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FLAVANOID EPOXIDES—XIII[1]

ACID AND BASE CATALYSED REACTIONS OF 2′-TOSYLOXYCHALCONE EPOXIDES. MECHANISM OF THE ALGAR–FLYNN–OYAMADA REACTION

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Abstract—2′-Tosyloxychalcone epoxide (**6a**) on reaction with alkali gave flavonol (**4a**) while similar treatment of 6′-methoxy-2′-tosyloxychalcone epoxide (**6b**), both at room temperature and at the boiling point of the reaction medium, afforded 5-methoxyaurone (**5b**). The latter result indicates that an epoxide is not an intermediate in the production of flavanols from 2′-hydroxy-6′-methoxychalcone epoxides on treatment with alkaline hydrogen peroxide (AFO Reaction) at the higher temperature. Epoxide **6a** on treatment with boron trifluoride etherate gave a mixture of flavanonol and flavonol while epoxide **6b** gave formyldesoxybenzoin (**9**) under similar conditions.

The Algar-Flynn-Oyamada[2] (AFO) reaction involves the alkaline hydrogen peroxide oxidation of 2′-hydroxychalcones firstly into flavanonols[3] (**3**) and then into flavonols (**4**) (Scheme I, route 1). If an OMe[4] or Me[5] substituent is present in the 6′-position of the chalcone, aurones (**5**) (Scheme I, route 2) rather than flavonols are obtained, provided the 2-[6] or 4-[7] positions do not carry an hydroxyl group, and that the reaction is effected at room temperature. When the reaction is carried out in MeOH or EtOH 6′-methoxychalcones give flavonols as the main products.[8] Dean and Podimuang[9] proposed routes 3 or 4 (Scheme I) for the formation of flavanonols and flavonols from 2′-hydroxychalcones in the AFO reaction rather than the previously accepted route which presumed the intermediate formation of a chalcone epoxide (route 1). The accepted routes (1 and 2) to 5-methoxyflavonols (at temperatures above 20°) and to 4-methoxyaurones from 2′-hydroxy-6′-methoxychalcones on AFO oxidation were retained by these authors.

The results we now report on the reactions of 6′-methoxy-2′-tosyloxychalcone epoxide are consistent with, but do not prove, route 2 to aurone but they are not in accord with route 1 to flavonols from 2′-hydroxy-6′-methoxychalcones in the AFO reaction carried out at the boiling point of the reaction medium.

2′-Tosyloxychalcone epoxide (**6a**) and 6′-methoxy-2′-tosyloxychacone epoxide (**6b**) were prepared by the action of alkaline H_2O_2 on the parent 2′-tosyloxychalcones. Treatment of epoxide **6a** with alkali at room temperature gave flavonol **4a**[11] while epoxide **6b** on similar treatment gave 5-methoxyaurone (**5b**) (along with, in one instance, a small amount of 6-methoxyflavanonol; **3b**). When the latter reaction was carried out in EtOH at the b.p. aurone **5b** was the only product.

Various suggestions have been presented as to why cyclisation of the putative AFO 6-methoxychalcone epoxide intermediate takes place by attack of the 2′-O′ group at the α-rather than at the β-position. One such suggestion is that displacement of the carbonyl group out of the plane of the phenolic ring by steric interaction with the 6′-methoxyl group increases the distance of the phenolic oxygen from the β-position more than from the α-position. Another is that the said steric interaction favours the product with the smaller heterocyclic ring.[12] Dean and Podimuang[9] suggested that such effects are not large and that at temperatures above 20° they diminish rapidly and pyrone derivatives are again the main products. However, the results of the present work indicate that once an intermediate chalcone epoxide is formed in the AFO reaction the presence of a 6′-methoxyl substituent plays a practically decisive role, over a range of temperatures, in determining the position of attack by the 2′-O^- group, i.e. α-position (route 2), on cyclisation to form products. A more plausible explanation for flavonol formation on the oxidation of 2′-hydroxy-6′-methoxy-chalcones at temperatures greater than 20° is that the inhibition to resonance between the 2′-O^- ion and the carbonyl group† caused by steric interaction between the 6′-methoxyl group and the ketone group, which facilitates epoxide formation, is overcome at higher temperatures and that the reaction then pro-

