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STEREOCHEMISTRY OF THE HALOLACTONISATION REACTION

THE REACTION OF *CIS*- AND *TRANS*- STILBENE-2-CARBOXYLIC ACIDS WITH HALOGENS

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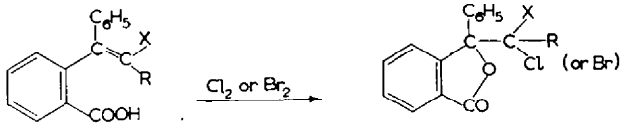
Abstract—The stereochemistry of the reaction of *cis*- and *trans*-stilbene-2-carboxylic acids with chlorine and bromine, yielding the two diastereoisomeric 3-phenyl-4-halo-3:4-dihydro*iso*coumarins (III) and (IV) has been investigated. The reactions are entirely stereospecific and involve intramolecular attack by the carboxyl group on an intermediate carbonium or halonium ion. The lactones (III) and (IV) yield the two 3-(α-hydroxybenzyl) phthalides (V) and (VI), with retention of configuration. Thionyl chloride transforms (V) and (VI) into the 3-(α-chlorobenzyl) phthalides (IX) and (X), with inversion. Steric effects are mainly responsible for the alternative formation of halolactones or normal dihalogenated derivatives in the reactions between unsaturated acids and halogens.

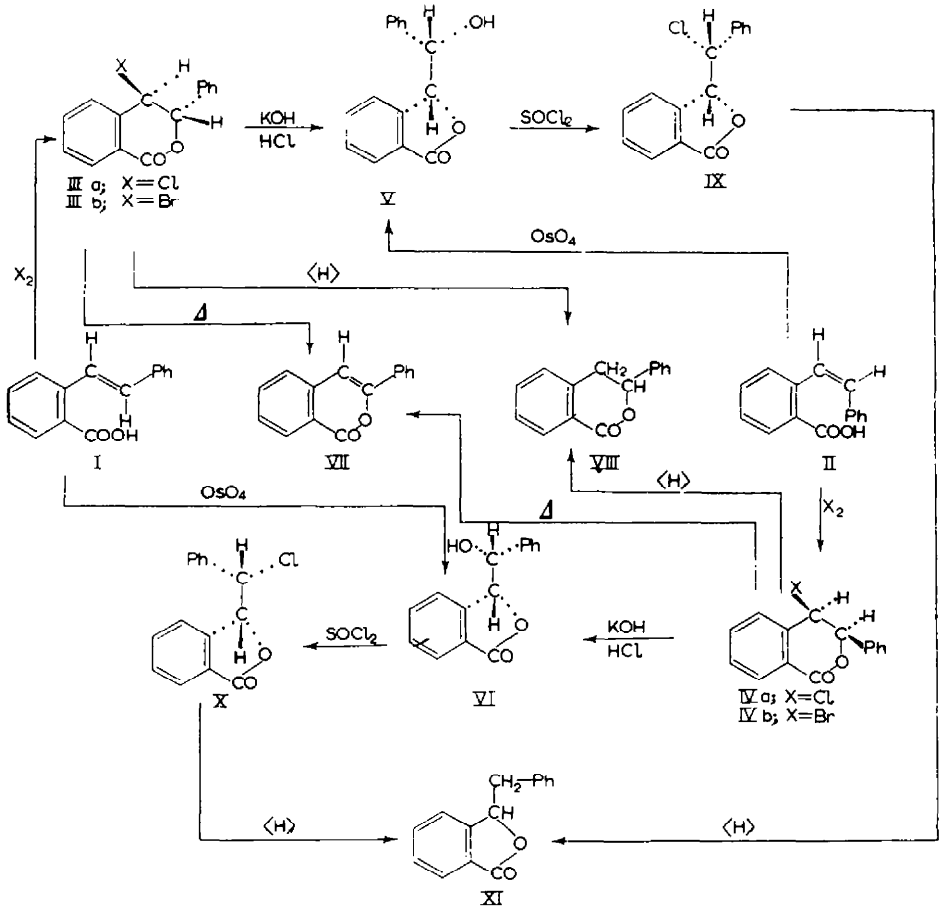
PREVIOUS work has shown[1] that halogenated phthalides are obtained in the reaction of chlorine or bromine with a series of derivatives of *o*-(α-phenylvinyl) benzoic acid. In order to understand the stereochemistry and mechanism of halolactonisations, the reaction has been applied to *trans*-stilbene-2-carboxylic acid (I) and its *cis*-isomer[2] (II).



