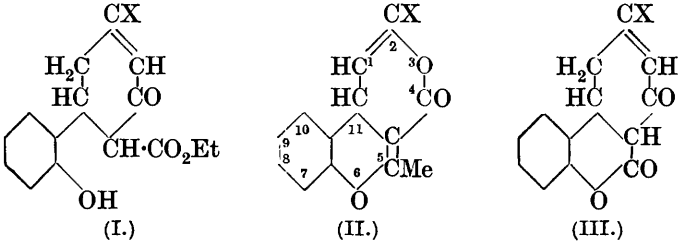
CXXXII.—*The Interaction of Ethyl Acetoacetate with Distyryl Ketones. Part III.* o-*Hydroxychlorodistyryl Ketones.*

By Isidor Morris Heilbron and Rowland Hill.

Experiments carried out by one of us (J., 1924, **125**, 2064; 1925, **127**, 2159) showed that ethyl acetoacetate reacted with *o*-hydroxydistyryl ketones to give *cyclo*hexenones and that the position taken up by the entering group could be determined by the fact that, when the β-ketonic ester attached itself to the styryl residue adjacent to the *o*-hydroxyl, the carbethoxy-group was eliminated, possibly owing to intermediate coumarin formation. The interactions of ethyl acetoacetate with *2′-chloro-2-hydroxydistyryl ketone* and with the *3′-* and *4′-chloro-isomerides* have now been investigated, and the results show that the previous deductions are by no means general. In each case, two products were isolated, a *cyclo*hexenone of molecular formula $C_{23}H_{21}O_4Cl$, and a very small quantity of a second substance of empirical formula $C_{21}H_{15}O_3Cl$, the yield of which decreases progressively as the chlorine atom passes from the ortho- to the para-position. Oxidation of the former by means of potassium permanganate in acetone solution gave the corresponding *o-*, *m-*, or *p*-chlorobenzoic acid, proving that, despite the presence of the carbethoxy-group, addition had taken place at the ethenoid linking adjacent to the *o*-hydroxy-group and consequently the *cyclo*hexenones must be formulated as (I).

The isomeric substances $C_{21}H_{15}O_3Cl$ may be represented either as *2-chlorostyryl-5-methyl-3 : 4-coumalo-6-benzopyrans* (II), or as chlorostyryldihydrocoumarino*cyclo*hexenones (III), resulting through the elimination of a molecule of alcohol from the corresponding *cyclo*hexenones (I). If the latter formulation be correct, it is reasonable to expect that the conversion of the *cyclo*hexenones

into (III) should be possible, but this we have failed to bring about under any of the conditions usually employed for effecting such



(I.) (II.) (III.)

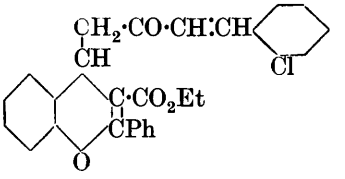
(X = *o*-, *m*-, or *p*-C_6H_4Cl·CH:CH.)

ring closures. Conversely, attempts to open the supposed dihydrocoumarin ring with formation of the free *cyclo*hexenones have been equally unsuccessful. It would thus seem that these substances cannot be dihydrocoumarino*cyclo*hexenones, and this view is supported by the fact that they fail to give the blood-red coloration with concentrated sulphuric acid characteristic of *cyclo*hexenones of this type (Borsche, *Annalen*, 1910, **375**, 145). They must consequently be formulated in accordance with (II), a type of ring formation reminiscent of that observed by Vorländer (*Annalen*, 1906, **345**, 155) and more recently by Kon and Nutland (J., 1926, 3101), who found that pulegone and *iso*pulegone reacted abnormally with ethyl sodiocyanoacetate, yielding, in place of the expected cyano-esters, the unsaturated cyano-lactones. In order more fully to test this point, 2′-chloro-2-hydroxydistyryl ketone was condensed with benzoylacetic ester. In this case, *cyclo*hexenone formation is precluded, and consequently, if our contentions are correct, a benzopyran and not a dihydrocoumarin derivative should be formed. The product actually isolated proved to be *ethyl* 4-o-*chlorostyracyl*-2-*phenyl*-1 : 4-*benzopyran*-3-*carboxylate* (IV), no trace of a dihydrocoumarin being obtained. The non-isolation of the corresponding coumalobenzopyran may possibly have been due to experimental difficulties, since the semi-solid fraction first deposited resisted all attempts at purification.

