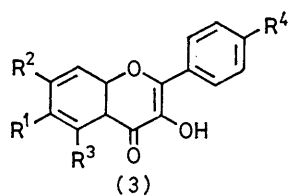
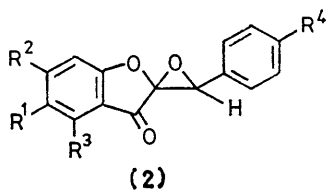
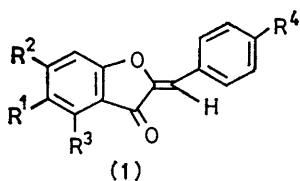


Flavonoid Epoxides. Part 16.¹ Synthesis and Base-catalysed Rearrangement of Aurone Epoxides

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A number of new aurone epoxides have been synthesised by an improved method of alkaline hydrogen peroxide epoxidation of aurones. Flavonols were the main products when the reaction period was prolonged. Aurone epoxides on reaction with base rearranged to flavonols and to aroylcoumaran-3-ones. Aurone epoxides may also be synthesised by the Darzens condensation.

THE oxidation of 2-arylmethylenecoumaran-3-ones (aurones) (1) by means of hydrogen peroxide in the presence of sodium or potassium hydroxide afforded aurone epoxides (2) and flavonols (3) but in relatively low



- | | |
|---|---|
| a; R ¹ = R ² = R ³ = R ⁴ = H | e; R ¹ = R ⁴ = H, R ² = R ³ = OMe |
| b; R ¹ = R ² = R ³ = H; R ⁴ = OMe | f; R ¹ = Me, R ⁴ = OMe, R ² = R ³ = H |
| c; R ¹ = Me, R ² = R ³ = R ⁴ = H | g; R ¹ = R ³ = H, R ² = R ⁴ = OMe |
| d; R ¹ = R ³ = R ⁴ = H, R ² = OMe | h; R ¹ = R ³ = H; R ² = OMe |
| | β-naphthyl in place
of C ₆ H ₄ -R ⁴ |

yields.² We wished to improve this method of synthesis of aurone epoxides, few of which have been described.² In the present work Triton B was found to be the base catalyst of choice for the reaction. The reaction times proved to be critical in determining optimum yields of aurone epoxides, because of the relative instability of these compounds in alkaline solution. Thus, for example, 6-methoxyaurone epoxide (2d), previously produced in 25% yield,² was obtained in yields of *ca.* 60% when 6-methoxyaurone (1d) was epoxidised at room temperature with hydrogen peroxide and Triton B

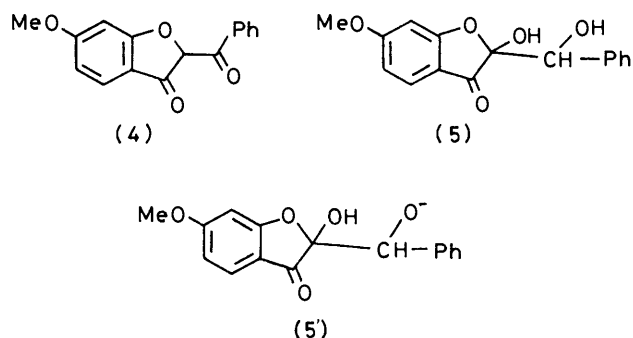
over a period of 40–60 min. The only major by-product from the reaction was 2-hydroxy-4-methoxybenzoic acid (20%); 10% of the starting aurone was recovered. When the duration of the reaction was extended from 1 h to 12 h, 7-methoxyflavonol (3d) was the main product (60%), and no epoxide was obtained.