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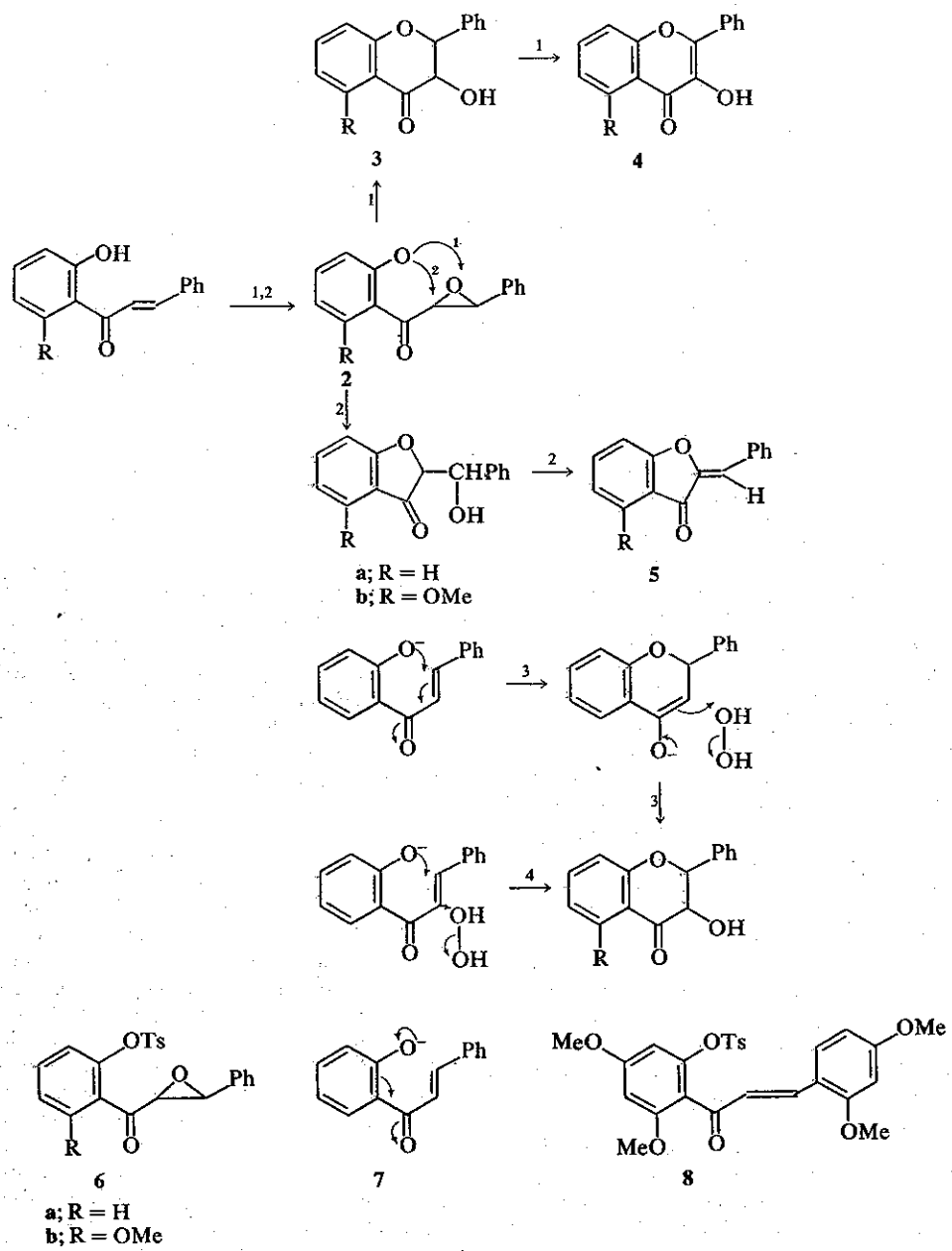
†The epoxidation of α,β-unsaturated ketones by the hydroperoxide ion is hindered because of the coulombic repulsion of the reagent as well as internal electronic inactivation as indicated in structure **7**.[9]

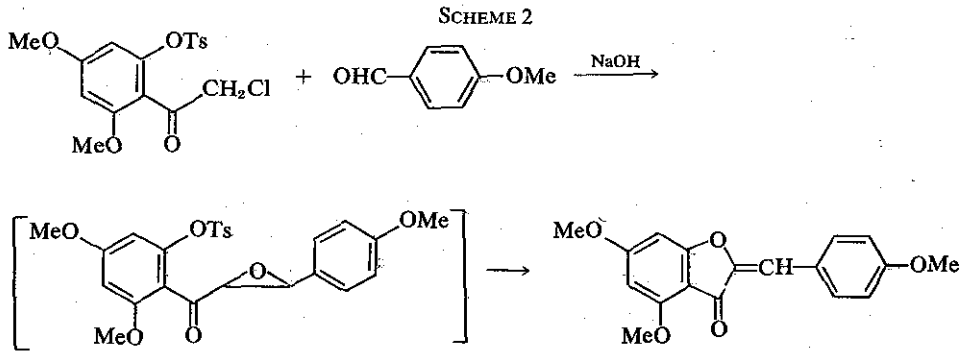
SCHEME 1



ceeds by routes 3 or 4 without the formation of an intermediate epoxide.

