242. *Synthetical Experiments in the* iso*Flavone Group. Part VI. The Reactions of some Keto-ethylene Oxides.*

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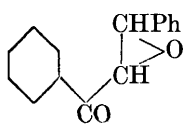
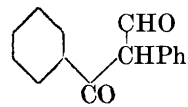
THE observation of Weitz and Scheffer (*Ber.*, 1921, **54**, 2344) that the keto-ethylene oxide (I) undergoes intramolecular change on treatment with sulphuric acid or hydrogen chloride in acetic acid at room temperatures to give formyldeoxybenzoin (II) suggested a possible convenient method of synthesis of *iso*flavones (III and derivatives), since a formyldeoxybenzoin with a hydroxyl group in the ortho-position to the carbonyl group would readily undergo ring-closure. Such a synthesis, if feasible, would be attractive in that it would relate the *iso*flavones to the chalkones (phenyl styryl ketones) from which the keto-ethylene oxides are obtained, and hence to the flavanones, flavones, flavonols, and anthocyanidins.



(I.)



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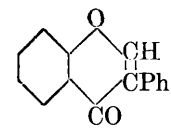


(III.)

A chalkone-oxide of the type (I) was first prepared by Widman (*Annalen*, 1913, **400**, 86) by the condensation of ω-chloroacetophenone and benzaldehyde in the presence of sodium ethoxide, the reaction being subsequently extended by him (*Ber.*, 1916, **49**, 477) and by Jörlander (*Ber.*, 1917, **50**, 406, 1457), and some of the properties of the products were investigated. Weitz and Scheffer (*loc. cit.*, p. 2327) later prepared the substances in a much simpler manner by direct oxidation of chalkones in aqueous-alcoholic alkaline solution by means of hydrogen peroxide.

2 : 4-Dimethoxyphenyl styryl ketone has now been oxidised by the method of Weitz and Scheffer to the corresponding oxide [IV; R = $C_6H_3(OMe)_2$] in excellent yield. When a suspension of (IV) in methyl alcohol was treated with a little concentrated

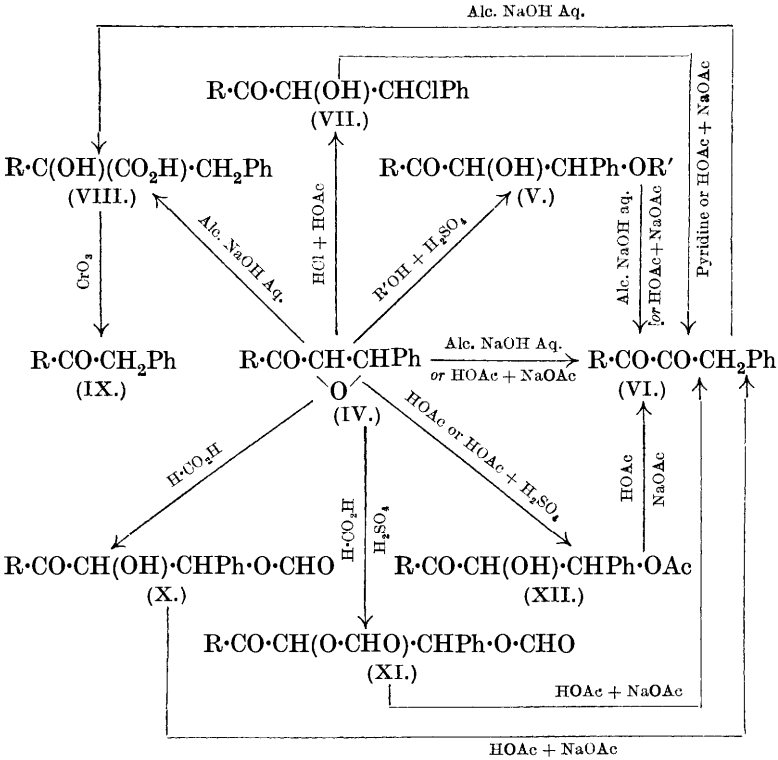
sulphuric acid, the oxide ring opened with production of 2 : 4-*dimethoxyphenyl* α-*hydroxy*-β-*methoxy*-β-*phenylethyl ketone* (V; R′ = Me); the corresponding 2 : 4-*dimethoxyphenyl* α-*hydroxy*-β-*ethoxy*-β-*phenylethyl ketone* (V; R′ = Et) was obtained similarly by the use of ethyl alcohol. These compounds, when boiled with acetic acid and sodium acetate for 2 hours or with aqueous-alcoholic sodium hydroxide for a few minutes, yielded 2 : 4-*dimethoxyphenyl benzyl diketone* (VI) (α-form, m. p. 71°), the constitution of which as an α-diketone was established by the formation of a *quinoxaline* on treatment with *o*-phenylenediamine. The production of this α-diketone also establishes the position of the alkoxy-groups in the compounds (V).