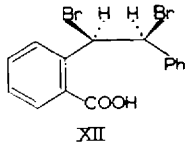
X = H, Cl, Br
R = CH_3, C_2H_5, C_6H_5

The acids (I) and (II) are almost quantitatively transformed by chlorine into chlorolactones of the formula $C_{15}H_{11}O_2Cl$, the *trans*-acid giving exclusively one, m.p. 110°, the *cis*-acid another, m.p. 147°. These lactones are not phthalides, as in the previously described cases,[1] but δ-lactone structures (IIIa) and (IVa), because, on pyrolysis, both give 3-phenyl*iso*coumarin (VII), and, on catalytic hydrogenation, 3-phenyl-3:4-dihydro*iso*coumarin (VIII). The reaction of (I) with bromine is described by Leupold,[3] who isolated a dibromoacid. Repetition of the bromination of (I), and (II), showed that Leupold's dibromoacid (XII) is formed from both (I) and (II),

[1] G. Berti, *Gazz. Chim. Ital.* **81**, 305 (1951).
[2] G. Berti, *Gazz. Chim. Ital.* **86**, 883 (1956).
[3] E. Leupold, *Ber. Dtsch. Chem. Ges.* **34**, 2829 (1901).



in variable amounts, depending on the solvent, (in the chlorination reactions the corresponding dichloroacid was not isolated). The *erythro*-configuration (XII) is assigned to the dibromoacid, as it is transformed by sodium iodide into *trans*-stilbene-2-carboxylic acid (I). Beside (XII), substantial amounts of bromolactones



XII

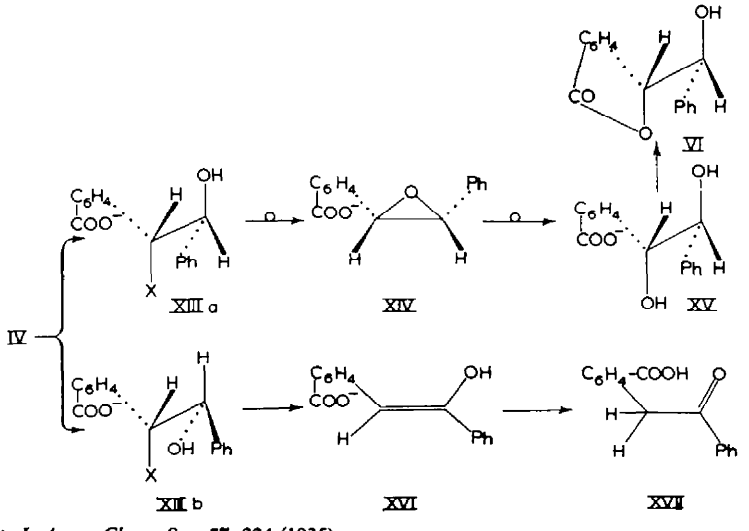
(III b) and (IV b) were obtained from these brominations: one, m.p. 92°, from the *trans*-acid and one, m.p. 138°, from the *cis*-acid, identical with the one prepared by Leupold from (XII).

These halolactonisation reactions are noteworthy, as the products are formed in a completely stereospecific way, because it is known that electrophilic additions to stilbene derivatives are not at all specific from the stereochemical point of view.[4]

[4] G. W. Wheland, *Advanced Organic Chemistry* p. 292. Wiley, New York (1949).

Treatment of the halolactones (III) and (IV) with ethanolic potassium hydroxide, followed by acidification, gives the hydroxyphthalides (V) and (VI). The lower-melting chloro- and bromolactones, obtained from the *trans*-acid (I), are quantitatively transformed into a hydroxyphthalide, m.p. 149°, the higher melting ones give the other phthalide, m.p. 103°, and substantial amounts of *o*-phenacylbenzoic acid (XVII). Both (V) and (VI) on pyrolysis give phthalide and benzaldehyde, in fairly good yield. Treatment with thionyl chloride transforms (V) and (VI) into the diastereo-isomeric chlorophthalides (IX) and (X), which, on catalytic reduction, yielded 3-benzylphtalide (XI).