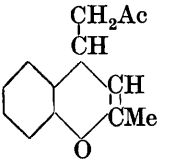
In the case of the *o*-hydroxymonostyryl ketones, the β-ketonic ester must of necessity condense adjacent to the hydroxyl group. Forster and Heilbron have already shown (J., 1924, **125**, 340) that the condensation of 2-hydroxystyryl methyl ketone with ethyl acetoacetate leads to 4-acetonyl-2-methyl-1 : 4-benzopyran (V), and a similar type of reaction occurs between 2-hydroxystyryl phenyl ketone and benzoylacetic ester. With 2-hydroxystyryl phenyl ketone, however, these authors state that the reaction leads, in very poor yield, to 3-acetyl-4-phenacyldihydrocoumarin (VI) together

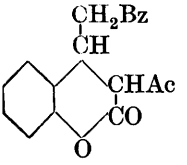
with a solid, m. p. 214°, to which no definite structure was assigned. This reaction has again been investigated under various conditions, but no trace of (VI) has been obtained, 4-*phenacyl*-2-*methyl*-1 : 4-*benzopyran* (VII) being isolated in good yield together with a minute quantity of the substance melting at 214°.

(IV.)

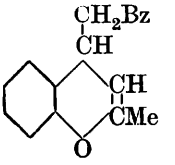


(V.)

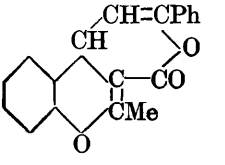




(VI.)



(VII.)



(VIII.)

The constitution of the pyran has been definitely settled by the fact that the condensation of acetylacetone and 2-hydroxystyryl phenyl ketone yields the same product, for which the pyran formula alone is possible. Analysis of the substance, m. p. 214°, indicates that its structure corresponds to 2-*phenyl*-5-*methyl*-3 : 4-*coumalo*-6-*benzopyran* (VIII), a result in complete harmony with the preceding observations.

An interesting point emerging from this investigation is the fact that, independent of the position of the chlorine atom, the ethyl acetoacetate enters the molecule of the chlorohydroxy-ketone adjacent to the hydroxyl, thus showing that the polar influence of this group completely overweighs that of the halogen substituent, independent of its position in the other styryl residue. The same holds for the *o*-methoxy-ketone, for from 4′-chloro-2-methoxydistyryl ketone ethyl 3-*o*-methoxyphenyl-5-*p*-chlorostyryl-Δ^5-*cyclo*hexen-1-one-2-carboxylate was formed, identical with the methyl ether prepared by direct methylation of the *cyclo*hexenone obtained from 4′-chloro-2-hydroxydistyryl ketone.

Experimental.

2′-Chloro-2-hydroxydistyryl Ketone.—2-Hydroxystyryl methyl ketone (30 g.) and *o*-chlorobenzaldehyde (30 g.) dissolved in aqueous sodium hydroxide (120 c.c. of 10%), heat being developed and a clear red solution produced. This was cooled, and a further 120 c.c. of alkali slowly added with constant stirring. After 15 hours, the

sodium salt of the distyryl ketone, which had separated in red, iridescent crystals, was dissolved in warm water, and the ketone liberated as a flocculent, yellow precipitate by carbon dioxide. *2′-Chloro-2-hydroxydistyryl ketone* crystallised from benzene after treatment with blood charcoal in light yellow needles, m. p. 153° (decomp. to a dark green liquid) (yield, 33 g.). It dissolved in aqueous alkali and in concentrated sulphuric acid to blood-red solutions. In place of the yellow form, the ketone was sometimes obtained as bright green plates (Found : C, 71·6; H, 4·6. $C_{17}H_{13}O_2Cl$ requires C, 71·7; H, 4·6%).