When the oxide (IV) was treated with hydrogen chloride in acetic acid, the ring opened to give 2 : 4-*dimethoxyphenyl* β-*chloro*-α-*hydroxy*-β-*phenylethyl ketone* (VII), which when boiled either with excess of pyridine or with acetic acid and sodium acetate gave the diketone (VI), thus proving that the chlorine atom is united to the β-carbon atom. Treatment of the oxide (IV) with boiling aqueous-alcoholic sodium hydroxide yielded a small amount of the diketone (VI), and a much larger amount of 2 : 4-*dimethoxyphenyl-benzylglycollic acid* (VIII), which is the sole product if the reaction is sufficiently prolonged. The constitution of the acid (VIII) follows from its ready oxidation by chromic acid in acetic acid to give 2 : 4-dimethoxyphenyl benzyl ketone (IX). The acid (VIII) was also prepared by boiling the diketone (VI) with aqueous-alcoholic sodium hydroxide. The facile conversion of phenyl benzyl diketone into phenylbenzylglycollic acid has been described by Malkin and Robinson (J., 1925, **127**, 369).

Simple solution of the oxide (IV) in anhydrous formic acid yielded 2 : 4-*dimethoxyphenyl* α-*hydroxy*-β-*formoxy*-β-*phenylethyl ketone* (X), the position of the formoxy-group being inferred from the structures assigned to the compounds (V) and (VII). The addition of a little concentrated sulphuric acid to the solution of (IV) in formic acid resulted in the esterification of the hydroxyl group with production of 2 : 4-*dimethoxyphenyl* αβ-*diformoxy*-β-*phenylethyl ketone* (XI). Treatment of the oxide (IV) in acetic acid with concentrated sulphuric acid, or with boiling acetic acid alone, gave 2 : 4-*dimethoxyphenyl* α-*hydroxy*-β-*acetoxy*-β-*phenylethyl ketone* (XII).

The compounds (X), (XI), and (XII) all yielded the α-diketone (VI) when boiled with acetic acid and sodium acetate, but in these experiments it was always obtained in the β-form, m. p. 86°. The α-diketone had previously been prepared as described in six different ways from compounds (IV), (V; R′ = Me), and (VII), and had always been obtained in the α-form, m. p. 71°, but after it had

been prepared from (X), (XI), and (XII) in the form of m. p. 86° repetition of the earlier experiments gave directly the higher-melting form. Further, a specimen of the α-form which had been kept for 8 weeks in a tube was found to have passed spontaneously into the β-form. This phenomenon is undoubtedly a case of dimorphism and not of keto-enol tautomerism, since neither form gives a ferric chloride reaction.



[R = 2 : 4-Dimethoxyphenyl]

The acyl derivatives (X), (XI), and (XII) when heated with aqueous sodium hydroxide are rapidly hydrolysed, probably first to the glycol, which is then decomposed into benzaldehyde and presumably ω-hydroxy-2 : 4-dimethoxyacetophenone (Slater and Stephen, J., 1920, **117**, 375), which is not stable towards hot alkaline solutions. This behaviour is in marked contrast to that exhibited by the ethers (V; R = Me and Et) and the chlorohydrin (VII) under similar conditions, which merely pass into the diketone (VI) without decomposition. This decomposition of the acyl derivatives of the glycol R·CO·CH(OH)·CHPh·OH appears to

resemble the production of methylglyoxal and then lactic acid from glucose by the action of alkalis.

