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FLAVANOID EPOXIDES—I

OXIDATION OF AURONES

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Abstract—Oxidation of aurones by alkaline hydrogen peroxide gave aurone epoxides and flavonols; with sodium peroxide the products were aroylcoumaran-3-ones and with t-butyl hydroperoxide in the presence of Triton-B the products were flavonols.

IN A previous communication it was reported[1] that the action of alkaline hydrogen peroxide on aurones led to the formation of flavonols. Thus, aurones I (b,d,e) gave the flavonols II (b,d,e) while in the case of aurone Ie the corresponding epoxide (IIIe) was also a product of the reaction. In an extension of this work it is now shown that aurones I; (a,f,g) also undergo ring expansion to form flavonols (Table 1). It was found that presence of small amount of benzoquinone in the reaction mixture favoured production of epoxide and depressed flavonol formation. In this way the aurones epoxides III (a,b,c,d,e) and VI were obtained. These compounds were difficult to isolate and while epoxides III (d,e) and IV were isolated in crystalline form, epoxides III (a,b,c) were estimated by titration. Confirmation of the titration figures was obtained when epoxides were found to rearrange almost quantitatively into the corresponding 4-hydroxy-3-phenylcoumarins.[2]

Alternative methods of synthesis of aurone epoxides were investigated. Yang and Finnegan[3] found that t-butyl hydroperoxide reacts with α-β-unsaturated ketones in benzene in the presence of Triton-B to form epoxides. When this method was applied to the aurones (Id and Ig) no epoxides were isolated but the corresponding flavonols were obtained in 32% and 25% yields respectively.

Another possible route to aurone epoxide formation was by base catalysed cyclization of aurone bromohydrins. With this procedure in mind, bromohydrin (VIIIa) was synthesized by heating a solution of 6,4'-dimethoxyaurone dibromide in aqueous acetone. However, treatment of this compound with aqueous sodium hydroxide gave flavonol (IIg), in high yield, rather than the corresponding epoxide. Treatment of bromohydrin (VIIIa) with various bases in non aqueous solvents did not effect a change in the compound.

When the aurones I (b,c,f,g) and IV were dissolved in pyridine and treated with sodium peroxide they gave the related aroylcoumaranones IX (b,c,f,g) and X.

[1] W. E. Fitzmaurice, W. I. O'Sullivan, E. M. Philbin, T. S. Wheeler and T. A. Geissman, *Chem. & Ind.* 652 (1955).
[2] M. Geoghegan, W. I. O'Sullivan and E. M. Philbin, *Tetrahedron.* **22**, 3215 (1966).
[3] N. C. Yang and R. H. Finnegan, *J. Amer. Chem. Soc.* **80**, 5845 (1958).

I

II

III

VII

(a; R = R′ = R″ = R‴ = H)
(c; R = CH_3; R′ = R″ = R‴ = H)
(e; R = R‴ = H; R′ = R″ = OCH_3)
(g; R = R″ = H; R′ = R‴ = OCH_3)

IX

(b; R = R′ = R″ = H; R‴ = OCH_3)
(d; R = R″ = R‴ = H; R′ = OCH_3)
(f; R = CH_3; R‴ = OCH_3; R′ = R″ = H)

IV

V

VI

X

VIII

a; R = H
b; R = $COCH_3$

EXPERIMENTAL

M.ps are uncorrected. EtOH was used for crystallizations if no solvent is mentioned. IR spectra: Beckman IR-5 spectrometer.

Preparation of aurones

The aurones listed were, unless otherwise stated, prepared by condensing the coumaran-3-one and appropriate arylaldehyde: Compd Ia had m.p. 106–108°. P. Friedländer and J. Neudorfer (*Ber. Dtsch. Chem. Ges.* **30,** 1082 (1897)) give m.p. 108°; compd Ib had m.p. 140°. J. E. Gowan, P. M. Hayden and T. S. Wheeler (*J. Chem. Soc.* 866 (1955)) give m.p. 138–139°; compd Ic had m.p. 116–118°. K. Auwers and K. Müller (*Ber. Dtsch. Chem. Ges.* **41,** 4238 (1908)) give m.p. 119°; compd Id had m.p. 145–148°. K. Auwers and P. Pohl (*Liebigs Ann.* **105,** 268 (1915)) give m.p. 145°; compd Ie, which was prepared by methylation of 2-benzylidene-6,7-dihydroxycoumaran-3-one, had m.p. 150–153°. P. Friedländer and R. Löwy (*Ber. Dtsch. Chem. Ges.* **29,** 2433 (1896)) give m.p. 148–149·5°; compd If had m.p. 150–152°. K. Auwers and L. Anschütz (*Ber. Dtsch. Chem. Ges.* **54,** 1556 (1921)) give m.p. 152°; compd Ig had m.p. 134–136°. T. B. Panse, R. C. Shah and T. S. Wheeler (*J. Univ. Bombay* **10,** pt. 3, 83 (1941)) give m.p. 134°; compd IV had m.p. 182–184°. E. P. O'Connor (*Ph.D. Thesis, N.U.I.* p. 100 (1956)) gives m.p. 182–184°.

