CCCLXXIX.—*The Interaction of Ethyl Acetoacetate with Distyryl Ketones. Part IV. Selective Addition to Unsymmetrical Chlorodistyryl Ketones.*

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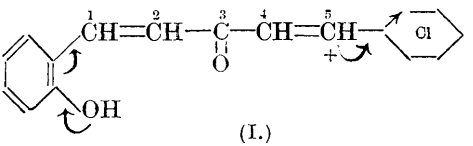
It was shown in Part III (Heilbron and Hill, J., 1927, 918) that when ethyl acetoacetate was condensed with *o*-hydroxychlorodistyryl ketones, the ester invariably attached itself to the ethenoid linkage adjacent to the *o*-hydroxyl, irrespective of the position of the chlorine atom in the opposing styryl residue. These results were unexpected, as in ketones of this type the double bond vicinal to the chlorine-containing styryl residue must, if direct addition occurs, be the more reactive owing to the development of a positive charge at C_5 (I) due to the capacity of the chlorine atom to act as an attractor for electrons.



(I.)

The addition of ethyl acetoacetate to the three isomeric *monochlorodistyryl ketones* and also to 2 : 3′-, 2 : 4′-, and 3 : 4′-*dichlorodistyryl ketones* has now been studied in the hope of arriving at some general idea of the effect of the position of the halogen atom upon the activation of the ethenoid linkages in a series of compounds free from the possible disturbing influence of an ortho-hydroxyl group.

The preparation of the monochlorodistyryl ketones was a matter

of considerable difficulty owing to the ease with which styryl methyl ketone condensed with the chloroaldehydes, giving high-melting, amorphous polymerisation products in presence of alcoholic sodium ethoxide. The desired results were ultimately attained by employing very low concentrations of alkali, as recorded in the following table :

		Alkali concentration (NaOEt),				
Ketone.	Aldehyde.	1—3 mols.	0·5 mol.	0·1 mol.	0·02—0·03 mol.	0·01 mol.
Methyl styryl ketone	*o*-Chlorobenzaldehyde	Amorphous solids	Oils	Oil	Ketone	Aldol
,,	*m*- ,,	,,	,,	,,	,,	Ketone
,,	*p*- ,,	,,	Ketone	Aldol	Aldol	Aldol

In all cases the aldols could be quantitatively converted into the distyryl ketones on treatment with boiling acetic anhydride.

It was found impossible to obtain the dichlorodistyryl ketones by alkali condensations owing to the extraordinarily easy fission of the monochlorostyryl methyl ketones in presence of alkali. For instance, 2-chlorostyryl methyl ketone and *m*-chlorobenzaldehyde reacted in presence of 0·05 mol. of aqueous alkali, yielding, not the anticipated 2 : 3′-dichlorodistyryl ketone, but the symmetrical 2 : 2′-dichloro-isomeride, a reaction obviously due to fission of the reacting monostyryl ketone (compare Heilbron and Buck, J., 1921, **119**, 1500). The desired compounds were all obtained as crystalline halochromic salts by condensation in presence of dry hydrogen chloride at 0°.

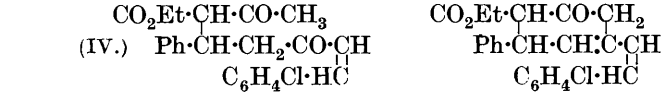
The addition of ethyl acetoacetate to the distyryl ketones offered no special difficulties when the reactants were condensed in presence of alcoholic sodium ethoxide (0·1 mol.). The *cyclo*hexenones were readily obtained in crystalline form. Only one product was isolated in every case except 2-chlorodistyryl ketone, which gave two isomeric *cyclo*hexenones (m. p. 137° and 109°), $C_{23}H_{21}O_3Cl$. These two compounds had not resulted by addition of the ester to both the ethenoid linkages yielding *ethyl 3-phenyl-5-o-chlorostyryl-*Δ^5*-cyclohexen-1-one-2-carboxylate* (II) and ethyl 3-*o*-chlorophenyl-5-styryl-Δ^5-*cyclo*hexen-1-one-2-carboxylate (III), for on oxidation both

(II.) $CO_2Et\cdot CH\cdot CO{-}CH$ / $Ph\cdot CH\cdot CH_2\cdot C\cdot CH$ / $C_6H_4Cl\cdot HC$