A similar series of reactions was carried out with the *oxide* of 2 : 4-*dimethoxyphenyl* p-*methoxystyryl ketone*, and here also no migration of the anisyl group was observed under any conditions, apart from the benzil–benzilic acid transformation of the α-diketone into the glycollic acid derivative.

An interesting case of isomerism was encountered with the analogue of (VI), namely, 2 : 4-*dimethoxyphenyl* p-*methoxybenzyl diketone*, which was obtained from two reactions as a mixture of non-interconvertible forms (A) and (B), melting at 102° and 115° respectively, both of which gave the same *quinoxaline*. A mixture of (A) and (B) melted at a considerably lower temperature than either. Form (B) has a slightly deeper yellow colour than (A), and gives the more intense ferric chloride reaction. The substances are probably best regarded as the two possible stereoisomerides (*cis* and *trans*) of the enol form of the diketone, but it is not impossible that (B) is one of the enolic forms whilst (A) is the keto-form which, in alcoholic solution, is in equilibrium with the other enolic form. The tautomerism of phenyl benzyl diketone and phenyl *p*-methoxybenzyl diketone has been investigated by Moureu (Dufraisse and Moureu, *Bull. Soc. chim.*, 1927, **41**, 1607; Moureu, *Compt. rend.*, 1929, **188**, 504, 1557), who has isolated *cis*- and *trans*-enolic forms as well as the true diketone, but in these cases interconversion of the two enolic forms occurred above their melting points.

Attempts were made to oxidise 2-acetoxy-4-methoxyphenyl styryl ketone and 2 : 4-diacetoxyphenyl styryl ketone with hydrogen peroxide in aqueous-alcoholic solution, but even at 0° the reaction merely resulted in the hydrolysis of the acetoxy-groups. In order to avoid the use of alkali 2 : 4-dimethoxyphenyl styryl ketone and 2-acetoxy-4-methoxyphenyl styryl ketone were treated in ethereal or ethereal-acetone solution with perbenzoic acid, but in all cases the compounds were recovered unchanged (compare Weitz and Scheffer, *loc. cit.*, p. 2331).

The chief point of interest in this work in connexion with the synthesis of *iso*flavones is the simple method which it offers of preparing a large variety of deoxybenzoins, $R{\cdot}CO{\cdot}CH_2R'$, starting from acetophenones, $R{\cdot}CO{\cdot}CH_3$, and passing through the chalkones, the ethylene oxides, and the glycollic acid derivatives, the reactions being almost quantitative at each stage.

EXPERIMENTAL.

Oxide of 2 : 4-*Dimethoxyphenyl Styryl Ketone* [IV; $R=C_6H_3(OMe)_2$] A solution of 2 : 4-dimethoxyphenyl styryl ketone (21·6 g.) in hot

methyl alcohol (280 c.c.) was cooled to 25° without disturbance, and to the supersaturated solution was quickly added 15% hydrogen peroxide (24 c.c.) and then 2*N*-sodium hydroxide (20 c.c.). The partly separating chalkone dissolved on gentle agitation during 4 minutes, the temperature rising to 36°, and colourless, nacreous, flat prisms then formed; they were washed with cold methyl alcohol and dried (yield, 20 g.); m. p. 118°, unaltered by recrystallisation from methyl alcohol (Found : C, 72·1; H, 5·7. Calc. for $C_{17}H_{16}O_4$: C, 71·8; H, 5·6%). Jörlander (*loc. cit.*) describes the compound as colourless prisms, m. p. 116°, from alcohol.