Four new aurone epoxides, (2a), (2c), (2e), and (2h), were produced on treatment of the corresponding aurones for appropriate times with hydrogen peroxide and Triton B. Although no precise kinetic study of the reaction was carried out, it was observed that the substitution pattern of the aromatic rings of the aurone had a marked effect on the rate of epoxidation. Because epoxidation proceeds by nucleophilic addition of the hydroperoxide species to the olefin group³ of the aurone, the rate of epoxidation should be increased by electron-withdrawing, and decreased by electron-donating substituents on the aromatic nuclei. This was found to be the case. Thus unsubstituted aurone (1a) yielded *ca.* 60% aurone epoxide (2a) in 30–35 min, while a reaction period of 3 h was required to give a similar yield of 4,6-dimethoxyaurone epoxide (2e) from aurone (1e). In each case no more than a trace of the corresponding flavonol was produced under these optimum conditions. Aurones substituted in the 4'-position with a methoxy-group were found to be singularly unreactive towards this reagent, no epoxides being produced. Thus aurones (1b), (1g),² and (1f) were almost totally recovered after reaction periods of 1 h. *m*-Chloroperbenzoic acid successfully epoxidised these aurones and is thus complementary to alkaline hydrogen peroxide as an epoxidising reagent.⁴ When the alkaline hydrogen peroxide oxidations of the latter aurones were allowed to proceed for periods of 24 h the corresponding flavonols in yields of not more than 10% were obtained.

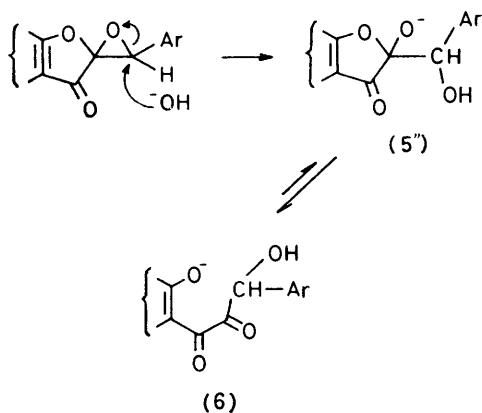
The contention that epoxides are intermediates in the formation of flavonols in the above reactions was supported when it was found that 6-methoxyaurone epoxide (2d) in benzene, on treatment with methanolic Triton B for 0.5 h, gave 7-methoxyflavonol (3d) in 50% yield. A 7% conversion of epoxide (2d) into flavonol (3d) was effected in acetone solution on reaction with 10% aqueous sodium hydroxide for 1 h at room temperature; 46% of the epoxide was recovered unchanged.

The mechanism for flavonol formation from aurone

epoxides has not been studied, though a number of possibilities have been considered. Nucleophiles displace the epoxide oxygen of $\alpha\beta$ -epoxyketones by attack either at the α -position or, more frequently, at the β -position.⁵ Thus, possible initial steps in a mechanism



(e.g. Scheme 1) for flavonol formation from aurone epoxides might involve hydroxide-ion attack at the β -position [or at the α -position to give anion (5')] followed by proton migration] to form glycol anion (5'') or its more stable ring-chain tautomer (6). However, this mechanism was not supported when it was found that

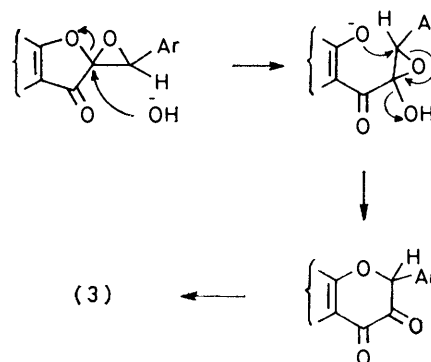


SCHEME 1

aurone glycol (5),⁶ which should readily afford phenoxide ion (6) from its open-chain tautomer, yielded only fission products on treatment with dilute alkali. The occurrence of ring-chain tautomerism in 2-benzyl-2-hydroxycoumaranones, which are alkali-soluble, has been observed by a number of workers.⁷ An alternative pathway which might be considered is outlined in Scheme 2. It involves initial attack at the α -carbon atom, but instead of decyclisation of the oxiran ring, with concomitant release of steric strain, to produce the unstable anion (5'), the furanone ring is decyclised to produce a resonance-stabilised acylphenoxide ion. However further work is required before the mechanism of this reaction can be established.