(III.) $CO_2Et\cdot CH\cdot CO{-}CH$ / $C_6H_4Cl\cdot CH\cdot CH_2\cdot C\cdot CH$ / $PhHC$

isomerides yielded *o*-chlorobenzoic acid without any trace of benzoic acid. The compounds may possibly be position isomerides. Of these, the higher-melting *cyclo*hexenone has probably the formula ascribed (II), since treatment of *ethyl* (*γ-keto-α-phenyl-ε-2-chlorophenyl-*Δ^δ*-pentenyl*)*acetoacetate* (IV) with sodium ethoxide readily

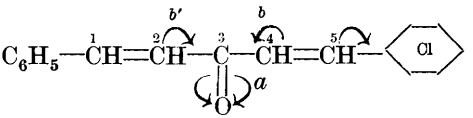
yields this product. On the other hand, the lower-melting isomeride, which is obtained only in poor yield, may be formed from the enolic form of (IV)—a reaction which is reminiscent of the coumalobenzopyran formation (Heilbron and Hill, *loc. cit.*); subsequent loss of water would then yield *ethyl* 3-*phenyl*-5-o-*chlorostyryl*-Δ^4-cyclo*hexen*-1-*one*-2-*carboxylate* (V). Alternatively, it is equally possible that the two compounds are stereoisomerides.



None of the *cyclo*hexenones described in this communication produces the blood-red coloration with concentrated sulphuric acid originally observed by Borsche (*Annalen*, 1910, **375**, 145) and considered indicative of *cyclo*hexenones of this type.

The constitutions of the *cyclo*hexenones were determined by oxidation with potassium permanganate in acetone solution (Heilbron and Hill, *loc. cit.*). Each mono-substituted *cyclo*hexenone yielded the corresponding chlorobenzoic acid, and the fact was thus established that, irrespective of the position of the chlorine atom, the ethyl acetoacetate enters the molecule at the ethenoid linkage vicinal to the non-substituted benzene nucleus. Provided the initial reaction consists in the *direct* addition of the negative ester ion to the unsaturated centre, these results are again wholly at variance with the electronic conceptions of reactivity, which demand the formation of *cyclo*hexenones from which benzoic acid would be produced on oxidation.

It would thus seem that the mechanism of the reaction cannot consist in simple addition to a double bond. An alternative explanation, and one in harmony with the experimental results, can be found if the assumption is made that the activation of the ethenoid linkage is dependent upon the known tendency of the carbonyl oxygen atom to gain a negative charge. In such a case the following electronic conditions would obtain :



Process *a* is now the primary source of activation : process *b*, although secondary, is nevertheless essential. The latter effect must obviously be inhibited by the opposing general effect produced by the presence of the chlorine atom in the substituted styryl residue, a condition which does not apply to process *b'*. As a consequence, the addition of the ester would inevitably affect the ethenoid linkage of

the unsubstituted styryl residue, as carbon atom C^1 now forms the terminal atom of the true "crotonoid" system (compare Allan, Oxford, Robinson, and Smith, J., 1926, 403).

The question of the addition to the dichlorodistyryl ketones is a complex one. Here the inhibitions of phases *b* and *b'* due to the strong general effect of the halogen atoms must become very nearly equal. Consequently, the negative ester ion will attach itself to either C^1 or C^5 according as the one or the other is more strongly influenced by the position of the chlorine atom in the respective aromatic nuclei. The actual effect is well illustrated in the case of the chlorobenzoic acids, where the order is $o>m>p$ as shown by their dissociation constants ($K = 0{\cdot}132$, $0{\cdot}0155$, and $0{\cdot}0093$, respectively). Exactly similar relationships apply to the *cyclo*hexenones. For instance, 2 : 3'-dichlorodistyryl ketone forms *ethyl* 3-o-*chlorophenyl*-5-m-*chlorostyryl*-Δ^5-cyclo*hexen*-1-*one*-2-*carboxylate*, from which *m*-chlorobenzoic acid is produced on oxidation. Similarly, the *cyclo*hexenones formed from both 2 : 4'- and 3 : 4'-dichlorodistyryl ketones yield *p*-chlorobenzoic acid.

EXPERIMENTAL.