2 : 4-*Dimethoxyphenyl* α-*Hydroxy*-β-*methoxy*-β-*phenylethyl Ketone* (V; R′ = Me).—A suspension of the preceding oxide (4 g.) in methyl alcohol (20 c.c.) was shaken with a mixture of methyl alcohol (20 c.c.) and concentrated sulphuric acid (5 c.c.), and the pale yellow solution obtained was warmed to 40°; on cooling, colourless prisms separated. Water (75 c.c.) was now slowly added with stirring; the *ketone*, after being washed with cold water, then with a little cold methyl alcohol and dried at a moderate temperature (yield, 3 g.), crystallised from methyl alcohol in compact, obliquely truncated prisms, m. p. 133° (Found : C, 68·2; H, 5·7. $C_{18}H_{20}O_5$ requires C, 68·4; H, 6·3%). The substance slowly reduces Fehling's solution, is unaltered by boiling with methyl-alcoholic sulphuric acid (6 : 1) for 1 hour, and, like the following ethoxy-compound, dissolves in concentrated sulphuric acid with a yellow colour which quickly becomes more orange.

2 : 4-*Dimethoxyphenyl* α-*hydroxy*-β-*ethoxy*-β-*phenylethyl ketone* (V; R′ = Et), prepared similarly, crystallised from alcohol in small colourless prisms, m. p. 98° (Found : C, 69·1; H, 6·6. $C_{19}H_{22}O_5$ requires C, 69·1; H, 6·7%).

2 : 4-*Dimethoxyphenyl Benzyl Diketone* (VI).—α-*Form*. The methoxy-compound (V; R′ = Me) (1 g.) was boiled for 2 hours with acetic acid (10 c.c.) and sodium acetate (2 g.); the *product*, precipitated by addition of water, crystallised from alcohol in faintly yellow, compact prisms, m. p. 71° (Found : C, 72·1; H, 5·7. $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·6%). The same product was obtained when compound (V; R′ = Me) was boiled in alcoholic solution for 2—3 minutes with a few drops of aqueous sodium hydroxide, the orange solution diluted with water, and the precipitate crystallised from alcohol. The substance gives no coloration with alcoholic ferric chloride, but dissolves in hot dilute aqueous sodium hydroxide with a yellow colour. Its reaction towards concentrated sulphuric acid is similar to that given by compound (V; R′ = Me). In presence of alcohol it readily reduces warm Fehling's solution.

β-*Form.* The compounds (X), (XI), and (XII) (described below) and the oxide (IV) were each (1 part) boiled for 2 hours with acetic acid (5 parts) and anhydrous sodium acetate (2 parts). Addition of water gave products which crystallised from alcohol (charcoal) in very light yellow, flat, bipyramidal crystals, m. p. 86° (Found: C, 72·0; H, 5·7. $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·6%). The substance showed no depression in melting point in intimate mixture with a specimen of the diketone (VI) which originally melted at 71° but whose melting point had risen to 86° on keeping.

2-(2′ : 4′-*Dimethoxyphenyl*)-3-*benzylquinoxaline.*—The preceding compound (0·71 g.) in alcohol (5 c.c.) was heated for a few minutes with *o*-phenylenediamine (0·27 g.). The *product* which separated on cooling, crystallised from alcohol in colourless prisms, m. p. 108—109° (Found: N, 7·9. $C_{23}H_{20}O_2N_2$ requires N, 7·9%). It dissolved in concentrated sulphuric acid with an intense maroon colour which soon became more brown and finally bright orange-red.

2 : 4-*Dimethoxyphenyl* β-*Chloro*-α-*hydroxy*-β-*phenylethyl Ketone* (VII).—The cherry-red solution obtained by passing hydrogen chloride into a suspension of the oxide (IV) (2 g.) in acetic acid (20 c.c.) cooled in water was diluted with water (75 c.c.) after 5 minutes; the precipitated *chlorohydrin*, after being washed with water, crystallised from methyl alcohol, in which it was rather sparingly soluble, in colourless, highly refracting prisms (1·3 g.), m. p. 131° (Found: Cl, 10·8. $C_{17}H_{17}O_4Cl$ requires Cl, 11·1%).