When aurone epoxide (2d) in aqueous methanol was allowed to react with dilute alkali at 50 °C over a period of 4 h, besides flavonol (3d), 2-benzoyl-6-methoxycoumaran-3-one (4) was formed in 30% yield. Coumar-

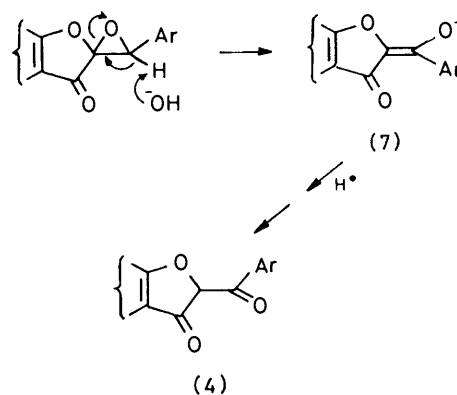
anone (4) was the main product (50%) when a benzene or dioxan solution of epoxide (2a) was treated with powdered sodium hydroxide. Base-catalysed rearrangements of $\alpha\beta$ -epoxyketones having an α -hydrogen generally give 1,2-diketones.⁸ However, Cromwell *et al.*⁹ found that 2-benzylidene-4,4-dimethyl-1-tetralone epoxide gave the corresponding 1,3-diketone derivative on reaction in benzene with sodium amide. A mechanism for the formation of β -diketone (4), analogous to that suggested by Cromwell *et al.*⁹ for the formation of the corresponding tetralone derivative, is outlined in Scheme



SCHEME 2

3. The formation of β -diketone (4) under such relatively mild conditions was unexpected and further study of the reaction is warranted.

The *trans*-configuration has been assigned to aurone epoxides (2) produced by alkaline hydrogen peroxide epoxidation.⁴ Both *cis*- and *trans*-6-methoxyaurones gave stereoselectively the same *trans*-aurone epoxide on alkaline hydrogen peroxide epoxidation. In the reaction with *cis*-6-methoxyaurone, from which was obtained a 24% yield of the *trans*-aurone epoxide (2d) and 35% of the starting *cis*-aurone, there was no evidence for the

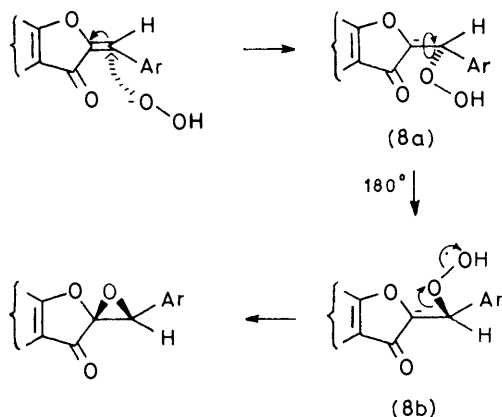


SCHEME 3

presence of *cis*-6-methoxyaurone epoxide. The mechanism suggested for the production of the *trans*-epoxide, analogous to that suggested by Zimmerman *et al.*¹⁰ for similar reactions, is outlined in Scheme 4. There was also no evidence in the product of the *trans*-aurone (1d) which

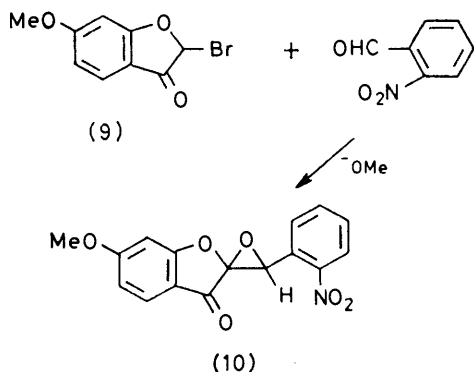
may indicate that no equilibration took place prior to epoxidation, but it does not rule out the possibility that at least some of the *cis*-aurone isomerised but that the rate of epoxidation of the resulting *trans*-isomer was more rapid than the equilibration rate.

That the epoxide formed on alkaline hydrogen peroxide epoxidation of both *cis*- and *trans*-aurones had the *trans*-configuration might have been predicted from



SCHEME 4

the following consideration. The most favourable conformations of the anion intermediate (8) for epoxide formation are those having the oxygen atoms of the hydroperoxide moiety perpendicular to the plane of the furanone ring. Greater hindrance to the achievement of this orientation might be expected in conformation (8a) than in conformation (8b), due to the greater steric interaction between the β -aryl and ketone groups in (8a) than between the β -aryl group and the oxygen heteroatom in (8b).