Two further experiments gave results which are in agreement with these conclusions. When 2′-tosyloxy-2,4,4′,6′-tetramethoxychalcone (**8**) in MeOH was allowed to react with alkaline H_2O_2 at room temperature for 24 h the corresponding flavanonol was obtained in low yield. This result suggests that hydrolysis of the tosylate group had taken place and that the partial deactivation of the α,β-unsaturated ketone moiety by the 2′-O^- ion (which is not fully conjugated with the carbonyl group) and by the 2′- and 4′-methoxyl groups disfavoured epoxide formation and the reaction proceeded by the alternative routes 3 or 4. Had epoxidation occurred the corresponding aurone would have been the expected product. In another experiment 2-chloro-4′,6′-dimethoxy-2′-tosyl-oxyacetophenone on condensation with anisaldehyde under alkaline conditions afforded 4,4′,6-trimethoxyaurone.[12] It is probable that this reaction proceeded by a Darzens type condensation

SCHEME 2

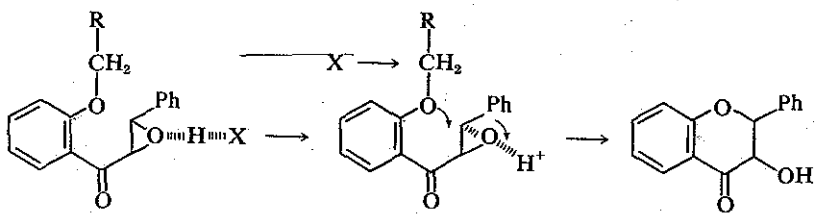


to give an intermediate epoxide[13] which then cyclised to the aurone (Scheme 2). Attempts to isolate tosyloxychalcone epoxides in the latter two reactions were without success.

Reactions of 2′-tosyloxychalcone epoxides with boron trifluoride

The reaction of epoxide **6a** with boron trifluoride etherate under N_2 afforded a mixture of flavanonol (**3a**; 70%) and flavonol (**4a**; 10%). When air was not excluded from the reaction the yields were 33% of **3a** and 37% of **4a**. The action of $BF_3.Et_2O$ on epoxide **6b** produced α-formyldesoxybenzoin **9**, which on heating with alkali gave desoxybenzoin **10**.

Flavanonols are produced by the reaction of 2′-benzyloxychalcone epoxides with acids and their formation was formulated as follows:[14]



A similar mechanism may be operative in the cyclisation of epoxide **6a** by means of BF_3-Et_2O. The steric factors, suggested earlier, which hindered attack of the 2′-O^- moiety at the β-position of 6′-methoxyl substituted chalcone epoxide in alkali would also, presumably, be operative in impeding attack of the 2′-tosyloxy group at the β-position in 6′-methoxy-2′-tosyloxychalcone epoxide on reaction with $BF_3.Et_2O$. An alternative pathway (Scheme 3) is followed with this compound involving migration of the aroyl group to produce the α-formyldesoxybenzoin **9**. The reaction of 4′-methoxyl substituted 2′-benzyloxychalcone epoxides with BF_3 was reported[15] to give analogous results.

EXPERIMENTAL

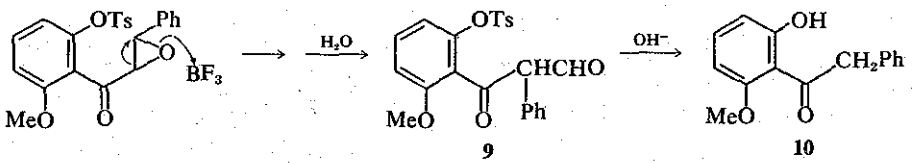
2′-Tosyloxychalcone. A mixture of 2′-hydroxychalcone (2·5 g), *p*-TsCl (1·5 g), K_2CO_3 (1·5 g) and dry acetone (15 ml) was heated under reflux for 2 h and added to water. The oil which separated was dissolved in ether and the resulting solution washed successively with $NaHCO_3$ (5%), NaOH (10%) and water and then dried (Na_2SO_4). The solid obtained on removal of solvent was recrystallised (MeOH) to give 2′-tosyloxychalcone (1·8 g), m.p. and m.m.p. 84° (IR spectrum identical with that of an authentic[16] sample).