2 : 4-*Dimethoxyphenylbenzylglycollic Acid* (VIII).—The oxide (IV) (2 g.) in alcohol (20 c.c.) was boiled for 2 hours with sodium hydroxide (1 g.) in water (4 c.c.). The orange solution was diluted with water, saturated with carbon dioxide, and extracted with ether [the extracts yielded a small amount of the diketone (VI), m. p. after recrystallisation, 71°]. The aqueous layer was acidified, and the solid (1·1 g.) recrystallised from dilute acetic acid, forming prismatic needles, m. p. 176° (efferv.) (Found: C, 66·8; H, 5·9. $C_{17}H_{18}O_5$ requires C, 67·2; H, 6·0%). The solution in concentrated sulphuric acid is yellow.

This *acid* was also obtained from the diketone (VI) (0·5 g.) by boiling with alcohol (10 c.c.) and sodium hydroxide (0·5 g.) in water (2 c.c.) for 2 hours, and isolated in the above manner.

2 : 4-*Dimethoxyphenyl Benzyl Ketone* (IX).—The preceding acid in warm acetic acid was treated with chromic acid (1·5 times the theoretical quantity) in acetic acid and after 1 minute the solution was diluted with water. Ether then extracted 2 : 4-dimethoxyphenyl benzyl ketone, m. p. (after purification) and mixed m. p. 56°.

2 : 4-*Dimethoxyphenyl* α-*Hydroxy*-β-*formoxy*-β-*phenylethyl Ketone* (X).—The oxide (IV) (5 g.) was treated with anhydrous formic acid (25 c.c.) and after 2 hours addition of water to the solution precipitated a dark green, sticky mass which subsequently solidified and a smell of phenylacetaldehyde was apparent. The *product*, crystallised twice from alcohol (charcoal), formed colourless prisms (1·4 g.), which after further crystallisation from acetic acid separated in almost rectangular plates or prisms, m. p. 154° (Found : C, 65·1; H, 5·5. $C_{18}H_{18}O_6$ requires C, 65·4; H, 5·5%). Its alcoholic solution gave no coloration with ferric chloride, but readily reduced warm Fehling's solution. The compound is decomposed by hot aqueous sodium hydroxide, benzaldehyde being evolved. Its orange-red solution in concentrated sulphuric acid darkens and evolves carbon monoxide when very gently warmed.

2 : 4-*Dimethoxyphenyl* αβ-*Diformoxy*-β-*phenylethyl Ketone* (XI).—The oxide (IV) (5 g.) in formic acid (50 c.c.) was treated with a mixture of formic acid (4 c.c.) and concentrated sulphuric acid (1 c.c.), giving a brown solution. After 2 hours addition of water gave a black tarry matter, which was washed and dissolved in alcohol; the crystalline *product*, recrystallised twice from alcohol (charcoal), gave pale yellowish-brown plates (1·6 g.), m. p. 141° (Found : C, 63·4; H, 5·1. $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·1%). In its chemical properties it resembles the preceding compound.

2 : 4-*Dimethoxyphenyl* α-*hydroxy*-β-*acetoxy*-β-*phenylethyl ketone* (XII), obtained when acetic acid replaced formic acid in the preceding preparation, and repeatedly purified from alcohol (charcoal), formed colourless compact crystals, m. p. 136° (Found : C, 64·3; H, 6·3. $C_{19}H_{20}O_6,C_2H_5{\cdot}OH$ requires C, 64·6; H, 6·7%. Found in material heated for 2 hours at 100° in a vacuum : C, 66·4; H, 5·8. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·8%). In its behaviour towards ferric chloride, alkalis, and Fehling's solution it resembles the two preceding compounds; its yellow solution in concentrated sulphuric acid slowly becomes orange and evolves no carbon monoxide on warming.

Oxide of 2 : 4-*Dimethoxyphenyl* p-*Methoxystyryl Ketone*.—This compound was prepared in the same way as the corresponding oxide (IV). The yield was 19 g., and a further small quantity was obtained by diluting the alcoholic liquors. It separated in nacreous irregular growths of fine prisms, m. p. 108° (Found : C, 68·9; H, 5·5. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·7%).