SCHEME 5

Preliminary studies have shown that aurone epoxides may also be synthesised by the Darzens condensation. 2-Bromo-6-methoxycoumaran-3-one (9) was condensed with a number of aryl aldehydes, the best results being obtained with 2-nitrobenzaldehyde, which gave aurone epoxide (10) (Scheme 5) in yields of 60–90%. Condensation of the bromo-ketone (9) with benzaldehyde under a variety of conditions gave lower yields (<30%)

of 6-methoxyaurone epoxide than obtained by the direct epoxidation of aurone (1d) with alkaline hydrogen peroxide. The *trans*-isomer (2d) was obtained in each case. The *trans*-configuration is also tentatively assigned to 6-methoxy-2-nitroaurone epoxide (10). Bromo-ketone (9) was prepared by the addition of bromine to an ethereal solution of 6-methoxycoumaran-3-one. When glacial acetic acid was the solvent, 5-bromo-6-methoxycoumaran-3-one, previously synthesised by a different route,¹¹ was obtained.

Sodium hypochlorite, which has been used to epoxidise certain $\alpha\beta$ -unsaturated ketones,^{1,12} failed to epoxidise aurone (1d) under similar conditions.

EXPERIMENTAL

¹H N.m.r. spectra were recorded on a Varian HR 60A spectrometer in deuteriochloroform, with trimethylsilane as internal reference. I.r. spectra were recorded on a Beckman IR5 spectrometer. Triton B (benzyltrimethylammonium hydroxide) was used as a 40% solution in methanol.

Aurone Epoxide (2d).—(1) *From trans-6-methoxyaurone.* Hydrogen peroxide (30 ml, 30%) and Triton B (10 ml) were added slowly and simultaneously to a solution of *trans*-aurone (1d)¹³ (10 g) in dioxan (600 ml) at room temperature. The solution was stirred for 40 min and was then diluted with a mixture of crushed ice and water. The resulting crude product was collected and dried *in vacuo* over calcium chloride. Crystallisation from chloroform–ligroin afforded *trans*-2-benzylidene-6-methoxy-2H-benzo[b]furan-3-one epoxide (2d) as a mixture of colourless cubes, m.p. and mixed m.p. 103 °C (lit.,² m.p. 103 °C), and colourless plates, m.p. 110 °C (total yield 6 g, 58%) (Found: C, 71.65; H, 4.6. Calc. for C₁₆H₁₂O₄: C, 71.63; H, 4.51%); τ 6.15 (3 H, 6-OMe), 5.46 (s, 1 H, epoxide-H), 3.46 (d, *J* 2 Hz, 1 H, 7-H), 3.30 (q, *J* 8 and 2 Hz, 1 H, 5-H), 2.55 (m, 5 H, Ph), and 4.40 (d, *J* 8 Hz, 1 H, 4-H); ν_{\max} . (KBr) 1 710 cm⁻¹ (C=O).

The aqueous filtrate was acidified and extracted with ether. The ether phase was extracted with a saturated aqueous solution of sodium hydrogencarbonate. Acidification of the aqueous extract yielded a white solid which crystallised from water as colourless needles of 2-hydroxy-4-methoxybenzoic acid (1.37 g, 20%), m.p. 154–155 °C alone or when mixed with an authentic sample (Found: C, 57.5; H, 4.8. Calc. for C₈H₈O₄: C, 57.14; H, 4.80%).

(2) *From trans- β -deuterio-6-methoxyaurone.* In a similar experiment, *trans*-2- α -deuterobenzyldene-6-methoxy-2H-benzo[b]furan-3-one¹⁴ (1.0 g) afforded *trans*-2-(α -deuterio-benzyldene)-6-methoxy-2H-benzo[b]furan-3-one epoxide (0.6 g, 58%), m.p. 103 °C alone or when mixed with a non-isotopic sample. The n.m.r. spectrum was identical to that of epoxide (2d) except for the absence of the peak at τ 5.46.