2-o-*Chlorostyryl*-5-*methyl*-3 : 4-*coumalo*-6-*benzopyran* (II).—A mixture of 2′-chloro-2-hydroxydistyryl ketone (20 g.), absolute alcohol (500 c.c.), ethyl acetoacetate (18 c.c.), and aqueous sodium hydroxide (40 c.c. of 20%) was left for 4 days at room temperature, and the orange-red deposit was then collected and repeatedly washed with dilute warm hydrochloric acid and with water. The dried product was crystallised from ethyl acetoacetate and again from much absolute alcohol, from which it separated in long, slender, orange-yellow needles, m. p. 183° (yield, 3·5 g.), sparingly soluble in the usual organic solvents. It dissolved slowly to an orange solution on being warmed with aqueous or alcoholic sodium hydroxide, and in concentrated sulphuric acid it gave an orange-red coloration (Found : C, 71·6, 71·8; H, 4·2, 4·4; Cl, 9·9, 9·9. $C_{21}H_{15}O_3Cl$ requires C, 71·9; H, 4·3; Cl, 10·1%). On boiling under reflux with alcoholic sodium ethoxide, the substance gradually dissolved; acidification then precipitated a solid, which was separated by means of ethyl acetate into two compounds, m. p. 121—122° and 211°, neither of which gave the analytical values required for a *cyclo*hexenone or a pyran derivative. The quantities of these solids were too small to allow of more detailed investigation.

Ethyl 3-o-*hydroxyphenyl*-5-o-*chlorostyryl*-Δ^5-cyclo*hexen*-1-*one*-2-*carboxylate* (I) was obtained, as a yellow, gummy mass which slowly hardened, by acidifying the filtrate of the above reaction mixture with dilute hydrochloric acid. After being washed, dried, and repeatedly crystallised from benzene in presence of animal charcoal, it was obtained in minute, yellow needles, m. p. 177—178° (yield, 7·5 g.). It was moderately easily soluble in the usual organic solvents and readily soluble in aqueous alkali and gave an intense red coloration with concentrated sulphuric acid (Found : C, 69·3; H, 5·4. $C_{23}H_{21}O_4Cl$ requires C, 69·6; H, 5·3%). Attempts to convert this *cyclo*hexenone into the corresponding dihydrocoumarino*cyclo*hexenone (III) by treatment with aqueous or alcoholic sodium hydroxide, by the use of sodium in xylene and by other means were unsuccessful.

Oxidation.—The hydroxy-*cyclo*hexenone (I) (1 g.), dissolved in acetone (75 c.c.), was treated with potassium permanganate in small quantities; *o*-chlorobenzoic acid, m. p. 134—135°, was isolated from the reaction mixture.

3-o-*Hydroxyphenyl*-5-o-*chlorostyryl*-Δ^5-cyclo*hexen*-1-*one.*—The ester (I) (1 g.) was dissolved in glacial acetic acid (20 c.c.) and boiled for 2 hours with sulphuric acid (10 c.c. of 20%). The resultant deep red liquid was poured on a mixture of ice and water, and the precipitated *cyclo*hexenone repeatedly crystallised from ethyl acetate, from which it separated in clusters of yellow plates, m. p. 209—210° (Found: C, 73·8; H, 5·4. $C_{20}H_{17}O_2Cl$ requires C, 74·0; H, 5·2%).

3′-*Chloro*-2-*hydroxydistyryl Ketone.*—The preparation was similar to that of the isomeric 2′-chloro-compound. The sodium salt separated completely, after 15 hours, in black plates with a brilliant green reflex. The *ketone* crystallised from benzene in golden-yellow plates (yield, 72%), m. p. 142—143° (decomp. to a dark green liquid) (Found: C, 71·6; H, 4·6%). This compound also exists in a green modification.