2-Chloro-β-hydroxy-β-phenylethyl Styryl Ketone.—A solution of styryl methyl ketone (20 g.) and *o*-chlorobenzaldehyde (19 g.) in alcohol (150 c.c.) and water (100 c.c.) was treated with aqueous sodium hydroxide (5·5 c.c. of 1%; 0·01 mol.) and kept at 0° for several days. The yellow oil obtained, which solidified on vigorous scratching, formed long, colourless needles, m. p. 79—80° (yield, 11 g.), after repeated crystallisation from absolute alcohol. By liberally seeding the reaction mixture with the aldol as soon as the condensate commenced to separate, the yield was increased to 31 g. (Found: C, 71·4; H, 5·3. $C_{17}H_{15}O_2Cl$ requires C, 71·2; H, 5·3%).

2-Chlorodistyryl ketone may be prepared directly as described above by increasing the alkali concentration to 0·03 mol. (16·5 c.c. of a 1% solution). The separated pale yellow oil gradually formed a semi-solid mass (10 days), from which the aqueous layer was decanted. The residue was taken up in ether and, after removal of solvent from the dried extract, yellow crystals were obtained mixed with a viscous oil, which was removed by extraction with a small quantity of alcohol. The solid residue was crystallised repeatedly from absolute alcohol, from which the pure *ketone* separated in short yellow needles, m. p. 82—83°. Alternatively, the ketone can readily be prepared by refluxing the aldol for 2 hours with acetic anhydride (Found: C, 76·2; H, 5·1. $C_{17}H_{13}OCl$ requires C, 76·0; H, 4·9%).

3-*Chlorodistyryl ketone*, prepared in an exactly similar manner to the 2-chloro-isomeride, separated from alcohol in large plates, m. p. 108—109° (Found : C, 75·6; H, 4·8%).

4-*Chloro*-β-*hydroxy*-β-*phenylethyl Styryl Ketone*.—A solution of styryl methyl ketone (8 g.) and *p*-chlorobenzaldehyde (7·5 g.) in alcohol (80 c.c.) and water (60 c.c.) was treated with aqueous sodium hydroxide (8 c.c. of 1%) at room temperature. The yellow oil obtained, which solidified, was crystallised first from alcohol and finally from benzene, from which the *aldol* separated in colourless needles, m. p. 108—109° (Found : C, 71·2; H, 5·3%). On treatment of the aldol with acetic anhydride in the usual way, an excellent yield of 4-chlorodistyryl ketone was obtained, which crystallised from alcohol in glistening, pale yellow leaflets, m. p. 134°. The distyryl ketone may also be prepared directly from its constituents if the concentration of the alkali be increased to 0·5 mol. This substance has previously been obtained by Straus and Blankenhorn (*Annalen*, 1917, **415**, 256), but working under their conditions, we have only succeeded in isolating the aldol.

2 : 3′-*Dichlorodistyryl Ketone*.—2-Chlorostyryl methyl ketone (20 g.), prepared by Vorländer's method (*Annalen*, 1897, **294**, 291), and *m*-chlorobenzaldehyde (15·8 g.) were dissolved in dry ether (60 c.c.) and saturated with dry hydrogen chloride at 0°; heat was developed and the solution rapidly assumed a deep purple colour. After the mixture had been kept for 3 days in the ice-chest, the crystalline, red, halochromic salt was collected, washed with dry ether, and dissolved in boiling alcohol. The solution was then treated with sufficient sodium carbonate solution to discharge the red colour. After removal of precipitated inorganic matter, the yellow filtrate was diluted with water, and the precipitated *distyryl ketone* recrystallised from aqueous alcohol. It formed long yellow needles, m. p. 67—68°, sparingly soluble in light petroleum, ether, and carbon disulphide (Found : C, 67·1; H, 3·7. $C_{17}H_{12}OCl_2$ requires C, 67·3; H, 3·9%).

2 : 4′-*Dichlorodistyryl ketone* was prepared in a similar manner. It crystallised from alcohol in yellow needles, m. p. 109° (Found : C, 67·5; H, 4·0%).

3-*Chlorostyryl Methyl Ketone*.—A solution of *m*-chlorobenzaldehyde (20 g.) in acetone (100 g.) was diluted with water to 2000 c.c. and then treated with aqueous sodium hydroxide (100 c.c. of 10%). The mixture was mechanically shaken for 48 hours, the separated oil extracted with ether, and the solution dried. After removal of solvent, the residual oil was distilled; the portion, b. p. 171°/20 mm., slowly crystallised at room temperature, forming yellow plates, m. p. 28—29° (yield, 17 g.). The *ketone* is readily soluble in the

usual organic solvents, but may be crystallised from light petroleum (Found: C, 66·1; H, 5·0. $C_{10}H_9OCl$ requires C, 66·5; H, 5·0%).