(3) *From cis-6-methoxyaurone.* In a similar experiment *cis*-6-methoxyaurone¹⁴ (100 mg) gave a solid [an examination of which by t.l.c. showed that neither *cis*-6-methoxyaurone epoxide nor *trans*-aurone (1d) were formed in the reaction] which crystallised from chloroform–ligroin to give pale yellow needles of starting *cis*-6-methoxyaurone (35 mg, 35%), m.p. and mixed m.p. 136–137 °C. The mother-liquor, on standing, deposited colourless cubes of *trans*-6-methoxyaurone epoxide (2d) (25 mg, 24%), m.p. and mixed m.p. 103 °C.

The following aurone epoxides were prepared by experi-

ments similar to that described above for the preparation of aurone epoxide (2d).

Aurone epoxide (2a). Aurone (1a)¹³ (1.0 g) over a period of 35 min afforded lustrous plates of *trans-2-benzylidene-2H-benzo[b]furan-3-one epoxide* (2a) (0.6 g, 56%), m.p. 133–134 °C (chloroform–ligroin), (Found: C, 75.9; H, 4.35. C₁₅H₁₀O₃ requires C, 75.62; H, 4.23%); ν_{\max} (KBr) 1 719 cm⁻¹.

Aurone epoxide (2c). Aurone (1c)¹³ (2.0 g), over a period of 40 min, gave *trans-2-benzylidene-5-methyl-2H-benzo[b]furan-3-one epoxide* (2c) (0.8 g, 38%), m.p. 111–112 °C (ligroin–methylene chloride) (Found: C, 76.25; H, 4.9. C₁₆H₁₂O₃ requires C, 76.18; H, 4.80%).

Aurone epoxide (2e). Aurone (1e)¹⁵ (1.0 g), over a period of 3 h, gave *trans-2-benzylidene-4,6-dimethoxy-2H-benzo[b]furan-3-one epoxide* (2e) (0.65 g, 61%), m.p. 170–180 °C (decomp.) (Found: C, 68.9; H, 5.0. C₁₇H₁₄O₅ requires C, 68.45; H, 4.73%); τ 6.19 (s, 3 H, OMe) 6.12 (s, 3 H, OMe), 5.49 (s, 1 H, epoxide-H), 3.96 (d, *J* 1.5 Hz, 1 H, 5-H), 3.86 (d, *J* 1.5 Hz, 1 H, 7-H), and 2.59 (m, 5 H, Ph); ν_{\max} (KBr) 1 720 cm⁻¹.

Aurone epoxide (2h). Aurone (1h) (see below) (2.0 g) over a period of 70 min gave *trans-2-(2-naphthylidene)-6-methoxy-2H-benzo[b]furan-3-one epoxide* (2h) (1.0 g, 48%), m.p. 124–134 °C (decomp.) (Found: C, 75.3; H, 4.65. C₂₀H₁₄O₄ requires C, 75.44; H, 4.43%); ν_{\max} (KBr) 1 745 cm⁻¹.

7-Methoxyflavonol.—A mixture of aurone (1d) (2.0 g), hydrogen peroxide (7 ml, 30%), and Triton B (3 ml) in acetone (120 ml) was kept at room temperature for 4 h. The mixture on dilution with ice-water gave a white solid which crystallised from ethanol as pale yellow needles of 7-methoxyflavonol (1.41 g, 67%), m.p. 176–178 °C alone or when mixed with an authentic sample.¹³

Synthesis of Aurone (1h).—Sodium hydroxide was added to a solution of 6-methoxy-2H-benzo[b]furan-3-one¹⁶ (10 g) and 2-naphthaldehyde (12.5 g) in ethanol (100 ml) at 60 °C and kept at this temperature for 1 h. The product, which began to separate almost immediately, was collected, and washed with dilute sulphuric acid and methanol. It crystallised from ethanol-dioxan as pale yellow silky needles of *trans-2-(2-naphthylidene)-6-methoxy-2H-benzo[b]furan-3-one* (1h) (15 g, 80%), m.p. 172 °C (Found: C, 79.05; H, 4.8. C₂₀H₁₄O₃ requires C, 79.45; H, 4.67%).