2′-Tosyloxy-6′-methoxychalcone was prepared in the same way from 2′-hydroxy-6′-methoxychalcone in 61% yield; white plates from MeOH, m.p. 82°; ν_{max} (KBr) 1639, 1592 cm^{-1} (Found: C, 67·1; H, 4·9; S, 7·7; MeO, 7·8. $C_{23}H_{20}O_5S$ requires: C, 67·6; H, 4·9; S, 7·6; MeO, 7·6%).

2′-Tosyloxy-2,4,4′,6′-tetramethoxychalcone (**8**) was similarly prepared from 2′-hydroxy-2,4,4′,6′-tetramethoxychalcone in 57% yield; white needles from MeOH, m.p. 137–138° (Found: C, 62·2; H, 5·3. $C_{26}H_{26}O_8S$ requires: C, 62·3; H, 5·2%).

Formation of 2′-tosyloxychalcone oxide **6a**. To a solution of 2′-tosyloxychalcone (4·5 g) in MeOH (60 ml) was added H_2O_2 (12 ml; 30%) and NaOH (5 ml; 8%) at 0°. After 1 h the mixture was acidified with HCl (10%) and

SCHEME 3



9 **10**

separated crystals recrystallised (EtOH) to give needles of 2′-tosyloxychalcone oxide (3·6 g), m.p. 132°. (Found: C, 67·3; H, 4·7; S, 8·2. $C_{22}H_{18}O_5S$ requires: C, 67·0; H, 4·6; S, 8·1%). ν_{max} (KBr) 1690–1700 cm^{-1}. τ($CDCl_3$; TMS), 7·65 (s, $—CH_3$), 5·88, 5·83 (d's, J 1·7 Hz, epoxidic protons) 2·0–2·95 (m, aromatic protons). KI test positive.

Formation of 2′-tosyloxy-6′-methoxychalcone oxide **6b**. To a suspension of 2′-tosyloxy-6′-methoxychalcone (1·8 g) in MeOH (50 ml) was added H_2O_2 (6 ml; 30%) and NaOH (2·5 ml; 8%) and the mixture stirred at room temp for 2 h. A white solid precipitated which was collected and recrystallised from EtOH to give plates of 2′-tosyloxy-6′-methoxychalcone (1·8 g) in MeOH (50 ml) was added H_2O_2 (6 ml; 30%) and NaOH (2·5 ml; 8%) and the mixture stirred at room temp for 2 h. A white solid precipitated which was collected and recrystallised from EtOH to give plates of 2′-tosyloxy-6′-methoxychalcone oxide (1·1 g), m.p. 120°. ν_{max} (KBr) 1704 cm^{-1}. KI test positive. (Found: C, 64·9; H, 4·9; S, 7·3; OMe, 6·7. $C_{23}H_{20}O_6S$ requires: C, 65·1; H, 4·7; S, 7·5; OMe, 7·3%).

Reaction of 2′-tosyloxy-2,4,4′,6′-tetramethoxychalcone **8** *with alkaline hydrogen peroxide*. To a suspension of **8** (2·3 g) in MeOH (35 ml) was added H_2O_2 (6 ml; 30%) and NaOH (2·5 ml; 8%). After 24 h a white solid separated which recrystallised (MeOH) to give needles of 2′,4′,5,7-tetramethoxydihydroflavonol (0·7 g), m.p. 178–180°. (Found: C, 63·5; H, 5·6. $C_{19}H_{20}O_7$ requires: C, 63·3; H, 5·66%).

Reaction of 2′-tosyloxychalcone oxide (**6a**) *with alkali*. To a solution of **6a** (0·5 g) in MeOH (60 ml) was added NaOH aq. (8 ml; 8%) and the mixture stirred for 15 h at 17° and then acidified with HCl (10%). The oil which separated was dissolved in ether and the solution extracted successively with $NaHCO_3$ (5%) and NaOH (10%). On removal of solvent a white compound was obtained which on recrystallisation (EtOH) gave unreacted **6a**, m.p. and m.m.p. 131°. Acidification of the NaOH extract with HCl (10%) gave flavonol (**4a**) (0·1 g; 34%) m.p. 169°, identical (m.p. and IR) with an authentic sample.