3 : 4′-*Dichlorodistyryl ketone*, prepared by condensation of the above ketone with *p*-chlorobenzaldehyde by means of dry hydrogen chloride, separated from alcohol in pale yellow plates, m. p. 134° (Found: C, 67·4; H, 3·9%).

Ethyl (*γ-Keto-α-phenyl-ε-2-chlorophenyl-*Δ^{δ}*-pentenyl*)*acetoacetate* (IV).—2-Chlorodistyryl ketone (2·5 g.) and ethyl acetoacetate (8 c.c.) were heated under reflux on the water-bath for 48 hours in presence of piperidine (12 drops). Treatment of the reaction mixture with aqueous alcohol produced a dark brown oil, which solidified. The crude *ketone*, repeatedly crystallised from absolute alcohol in presence of animal charcoal, formed colourless needles, m. p. 112°, which dissolved in concentrated sulphuric acid to an orange solution (Found: C, 69·5; H, 5·9. $C_{23}H_{23}O_4Cl$ requires C, 69·3; H, 5·8%).

Ethyl 3-*phenyl*-5-*o-chlorostyryl*-Δ^5-cyclo*hexen*-1-*one*-2-*carboxylate* (II) is readily obtained by gently warming the previous compound with alcoholic sodium ethoxide. It is more suitably prepared by the following direct method: 2-Chlorodistyryl ketone (20 g.), dissolved in a mixture of hot absolute alcohol (80 c.c.) and ethyl acetoacetate (12 g.), was heated for 15 minutes on a water-bath with alcoholic sodium ethoxide (18 c.c. of a 1% solution); the colour of the solution changed from yellow to orange and, on cooling, yellow crystals were slowly deposited. These were collected after 2 days and crystallised from dilute alcohol; the cyclo*hexenone* was then obtained in colourless feathery needles, m. p. 137°, sparingly soluble in cold alcohol and light petroleum, very soluble in chloroform and glacial acetic acid (yield, 10·5 g.). The solution in concentrated sulphuric acid is orange (Found: C, 72·2; H, 5·6. $C_{23}H_{21}O_3Cl$ requires C, 72·5; H, 5·5%).

Oxidation. The *cyclo*hexenone was dissolved in acetone and treated at room temperature with finely powdered potassium permanganate, added in small quantities at a time and in very slight excess. The solid residue was finely powdered and repeatedly extracted with boiling water, and the solution rendered acid. The colourless needles which were deposited on cooling were repeatedly crystallised from boiling water, and the product, m. p. 138—139°, was identified as *o*-chlorobenzoic acid (no depression of m. p. in admixture with an authentic specimen, m. p. 142°).

3-*Phenyl*-5-*o-chlorostyryl*-Δ^5-cyclo*hexen*-1-*one*.—A solution of the preceding ester (3 g.) in glacial acetic acid (50 c.c.) was refluxed for 1 hour with sulphuric acid (30 c.c. of 40%). The crude solid which separated on dilution of the reaction mixture crystallised from

alcohol in yellow plates, m. p. 142° (Found: C, 77·8; H, 5·2. $C_{20}H_{17}OCl$ requires C, 77·8; H, 5·5%).

Ethyl 3-*Phenyl*-5-o-*chlorostyryl*-Δ^4-cyclo*hexen*-1-*one*-2-*carboxylate*(?) (V).—The filtrate of the reaction mixture from which the crude Δ^5-*cyclo*hexenone ester had been separated yielded, after concentration and dilution with water, a viscous yellow oil which very slowly solidified in the ice-chest. The crude product separated from ethyl alcohol in colourless plates (3 g.), m. p. 107° (Found: C, 72·6; H, 5·5%). This isomeride dissolves in concentrated sulphuric acid to an orange solution and is more soluble in the usual solvents than the higher-melting Δ^5-compound. On oxidation, *o*-chlorobenzoic acid was isolated, but no trace of benzoic acid.