Reaction of Aurone Epoxide (1d) with Base.—(1) *With sodium hydroxide–acetone.* Sodium hydroxide (3 ml, 10%) was added to a solution of aurone epoxide (1d) (0.95 g) in acetone (80 ml) and the mixture was kept at room temperature for 1 h. The precipitate obtained on dilution of the solution with water and acidification was taken up in ether. The ethereal solution was extracted with sodium hydroxide (5%). The solid obtained on acidification of the alkaline extract was collected, washed with water, and crystallised from ethanol to give pale yellow needles of 7-methoxyflavonol (65 mg, 6.85%), m.p. 179–180 °C (lit.,¹³ m.p. 180 °C). The ether layer was washed with water and dried (anhydrous MgSO₄). The residual oil obtained on removal of the solvent crystallised from chloroform–ligroin as cubes of starting epoxide (2d) (0.44 g, 46%), m.p. and mixed m.p. 103 °C.

(2) *With methanolic Triton B–benzene.* Triton B (0.5 ml) was added to a solution of epoxide (2d) (0.1 g) in dry benzene (10 ml). After 30 min the benzene solution was washed successively with water and saturated aqueous copper acetate, and then extracted with dilute sodium hydroxide.

Acidification of the alkaline extract gave a solid which crystallised from methanol as 7-methoxyflavonol (0.05 g, 50%), m.p. and mixed m.p. 179–180 °C.

(3) *With aqueous sodium hydroxide–methanol.* Aqueous sodium hydroxide (0.5N; 2 ml) was added to a solution of epoxide (2d) (0.268 g) in water–methanol (50 : 50) (100 ml). The mixture was kept at *ca.* 50 °C for 4 h. The cooled solution was diluted with water (200 ml), neutralised with dilute hydrochloric acid, and extracted with ether. The ether solution was treated with a saturated aqueous solution of copper acetate. The blue-green solid which precipitated was collected (0.09 g), m.p. 300 °C (decomp.). The solid gave an identical i.r. spectrum to that of the copper chelate of an authentic sample of 6-methoxy-2-benzoylcoumaran-3-one.¹⁶ The organic layer was extracted with dilute sodium hydroxide (1%). Acidification of the alkaline extract afforded 7-methoxyflavonol, which crystallised from ethanol as fine yellow needles (0.09 g), m.p. 178–180 °C alone or when mixed with an authentic sample.

(4) *With powdered sodium hydroxide–benzene.* A mixture of epoxide (2d) (0.35 g) in dry benzene (30 ml) and powdered sodium hydroxide (0.5 g) was warmed gently on a steam-bath for 30 min. The benzene mixture on cooling was acidified, then washed with water and saturated aqueous sodium chloride. Ether was added to the benzene solution to give a total volume of 200 ml. The products, the copper chelate of 6-methoxy-2-benzoylcoumaran-3-one (0.20 g) and 7-methoxyflavone (0.03 g) were isolated and identified as in the previous experiment. Similar results were obtained when dioxan was used as solvent.

Reaction of Aurone Glycol (5) with Base.—Aqueous sodium hydroxide (25 ml, 0.5%) was added to a solution of 2-hydroxy-6-methoxy-2-(α -hydroxybenzyl)-2H-benzo[b]furan-3-one⁶ (5) (0.5 g) in water–methanol (50 : 50) (120 ml). The solution was kept at room temperature for 30 min, then acidified with dilute hydrochloric acid, diluted with water (100 ml), and extracted with aqueous sodium hydrogen-carbonate (5%) and with aqueous sodium hydroxide (1%, 50 ml). Acidification of the hydrogen carbonate extract afforded a cloudy suspension which was taken up in ether and dried (MgSO₄). The solid obtained on removal of the ether crystallised from water as colourless needles of 2-hydroxy-4-methoxybenzoic acid (0.15 g, 60%), m.p. and mixed m.p. 154 °C. Acidification of the sodium hydroxide extract gave no precipitate.

