (Found: C, 70.8; H, 4.8. Calc. for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51%), the compound was further characterised by the formation of the derivative, 2-hydroxy-6-methoxy-2-(α-methoxybenzyl)benzo-[*b*]furan-3(2*H*)-one, prepared by the methanolysis of the oxiran ring; m.p. 134 °C alone or when mixed with an authentic sample.[13]

Coumarin (10d) via *Rearrangement of Epoxide* (8d).—Boron trifluoride-diethyl ether (0.2 ml) was added to a solution of aurone epoxide (8d) [1] (50 mg) in dry benzene (10 ml) at room temperature. After 10 min the solution was washed with water and extracted with aqueous sodium hydrogen carbonate (5%). Acidification of the alkaline extract gave a white precipitate which was collected and washed with water. Crystallisation of the solid from ethanol afforded colourless needles of 4-hydroxy-5,7-dimethoxy-3-phenylcoumarin (10d) (40 mg, 50%), m.p. 204—205 °C (lit.,[15] m.p. 204—205 °C).

Coumarin (10e) via *Rearrangement of Epoxide* (8e).—Aurone epoxide (8e) [1] (50 mg) was similarly rearranged to give colourless needles (ethanol) of 4-hydroxy-7-methoxy-3-(2-naphthyl)-coumarin (10e) (40 mg, 80%), m.p. 262 °C (decomp.) (Found: C, 75.2; H, 4.6. Calc. for $C_{20}H_{14}O_4$: C, 75.46; H, 4.43%).

Epoxidation of Aurones with m-*Chloroperbenzoic Acid followed by Boron Trifluoride–Diethyl Ether Rearrangement to give Coumarins.*—(*a*) *Coumarin* (10a). A mixture of aurone (7a) (1 g), *m*-chloroperbenzoic acid (1 g), and dry benzene (150 ml) was heated under reflux for 40 min. The cooled solution was washed successively with sodium thiosulphate (5%), sodium hydrogen carbonate (5%) and water, and then dried ($MgSO_4$).

The dried benzene solution was treated with boron trifluoride–diethyl ether (3 ml), and kept at room temperature for 30 min. The solution was washed with water and extracted with sodium hydrogen carbonate (5%). The solid obtained on acidification of the alkaline extract was washed with water and crystallised from ethanol to give colourless needles of 4-hydroxy-3-(4-methoxyphenyl)coumarin (10a) (0.22 g, 21%), m.p. 239—240 °C (lit.,[16] m.p. 228—229°) (Found: C, 71.95; H, 4.5. Calc. for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51%).

(*b*) *Coumarin* (10b). Aurone (7b) (1 g) was similarly epoxidised; the product rearranged and was worked up to give colourless needles of 4-hydroxy-6-methyl-3-(4-methoxyphenyl)coumarin (10b) (0.3 g, 29%), m.p. 213 °C (Found: C, 71.95; H, 5.25. Calc. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00%).

(*c*) *Coumarin* (10c). Aurone (7c) (1 g) was similarly epoxidised; the product rearranged and was worked up to give colourless needles of 4-hydroxy-7-methoxy-3-(4-methoxyphenyl)coumarin (10c) (0.37 g, 35%), m.p. 223—224 °C (lit.,[16] m.p. 213—214 °C) (Found: C, 68.35; H, 4.7. Calc. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73%).

(*d*) *Coumarin* (10e). Aurone (7e) (1 g) was similarly epoxidised; the product rearranged and was worked up to give colourless needles of 4-hydroxy-7-methoxy-3-(2-naphthyl)-coumarin (10e) (0.28 g, 27%), m.p. 262 °C (decomp.) alone, or when mixed with an authentic sample (see above).

2-(α-*Chlorobenzyl*)-2-*hydroxy*-6-*methoxybenzo*[b]*furan*-3(2H)-*one* (11).—Aurone epoxide (3) (0.1 g) was added to absolute ethanol (20 ml) which had been previously saturated with anhydrous hydrogen chloride at 0 °C. The mixture was kept at 0 °C for 2 h and the solvent removed. The solid residue crystallised from benzene–ligroin in colourless needles of 2-(α-*chlorobenzyl*)-2-*hydroxy*-6-*methoxybenzo*[b]*furan*-3(2H)-*one* (11) (0.097 g, 85%), m.p. 127—128 °C (Found: C, 63.4; H, 4.5; Cl, 12.1. $C_{16}H_{14}ClO_4$ requires C, 63.02; H, 4.33; Cl, 11.64%); $\nu_{max.}$ 3 275 cm^{-1}; δ (taken shortly after dissolution in $CDCl_3$) 7.72—7.50 (m, Ph and 4-H), 6.74—6.42 (m, 5- and 7-H), 5.19 (s, α-H), and 3.92 (s, OMe). Signals at δ 5.36 and 3.84, of *ca.* 20% the intensities of the signals at 5.19 and 3.92, respectively, in this spectrum, had *ca.* equal intensities with these when the spectrum was measured again after 60 h.

Two similar experiments were carried out in which the solvents, instead of ethanol, were diethyl ether and benzene, both of which were saturated with anhydrous hydrogen chloride before the addition of the epoxide. The yields of chlorohydrin (11) were 70 and 68%, respectively.

Coumarin (1f).—A solution of 6-methoxyaurone epoxide (3) (0.1 g) in dry diethyl ether (20 ml) was saturated with anhydrous hydrogen chloride at 0 °C and the solution was kept at this temperature for 1 h. The solution was then washed with water and the solvent was removed from the dried solution to give a semi-solid which crystallised from benzene in needles of 4-hydroxy-7-methoxy-3-phenylcoumarin (1f) (0.08 g, 80%), m.p. 198—200 °C alone or when mixed with an authentic sample.[10]

7-*Methoxyflavanol* (12).—Aqueous sodium hydroxide (10%; 25 ml) was added to a solution of chlorohydrin (11) (0.5 g) in acetone (25 ml). The mixture, which separated into two layers, was shaken for 15 min and the aqueous layer was removed. The solid obtained on concentration of the upper (aq. acetone) layer was treated with hydrochloric acid (10%), and after 15 min the solid was collected and recrystallised from ethanol to give pale yellow needles of 7-methoxyflavonol, m.p. 177—178 °C alone or when mixed with an authentic sample prepared by the method of Gowan *et al.*[17]

Reaction of Benzofuran-3-ol Epoxide (5) *with Hydrogen Chloride.*—(*a*) Hydrogen chloride gas was passed through a solution of epoxide (5) (0.1 g) in diethyl ether (20 ml) at room temperature until the solution was saturated. The solid obtained on removal of the solvent crystallised from ethanol in pale yellow plates (0.081 g, 87%) of 6-methoxyaurone (1), m.p. 146—147 °C alone or when mixed with an authentic sample.

(*b*) Epoxide (5) (0.2 g) was added to absolute ethanol (15 ml) which had been previously saturated with hydrogen chloride gas at 0 °C and the solution was kept at this temperature for 1 h. Work-up as in the previous experiment gave 6-methoxyaurone (0.15 g, 80%), m.p. and mixed m.p. 146—147 °C.

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Received 2nd September 1982; *Paper* 2/1514