3-*Phenyl*-5-o-*chlorostyryl*-Δ^4-cyclo*hexen*-1-*one* (?) was prepared by a similar method to that employed for the preparation of the Δ^5-isomeride. It crystallised from absolute alcohol (blood-charcoal) in golden-yellow needles, m. p. 136—137°. A mixed melting point with 3-phenyl-5-*o*-chlorostyryl-Δ^5-*cyclo*hexen-1-one (m. p. 142°) produced a depression of more than 25° (Found: C, 77·4; H, 5·8%).

Ethyl 3-*phenyl*-5-m-*chlorostyryl*-Δ^5-cyclo*hexen*-1-*one*-2-*carboxylate* was prepared by the interaction of 3-chlorodistyryl ketone and ethyl acetoacetate by a similar method to that previously described. It separated from the diluted reaction mixture as a mobile yellow oil which slowly solidified. The pure cyclo*hexenone* was obtained by repeated crystallisation from methyl alcohol and formed yellow prisms, m. p. 105—106° (Found: C, 72·2; H, 5·4%). Oxidation with potassium permanganate yielded *m*-chlorobenzoic acid, m. p. 148—149°.

Ethyl 3-*phenyl*-5-p-*chlorostyryl*-Δ^5-cyclo*hexen*-1-*one*-2-*carboxylate*, prepared from 4-chlorodistyryl ketone, was obtained, after repeated crystallisation from alcohol, in prisms, m. p. 124—125° (Found: C, 72·2; H, 5·5%). The acid (m. p. 236°) produced on oxidation was identified as *p*-chlorobenzoic acid by comparison with an authentic specimen.

Ethyl 3-o-*chlorophenyl*-5-m-*chlorostyryl*-Δ^5-cyclo*hexen*-1-*one*-2-*carboxylate* separated from methyl alcohol in pale yellow needles, m. p. 108—109° (Found: C, 66·7; H, 4·8. $C_{23}H_{20}O_3Cl_2$ requires C, 66·5; H, 4·8%). It is sparingly soluble in light petroleum, carbon disulphide, and cold methyl alcohol, readily soluble in chloroform, acetone, and ethyl acetate. Oxidation under the usual conditions gave *m*-chlorobenzoic acid, m. p. 149—150°.

Ethyl 3-o-*chlorophenyl*-5-p-*chlorostyryl*-Δ^5-cyclo*hexen*-1-*one*-2-*carboxylate* crystallised from alcohol in slender yellow needles, m. p. 143° (Found: C, 66·3; H, 4·8%), and gave *p*-chlorobenzoic acid on oxidation.

Ethyl 3-m-*Chlorophenyl*-5-p-*chlorostyryl*-Δ^5-cyclo*hexen*-1-*one*-2-*carboxylate*.—3 : 4′-Dichlorodistyryl ketone (8 g.), dissolved in a minimum quantity of absolute alcohol (200 c.c.), and ethyl acetoacetate (5 g.) were refluxed for 15 minutes with sodium ethoxide (7·2 c.c. of a 1% solution). After concentration of the reaction mixture, yellow crystals were gradually deposited which were recrystallised from absolute alcohol. The purified cyclo*hexenone* separated in yellow prisms (6 g.), m. p. 122° (Found : C, 66·2; H, 5·1%), which dissolved in concentrated sulphuric acid to an orange-red solution. It is sparingly soluble in cold alcohol and carbon disulphide, readily soluble in acetone, benzene, and ethyl acetate. Oxidation gave *p*-chlorobenzoic acid, m. p. 236—238°, which was identified in the usual manner.

2 : 2′-*Dichlorodistyryl Ketone*.—2-Chlorostyryl methyl ketone (9 g.) and *m*-chlorobenzaldehyde (7 g.) were dissolved in alcohol (60 c.c.) and the solution was rendered just turbid by dilution with water. Aqueous sodium hydroxide (10 c.c. of a 1% solution) was added with vigorous shaking. The mobile yellow oil that separated was removed by extraction with ether and dried over anhydrous sodium sulphate. The oily residue left after removal of solvent was dissolved in ethyl acetate; crystals were then slowly deposited. The crude substance was recrystallised first from alcohol and finally from ethyl acetate, giving yellow needles, m. p. 124° (Found : C, 67·0; H, 4·1%), which were identified as 2 : 2′-dichlorodistyryl ketone by comparison with a specimen of the ketone prepared in the usual manner.

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