Alkaline hydrogen peroxide oxidation of aurones

Method A. A mixture of the aurone (2 g), H_2O_2 (0·6 to 1·5 g), KOH (0·6 to 1 g), water (6 g) and, except where otherwise stated, acetone (80 ml) was kept for approx. 1 hr at room temp, then added to water, acidified and extracted with ether. The ethereal soln was washed with 10% Na_2CO_3aq and extracted with 5% NaOHaq to separate flavonols which were recovered on acidification. The flavonols were identified by mixed m.ps with authentic samples. The neutral residues[4] obtained on removal of the solvent from the ethereal solns were crystallized from EtOH yielding unchanged aurones. The results are shown in Table 1.

TABLE 1. ALKALINE HYDROGEN PEROXIDE OXIDATION OF AURONES BY METHOD A

	Corresponding flavonol			
Aurone	Yield	m.p.	lit m.p.	Ref
Ia	Trace	163°	169°	5
Ib	2·5%	230–232°	235°	6
Ic	Trace[a,b]	—		
Id	3 to 38%[c]	176–179°	181°	6
Ie	10%	200–202°	203°	8
If	2·5%	188–192°	191–192°	7
Ig	4%	190–192°	195°	6
IV	Trace[a]	—		

[a] Gave coloration with ethanolic $FeCl_3$.
[b] MeOH–dioxan was used as solvent.
[c] Result of a large number of experiments.

Method B. The following experiments were carried out as in Method A except that the H_2O_2 and NaOH solns were added gradually to the reaction mixture over a period of 20 to 30 min. Benzoquinone was also added in most[8] of the experiments. Before the neutral fractions of the products

[4] In the first series of experiments (Table 1; Method A) the residues were not tested for the presence of aurone epoxides before crystallization. Possibly the ethanolic mother liquors contained some of these compds.
[5] L. Reichel and J. Steudel, *Liebigs Ann.* **553,** 90 (1942).
[6] J. Algar and J. P. Flynn, *Proc. Roy. Irish Acad.* **42B,** 5 (1934).
[7] S. O. Limaye and D. B. Limaye, *Rasayanam* **2,** 44 (1952).
[8] F. Dobrzynski and St. v. Kostanecki, *Ber. Dtsch. Chem. Ges.* **37,** 2808 (1904).

were purified they were tested with KI in glacial AcOH for the presence of aurone epoxides. In some instances the epoxide content was estimated by titration of the liberated iodine. On crystallization of the neutral fraction unchanged aurone separated first. The more soluble aurone epoxides were obtained from the mother liquors.

2-Benzylidene-6-methoxycoumaran-3-one epoxide (IIId)

The product the reaction of 2-benzylidene-6-methoxycoumaran-3-one (3 g), with H_2O_2 (12 ml; 15%), NaOH (9 ml; 12%) and benzoquinone (0·3 g) by Method B, was fractionally crystallized from acetone. The crystals of IIId which were obtained from the final mother liquor recrystallized from pet. ether in cubes, m.p. 100–103°. (Found: C, 71·7; H, 4·5; OMe, 11·5. $C_{16}H_{12}O_4$ requires: C, 71·6; H, 4·5; OMe, 11·6%), ν_{max} 1710 cm^{-1} (C=O). The compound gave a brown-red colour on addition to KI in glacial AcOH acid. Its NMR spectrum[10] at 60 Mc/s with reference to internal TMS had singlets at 6·15 τ (CH_3O) and 5·46 τ (epoxidic proton); doublets at 3·46 τ (7H; J = 2 c/s) and 2·40 τ (4H; J = 8 c/s); a quartet at 3·3 τ (5H; J = 2 and 8 c/s) and a multiplet at 2·55 τ (C_6H_5).

Estimation of epoxide

The epoxide content in the products of two similar experiments was estimated as follows: Glacial AcOH (5 ml) and KI (0·5 g) were added to 0·05 g of the neutral product and the mixture heated to 50° for 5 min. The cooled mixture was diluted and the liberated I_2 titrated with N/100 $Na_2S_2O_3$. The percentage yields of epoxide (based on aurone used) in the two experiments were 25% and 26%.