5-Bromo-6-methoxy-2H-benzo[b]furan-3-one.—Bromine (0.94 ml) in glacial acetic acid (0.94 ml) was slowly added to a stirred slurry of 6-methoxycoumaran-3-one¹² (3.0 g), glacial acetic acid (6 ml), and aqueous hydrochloric acid (10%, 6 ml) at 0 °C and the mixture was stirred at this temperature for a further 30 min. The precipitate which separated on dilution of the mixture with water (100 ml) crystallised from ligroin as pale yellow needles (3.0 g, 67%) of the title compound m.p. 187–188 °C (lit.,¹¹ m.p. 186 °C); τ 6.01 (s, 3 H, OMe), 5.35 (s, 2 H, 2-H), 3.40 (s, 1 H, 7-H), and 2.20 (s, 1 H, 4-H).

2-Bromo-6-methoxy-2H-benzo[b]furan-3-one (9).—Bromine (16 g, 0.1 mol) was added dropwise over a period of 10 min to a solution of 6-methoxycoumaran-3-one (16.4 g, 0.1 mol) in ether (800 ml) and stirring was continued for 40 min. The resulting red solution was washed with aqueous sodium hydrogen carbonate (5%) and water, dried (Na₂SO₄), treated with charcoal, and filtered. The resulting yellow solution was diluted with n-heptane and allowed to stand. On slow evaporation of the solvent yellow crystals of the

title compound (9) deposited, m.p. 95 °C (decomp.) (Found: C, 44.1; H, 3.15; Br, 33.0. $C_9H_7BrO_3$ requires C, 44.47; H, 2.90; Br, 32.87); τ 6.05 (s, 3 H, OMe), 3.48 (s, 1 H, 2-H), 3.38 (d, J 2.1 Hz, 1 H, 7-H), 3.20 (q, J 2.1 and 8.3 Hz, 1 H, 5-H), and 2.28 (d, J 8.3 Hz, 1 H, 4-H).

Synthesis of Aurone Epoxides (2d) and (10) by Darzens Condensations.—(1) *Aurone epoxide (10)*. A methanolic solution of sodium methoxide (0.01 mol) was added dropwise to a solution of bromo-ketone (9) (2.43 g, 0.01 mol) and 2-nitrobenzaldehyde (1.51 g, 0.01 mol) in benzene (50 ml) and the resulting solution was stirred for 25 min. The solution was then washed with water, dried (Na_2SO_4), and treated with charcoal. The product (2.93 g, 89%), m.p. 85 °C, crystallised on slow evaporation of the benzene on the rotary evaporator. It recrystallised from benzene to give 6-methoxy-2-(2-nitrobenzylidene)-2H-benzo[b]furan-3-one epoxide (10), m.p. 97–98.5 °C (Found: C, 61.55; H, 3.75; N, 4.2. $C_{16}H_{11}NO_6$ requires C, 61.35; H, 3.54; N, 4.47%); τ 6.13 (s, 3 H, OMe), 4.90 (s, 1 H, β -H), 3.50 (d, J 2 Hz, 1 H, 7-H), 3.22 (q, J 9 and 2 Hz, 1 H, 5-H), 2.26 (d, J 9 Hz, 1 H, 4-H), and 1.5–2.6 (complex multiplet, 3', 4', 5', and 6'-H); ν_{max} (KBr) 1 706 cm^{-1} .

(2) *Aurone epoxide (2d)*. A methanolic solution of sodium methoxide (0.01 mol) was added to coumaranone (9) (2.43 g, 0.01 mol) and benzaldehyde (2 ml) in dioxan (50 ml) and the mixture was stirred for 20 min and then poured into ice-water (400 ml). The product was taken up in chloroform, and the chloroform solution was washed with sodium metabisulphite, dried (Na_2SO_4) and reduced in volume to 10 ml. Light petroleum (b.p. 100–120 °C) (50 ml) was added and on slow evaporation of the solvent, crystals of epoxide (2d), m.p. 93–98 °C, separated. Its n.m.r. spectrum was identical to that of an authentic sample

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