2-m-*Chlorostyryl*-5-*methyl*-3 : 4-*coumalo*-6-*benzopyran*, after preliminary purification from ethyl acetoacetate, crystallised from absolute alcohol in aggregates of orange-red needles, m. p. 170°, which are sparingly soluble in the ordinary organic solvents (yield, 8%) (Found: C, 71·5; H, 4·4%).

Ethyl 3-o-*hydroxyphenyl*-5-m-*chlorostyryl*-Δ^5-cyclo*hexen*-1-*one*-2-*carboxylate* was obtained from the filtrate and separated from benzene in small, yellow cubes (yield, 30%), m. p. 169° (Found: C, 69·5; H, 5·5%). Oxidation with potassium permanganate in cold acetone solution yielded *m*-chlorobenzoic acid, m. p. 148—149°. 3-o-*Hydroxyphenyl*-5-m-*chlorostyryl*-Δ^5-cyclo*hexen*-1-*one* crystallised from ethyl acetate in bright yellow rhombs, m. p. 221° (Found: C, 73·7; H, 5·5%).

4′-*Chloro*-2-*hydroxydistyryl ketone* crystallised from benzene, after treatment with charcoal, in pale yellow plates (yield, 67%), m. p. 152° (decomp. to a dark green liquid) (Found: C, 71·8; H, 4·8%).

2-p-*Chlorostyryl*-5-*methyl*-3 : 4-*coumalo*-6-*benzopyran* crystallised with difficulty from ethyl acetoacetate in clusters of cream-coloured needles (yield, 1%), m. p. 261—262° (Found: C, 72·1; H, 4·1%). It dissolves in concentrated sulphuric acid to an orange-red solution and is very sparingly soluble in the usual organic solvents.

From the filtrate from which the above compound was separated, *ethyl* 3-o-*hydroxyphenyl*-5-p-*chlorostyryl*-Δ^5-cyclo*hexen*-1-*one*-2-*carboxylate* was obtained as a brown gum on rendering the solution acid. It was repeatedly crystallised from benzene and from ethyl

acetate–light petroleum and was thus obtained in large, golden-yellow plates (yield, 33%), m. p. 199—200° (Found: C, 69·7; H, 5·5%). On oxidation with potassium permanganate in acetone solution it gave *p*-chlorobenzoic acid, m. p. 237°. Methylation with methyl sulphate in acetone solution yielded the methyl ether (m. p. 160°) identical with that obtained by the direct condensation of 4′-chloro-2-methoxydistyryl ketone with ethyl acetoacetate.

3-o-*Hydroxyphenyl*-5-p-*chlorostyryl*-Δ^5-cyclo*hexen*-1-*one* was readily obtained by hydrolysing the above ester with 20% sulphuric acid in acetic acid solution. It separated from ethyl acetate in yellow prisms, m. p. 176° (Found: C, 74·3; H, 5·2%).

4′-*Chloro*-2-*methoxydistyryl Ketone*.—The dry sodium salt of 4′-chloro-2-hydroxydistyryl ketone, prepared by condensation as already described, was dissolved in acetone and heated with a slight excess of methyl iodide under reflux for 1 hour. After removal of sodium iodide, the reaction mixture was diluted with water; the yellow oil that separated solidified on being scratched and then crystallised from aqueous acetone in slender, yellow needles, m. p. 74—75° (yield from sodium salt, 92%) (Found: C, 72·5; H, 5·2. $C_{18}H_{15}O_2Cl$ requires C, 72·4; H, 5·0%).