2 : 4-*Dimethoxyphenyl* α-*hydroxy*-β-*methoxy*-β-p-*methoxyphenylethyl ketone* was prepared in the same way as the corresponding compound (V, R′ = Me), but with 1½ times the quantity of methyl alcohol and warming to 60°. It separated from alcohol in minute colourless

crystals, m. p. 143—144° (Found: C, 66·0; H, 6·3. $C_{19}H_{22}O_6$ requires C, 65·9; H, 6·3%). When it was boiled for 5 minutes in alcoholic solution with a little aqueous sodium hydroxide, and the yellow solution diluted and saturated with carbon dioxide, a solid separated which crystallised from alcohol as a mixture of very pale yellow leaflets, m. p. 102°, and yellow prismatic needles, m. p. 115°, identical with the (A) and the (B) form of 2 : 4-*dimethoxyphenyl* p-*methoxybenzyl diketone* described below.

2 : 4-*Dimethoxyphenyl*-p-*methoxybenzylglycollic acid* was prepared in the same way as the corresponding acid (VIII) but with double quantities. It was precipitated (1·4 g.) in colourless crystals, which separated from dilute acetic acid in microscopic prisms, m. p. 177° (efferv.) (Found: C, 65·1; H, 5·9. $C_{18}H_{20}O_6$ requires C, 65·1; H, 6·0%).

Enolic Forms of 2 : 4-*Dimethoxyphenyl* p-*Methoxybenzyl Diketone.*—The ethereal extracts of the solution saturated with carbon dioxide from the previous preparation (see preparation of VIII) yielded an oil which rapidly solidified and was then crystallised from alcohol (yield, 1·6 g.). A second crystallisation yielded pale yellow leaflets (A); the decanted solution deposited small yellow prisms (B).

Substance (A), m. p. 102° (Found: C, 68·8; H, 5·7. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·7%), gave a weak brownish colour with alcoholic ferric chloride, dissolved readily in hot dilute aqueous sodium hydroxide to a yellow solution, but was scarcely soluble in cold alkalis. Heated with *o*-phenylenediamine (1 mol.) in alcohol, it gave 2-(2′ : 4′-*dimethoxyphenyl*)-3-p-*methoxybenzylquinoxaline*, which crystallised from alcohol in compact prisms, m. p. 76—79° (Found: N, 7·5. $C_{24}H_{22}O_3N_2$ requires N, 7·3%).

Substance (B), recrystallised from alcohol, formed somewhat bright yellow, prismatic needles, m. p. 115° with slight previous softening (Found: C, 68·9; H, 5·3. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·7%). It gave a *quinoxaline*, m. p. 75—78°, identical (mixed m. p.) with that prepared from (A), both forming in concentrated sulphuric acid deep maroon solutions which soon turned brown and then cherry-red.

The bright orange-red solutions of (A) and (B) in concentrated sulphuric acid were indistinguishable, but the ferric chloride reaction of (B) was rather more red and intense than that of (A). A mixture of (A) and (B) melted between 90° and 100°.

2 : 4-*Dimethoxyphenyl* p-*Methoxybenzyl Ketone.*—2 : 4-Dimethoxyphenyl-*p*-methoxybenzylglycollic acid was oxidised by chromic acid in acetic acid as described in the preparation of 2 : 4-dimethoxyphenyl benzyl ketone (IX). The solid neutral product separated

from alcohol in colourless thin prisms, m. p. 84°, not depressed on admixture with a specimen of the same compound prepared by the method described below.

2 : 4-Dihydroxyphenyl *p*-methoxybenzyl ketone (Baker and Eastwood, J., 1929, 2902; this ketone, ononetin, has since been obtained by degradation of the glucoside ononin of *Ononis spinosa* by Wessely and Lechner, *Monatsh.*, 1931, **57**, 395, who also synthesised it by the method previously employed by Baker and Eastwood) was treated with excess of methyl sulphate and alkali, and yielded a non-phenolic product, which, after crystallisation from ethyl alcohol and then from methyl alcohol, melted at 84° (Found : C, 71·0; H, 6·2. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%).

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