5-Methyl-2β-naphthylidenecoumaran-3-one epoxide (VI)

This compd was isolated by fractional crystallization of the product of oxidation of IV by Method B. The solvent used in this experiment was dioxan–acetone (25:30). Epoxide VI crystallized from pet. ether in needles, m.p. 130–131°. (Found: C, 79·4; H, 4·3. $C_{20}H_{14}O_3$ requires: C, 79·5; H, 4·7%,) ν_{max} 1720 cm^{-1} (C=O).

2-Benzylidene-6,7-dimethoxycoumaran-3-one epoxide (IIIe)

Method C. Compd Ie (1 g) was suspended in a 50/50 mixture of dioxan and MeOH, benzoquinone (0·1 g) was added and the mixture cooled to 0°. H_2O_2 (30%; 5 ml) and NaOHaq (24%; 5 ml) were added during an hr and the mixture stirred for a further hr. Filtration of the reaction mixture gave a solid (0·4 g) which crystallized from AcOEt to give IIIe in needles, m.p. 164–166° (lit.[1] m.p. 157°). (Found: C, 68·3; H, 4·7; OMe, 20·9. $C_{17}H_{14}O_5$ requires: C, 68·45; H, 4·7; OMe, 20·8%), ν_{max} 1710 cm^{-1} (C=O). It gave a positive KI–AcOH test.

Oxidation of aurone (Ic)

Method D. H_2O_2 (15%; 10 ml) and NaOHaq (12%; 10 ml) were added to a mixture of 5-methylaurone (10 g) and benzoquinone (0·05 g) in dioxan (200 ml). Similar additions of peroxide and alkali were made at ½hr intervals until 40 ml of each soln was added. After 12 hr at 0° the mixture was diluted with water (600 ml) and the resulting slurry extracted with ether. The ethereal solution was washed consecutively with 1% NaOHaq, saturated $Na_2S_2O_3$aq and saturated NaClaq. Aurone Ic (5 g) separated on concentration of the dried ethereal solution. On removal of the ether a residual oil (2·1 g) was obtained which failed to crystallize from the usual solvents. It released I_2 from KI in AcOH and showed an epoxide[11] content of 60% (representing an overall yield of 12·6%) when titrated with N/100 $Na_2S_2O_3$.

Oxidation of aurone (Ia)

Aurone Ia (5 g) was oxidized according to Method D. After removal of unchanged aurone (3 g), an oil (1·0 g) was obtained which failed to crystallize from the usual solvents. It liberated I_2

[9] When benzoquinone was present in the reaction mixture no flavonol was obtained (except in one instance, that of the oxidation of aurone (Ib)).

[10] We are indebted to Dr. G. R. Bedford of Imperial Chemical Industries Ltd., Pharmaceuticals Division, Macclesfield, Cheshire, for this determination.

[11] In a subsequent paper[2] it will be shown that the epoxide is converted into the corresponding tetronic acid by means of borontrifluoride etherate.

from KI in AcOH and on estimation with N/100 $Na_2S_2O_3$ showed an epoxide[11] content of 50%, representing an overall yield of 10% epoxide.

Attempted oxidation of aurone (Ig)

An attempt to epoxidize Ig by Method D failed and the unchanged aurone was recovered almost quantitatively.

Oxidation of aurone (Ib)

Oxidation of this aurone by Method B gave a mixture, m.p. 134–136° which had a 10·7% epoxide content as shown by the method of estimation described above.

Oxidation of aurones (Id) *and* (Ig) *by* t-*butyl hydroperoxide*

7-Methoxyflavonol. A mixture of Id (1·25 g), t-butyl hydroperoxide (0·75 ml), methanolic Triton B (0·07 ml; 35%) and dry benzene (100 ml) was stirred for 3 hr. The benzene layer was washed with a sat NaClaq and then extracted with 5% NaOHaq. Acidification of the alkaline extract gave 7-methoxyflavonol which separated from EtOH (95%) in fine yellow needles (0·4 g; 32%), m.p. 178–180° which was not depressed on admixture with an authentic sample.[6] The benzene solution which gave a negative KI–AcOH test was discarded.

4′,7-Dimethoxyflavonol. In a similar reaction to the previous one Ig (1·49 g) was converted into 4′,7-dimethoxyflavonol (0·3 g; 25% yield), m.p. and mixed m.p. 192–193°.