Ethyl 3-o-*Methoxyphenyl*-5-p-*chlorostyryl*-Δ^5-cyclo*hexen*-1-*one*-2-*carboxylate*.—The above ketone (5 g.) was dissolved in absolute alcohol (40 c.c.) and refluxed for 3 hours on a water-bath with ethyl acetoacetate (3 g.) and alcoholic sodium ethoxide (1·6 g.). The hot solution, which was filtered from a small quantity of sodium carbonate, deposited, on cooling, an orange-yellow solid; this was crystallised from methyl alcohol, the cyclo*hexenone* (4 g.) being obtained in small, yellow, rhombohedral plates, m. p. 160° (Found: C, 69·8; H, 5·7. $C_{24}H_{23}O_4Cl$ requires C, 70·2; H, 5·6%). The solution in concentrated sulphuric acid is carmine-red.

Ethyl 4-o-*Chlorostyracyl*-2-*phenyl*-1 : 4-*benzopyran*-3-*carboxylate* (IV).—A hot solution containing 2′-chloro-2-hydroxydistyryl ketone (10 g.), ethyl benzoylacetate (9 g.), and alcohol (50 c.c.) was treated with sodium ethoxide solution (1·7 g. of Na), and the whole left at room temperature for 60 hours. The reaction mixture was then diluted with water and separated from a small quantity of a dark-coloured oil, which gradually solidified but resisted subsequent efforts at purification. The filtrate was diluted to 2000 c.c. and mechanically stirred for several days. On addition of sodium chloride (100 g.), a yellow solid was precipitated which, when crystallised repeatedly from absolute alcohol, separated in colourless needles, m. p. 144—145°. These contain half a mol. of alcohol of crystallisation, which is removed on heating for 5 hours at 110°; the anhydrous compound melts at 195°. The substance slowly

dissolves on warming with aqueous sodium hydroxide and gives a yellow solution with concentrated sulphuric acid (Found : C, 73·0; H, 5·2. $C_{28}H_{23}O_4Cl$ requires C, 73·3; H, 5·0%).

2-*Phenyl*-5-*methyl*-3 : 4-*coumalo*-6-*benzopyran* (VIII).—A mixture of 2-hydroxystyryl phenyl ketone (11 g.), ethyl acetoacetate (6·5 c.c.), and alcohol (100 c.c.) was treated with alcoholic sodium ethoxide (2·5 g. of Na), and the red solution kept for 18 hours at room temperature. The small quantity of brown solid which separated on dilution with water was repeatedly crystallised from benzene in presence of blood charcoal. The pure substance was thus obtained, in very small yield, in colourless needles, m. p. 214° (Found : C, 78·9; H, 4·6. Calc. for $C_{19}H_{14}O_3$: C, 78·6; H, 4·8%). These figures agree well with those given by Forster and Heilbron (*loc. cit.*, p. 345).

4-*Phenacyl*-2-*methyl*-1 : 4-*benzopyran* (VII) was precipitated from the filtrate of the above reaction mixture on addition of dilute hydrochloric acid. The brown, gummy mass was allowed to harden and repeatedly crystallised from absolute alcohol in the presence of blood charcoal. The *pyran* forms colourless plates, m. p. 171°, which are moderately easily soluble in alcohol, insoluble in cold aqueous alkali, but readily soluble in the hot solution (Found : C, 81·5; H, 6·0. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%).

Condensation of Acetylacetone with 2-*Hydroxystyryl Phenyl Ketone.*—A boiling solution of 2-hydroxystyryl phenyl ketone (7·5 g.) in alcohol (30 c.c.) and aqueous sodium hydroxide (7·5 c.c. of 40%) was treated with acetylacetone (6 g.) and refluxed for 30 minutes; a further quantity of acetylacetone (6 g.) was then added. After 1 hour, a small quantity of inorganic matter was removed, and the clear solution, on cooling, deposited a mass of yellow needles; a further quantity was obtained by diluting the filtrate. The combined fractions crystallised from alcohol in large, colourless plates, m. p. 169—170°. A mixed melting point with 4-phenacyl-2-methyl-1 : 4-benzopyran, prepared as described above, showed no depression.

We desire to express our thanks to the United Alkali Co., Ltd., for a grant to one of us (R. H.) which enabled this research to be carried out.

THE UNIVERSITY, LIVERPOOL. [*Received, March 9th,* 1927.]