Similar experiments were run with **6a** except that reaction times, temperatures and concentrations of NaOH were altered. In each case, only flavonol **4a** was obtained. The following conditions were used and the yields of **4a** (%) obtained: **6a** (0·7 g), NaOH (14 ml, 8%), 70°, 2 h, **4a** (52%); **6a** (1 g), NaOH (20 ml; 16%), 70°, 2 h, **4a** (98%); **6a** (1 g), NaOH (50 ml; 8%), 0°, 18 h, **4a** (65%).

Reaction of 2′-tosyloxy-6′-methoxychalcone oxide (**6b**) *with alkali*. To a suspension of **6b** (0·5 g) in MeOH (200 ml) was added NaOH (16 ml; 16%) and the mixture stirred for 24 h at room temp. The mixture was acidified with HCl (10%) and the MeOH removed. On chromatographying (silica gel) the residual solid gave two compounds. The first recrystallised (EtOH aq) to give needles Of 4-methoxyaurone (**5b**) (0·3 g), m.p. and m.m.p.[17] 150°. The second on recrystallisation from EtOAc gave needles of 5-methoxydihydroflavonol (**3b**) (10 mg), m.p. 200° (decomp.); no depression on admixture with an authentic sample.[18]

Similar experiments were run with **6b** except that reaction times, temperatures and concentrations of NaOH were altered. In each case only aurone **5b** was obtained. The following conditions were used and the yield of aurone **5b** (%) is given: **6b** (0·35 g), NaOH (5 ml; 12%), 17°, 24 h, **5b** (85%); **6b** (0·5 g), NaOH (8 ml; 16%), 70°, 2 h, **5b** (98%).

Reaction of 2′-tosyloxychalcone oxide **6a** *with* BF_3.Et_2O. To a solution of oxide **6a** (0·5 g) in dry ether (25 ml) in an atmosphere of N_2 was added BF_3.Et_2O (6 ml; 45%) and the mixture allowed react at 15° for 0·5 h and then added to ice. The resulting oil was dissolved in ether and the ethereal solution extracted successively with $NaHCO_3$ (5%) and NaOH (5%). Evaporation of the dried (Na_2SO_4) ethereal solution gave dihydroflavonol (**3a**) (0·24 g), m.p. and m.m.p. 181°. No material was isolated on acidification and ether extraction of the alkaline extracts.

The reaction was repeated at 35° in air. The neutral ether fraction afforded dihydroflavonol (**3a**) (0·12 g) and the NaOH extract on neutralisation with HCl (10%) gave flavanol (**4a**) (0·12 g), m.p. 169°.

Reaction of 2′-tosyloxy-6′-methoxychalcone oxide (**6b**) *with* BF_3.Et_2O. To a suspension of oxide **6b** in dry ether (25 ml) was added BF_3.Et_2O (6 ml; 45%) and the mixture left at room temp for 0·5 h then added to water. After 24 h the white solid which separated was recrystallised (EtOH) to give plates of *3-(6-methoxy-2-tosyloxyphenyl)-3-oxo-2-phenylpropanal* (**9**; 0·4 g), m.p. 137–138°. (Found: C, 65·2; H, 4·8; S, 6·7; OMe, 7·9. $C_{23}H_{20}O_6S$ requires: C, 65·1; H, 4·7; S, 7·5; OMe, 7·3%.) ν_{max} (KBr) 1623 cm^{-1}. **9** gave a yellow colour with $FeCl_3$ (EtOH) and formed a copper chelate.

Deformylation of desoxybenzoin **9**. A solution of desoxybenzoin (**9**; 0·2 g) in ethanolic KOH (2N; 25 ml) was heated under reflux for 2 h. The cooled mixture was acidified with dil. HCl and the EtOH removed under reduced pressure. The residual liquid was taken up in ether. The solid obtained on removal of the solvent from the dried ethereal solution crystallised from aq. EtOH as white plates of *2′-hydroxy-6′-methoxy-2-phenylacetophenone* (0·1 g), m.p. 71°. (Found: C, 74·8; H, 6·0; OMe, 11·5; $C_{15}H_{14}O_3$ requires: C, 74·4; H, 5·8; OMe, 12·8%). ν_{max} (KBr) 1615–1620 cm^{-1}. It gave a positive ethanolic $FeCl_3$ test.

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