*Synthesis of 2-bromo-6-methoxy-2(ω-hydroxy-*p*-methoxybenzyl)coumaran-3-one* (VIIIa)

A soln of 2-bromo-6-methoxy-2-(ω-bromo-*p*-methoxybenzyl)coumaran-3-one[12] (5·0 g) in aq acetone (20:80; 400 ml) was heated under reflux for 30 min, cooled and diluted with water (600 ml). The precipitated bromohydrin of VIIIa crystallized from ligroin in pale yellow needles (3·5 g), m.p. 166–172° (dec) ν_{max} 3448 cm^{-1}. It released I from KI in AcOH (indicating that the Br atom is in the α-position to the C=O group). This compound, which was unstable, on acetylation with Ac_2O (perchloric acid catalysed) gave *2-bromo-6-methoxy-2(ω-acetoxy-*p*-methoxybenzyl)coumaran-3-one* (VIIIb) in cubes, m.p. 161–162°, from ligroin. (Found: C, 54·2; H, 4·1; Br, 19·1. $C_{19}H_{17}O_6Br$ requires: C, 54·16; H, 4·04; Br, 19·0%.)

Action of aqueous alkali on VIIIa

A mixture of VIIIa (1·95 g) 0·5N NaOH (10 ml) and dioxan (50 ml) was kept at 50° for 15 min, cooled, diluted with water and extracted with ether. Acidification of the NaOHaq extract of the ethereal layer yielded 4′,7-dimethoxyflavonol which separated from MeOH in yellow crystals (1·1 g; 71% yield), m.p. and mixed[6] m.p. 192–193°.

Formation of acylcoumaranones from aurones

In a typical experiment sodium peroxide was added to the aurone (2 g) in pyridine (10 ml) and the mixture heated under reflux ($CaCl_2$ guard) for 2 hr. The precipitate obtained on acidification of the cooled mixture was taken up in ether and the soln shaken with saturated aq copper acetate. The insoluble cupri-acylcoumaranone formed was collected, suspended in ether and decomposed with dil. H_2SO_4. The free acylcoumaranone which was recovered from the ethereal layer was identified by a mixed m.p. with an authentic sample.

The following 2-acylcoumaran-3-ones were thus prepared (the percentage yields given are based on the quantities of copper chelate formed). 2-Anisoylcoumaran-3-one (IXb), 6%, m.p. 110–112° undepressed on admixture with a sample synthesized independently (see below). 2-Anisoyl-5-methylcoumaran-3-one (IXf), 4%, m.p. 138–142° (lit.[13,14] m.p. 145·5°). 2-Benzoyl-5-methylcoumaran-3-one (IXc), 6%, m.p. 109–111° (lit.[13] m.p. 112°). 5-Methyl-2-β-naphthoylcoumaran-3-one (X), 30%, m.p. 120° (lit.[14] m.p. 125–126°. 2-Anisoyl-6-methoxycoumaran-3-one (IXg), m.p. 110–113° (lit.[15] m.p. 114–115°). In this experiment the working up procedure was as follows. The reaction

[13] T. B. Panse, R. C. Shah and T. S. Wheeler, *J. Univ. Bombay* **10**, Pt. 3, 83 (1941).
[14] K. Auwers, *Ber. Dtsch. Chem. Ges.* **43**, 2197 (1910).
[14] E. M. Philbin, W. I. O'Sullivan and T. S. Wheeler, *J. Chem. Soc.* 4174 (1954).
[15] S. K. Grover, A. C. Jain, S. K. Mathur and T. R. Seshadri, *Indian J. Chem.* **1** (9), 382 (1963).

mixture was diluted with water and filtered. CO_2 gas was passed through the filtrate and the red solid (0·48g) which precipitated was extracted with ligroin (soxhlet) to give IXg in poor yield.

Independent synthesis of IXb

A mixture of ω-chloro-2-hydroxyacetophenone (5 g) and anisoyl chloride (5 g) was heated at 160° for 4 hr. The product crystallized from EtOH (charcoal) in prisms of *ω-chloro-2-anisoyloxyacetophenone* (5 g), m.p. 97–98°. (Found: C, 63·1; H, 4·3; Cl, 11·1. $C_{16}H_{13}O_4Cl$ requires: C, 63·1; H, 4·3; Cl, 11·6%.) A mixture of ω-chloro-2-anisoyloxyacetophenone (2 g) and NaH (0·15 g) in dioxan (20 ml) was kept and shaken occasionally, at room temp for 2 hr. The mixture was diluted with water and filtered. The filtrate was acidified and the resulting precipitate (1·87 g) crystallized from EtOH (charcoal), in pale yellow needles of IXb, m.p. 112–113°. (Found: C, 72·1; H, 4·5; $C_{16}H_{12}O_4$ requires: C, 71·6; H, 4·5%.)