The higher-melting bromolactone, obtained from *cis*-stilbene-2-carboxylic acid (II), is transformed almost quantitatively into 3-phenyl*iso*coumarin (VII), when refluxed with an alcoholic solution of potassium acetate, whilst its diastereoisomer is recovered unchanged from the same treatment, indicating a *trans*-disposition of halogen and β-hydrogen in the former lactone. Consequently, the higher melting halolactones obtained from (II) should have configuration (IV). This is further confirmed by the fact, that only the halolactones derived from (II) give with potassium hydroxide the salt of *o*-phenacylbenzoic acid (XVII). In order to explain this difference it is necessary to examine the probable mechanisms of the two alternative reactions, the one leading to the salt of α,α'-dihydroxydibenzyl-2-carboxylic acid (XV) and the other yielding the salt of (XVII). The first step in the reaction of strong bases with (III) and (IX) is the opening of the lactone rings, with formation of the corresponding hydroxyhaloacids. The lactones with configuration (IV) are therefore transformed into (XIII), which on further action of the base yields (XV), probably through an intermediate epoxide (XIV), in accordance with the accepted mechanism for the conversion of halohydrins into glycols.[5] When the solution of (XV) is acidified, the more stable γ-lactone (VI) is formed. The ion (XIII) can also lose hydrogen chloride to form the enol (XVI), instead of the epoxide (XIV); the enol, when treated with acid, gives (XVII). It is evident that, starting from lactones of type (IX), the conformation (XIII a), leading to (XIV), is sterically hindered, and the two aromatic



[5] P. Bartlett, *J. Amer. Chem. Soc.* **57**, 224 (1935).

groups are *cis* to each other in the transition state, while the conformation (XIII b) leads to (XVII), through a transition state free of such hindrance. The opposite situation will apply to the lactones of type (III). The fact that the latter do not yield even traces of the acid (XVII) is therefore in agreement with the assigned configurations. An alternative mechanism for the formation of (XVII) from (IV), involving first the elimination of hydrogen chloride or bromide from the halolactones, followed by the opening of the ring of the 3-phenyl*iso*coumarin thus formed, to give (XVI), would lead to the same conclusions.

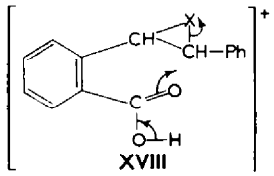
The mechanism proposed for the conversion of the halolactones (III) and (IV) to the hydroxyphthalides (V) and (VI), involving two inversions, should lead to products having the same configurations as the starting materials. This was proved by treating the acids (I) and (II), and their methyl esters, with osmium tetroxide.[6] It was not possible to isolate the dihydroxylated acids, but the products had the hydroxylactonic structures (V) and (VI); only the higher-melting hydroxyphthalide (V) was obtained from the *cis*-acid, and the lower-melting one from the *trans*-acid. The *cis*-dihydroxylation product from the *cis*-acid has the *erythro*-configuration, corresponding, after lactonisation, to (V), the one from the *trans*-acid the *threo*-configuration, leading to (VI), in agreement with the hypothesis that the *erythro*-compound has the higher melting point.

The configurations of the two chlorophthalides (IX) and (X), obtained from (V) and (VI) with thionyl chloride, can be assumed with fair certainty from a comparison of the melting points, showing that the replacement of the hydroxyl group by chlorine takes place with inversion: the chlorophthalide, m.p. 107°, is obtained from (V), and should have the *threo*-configuration (IX), while the other chloro-derivative, is formed from (VI), and should therefore be the *erythro*-form (X).

The possibility that the halolactones are formed through an elimination of HCl or HB_2 from dihalogenated acids of type (XII) can be ruled out. Such a mechanism should give halolactones with opposite configurations of those found, assuming that one of the halogen atoms is displaced by the carboxyl group with inversion. This happens in the case of the transformation (XII) → (IV b), and Weinstock[7] showed that the pyrolytic transformation of γ-bromoesters into lactones takes place with inversion. The same isomer of (XII) being obtained in the bromination of (I) and (II), clearly shows that (XII) cannot be an intermediate in a stereospecific halolactonisation; furthermore, (XII) is stable under the conditions used for the reactions and is lactonised only on prolonged heating of its acetic acid solution.

An acceptable mechanism must involve an attack by the carboxyl group on the intermediate ion formed by interaction between the halogen and the double bond. This ionic intermediate could be either a halonium ion,[8] (XVIII), or a π-complex[9] or an open carbonium ion, provided that the attack by the carboxyl group takes place more rapidly than the rotation around the α,β-bond, to account for the observed stereospecificity. A restriction of such rotation could be explained by an electrostatic interaction between the positive centre and the halogen atom, according to de la Mare and Pritchard.[10] A mechanism of this type had been assumed in our previous

[6] N. A. Milas and S. Sussmann, *J. Amer. Chem. Soc.* **59**, 2345 (1937).
[7] J. Weinstock, *J. Amer. Chem. Soc.* **78**, 4967 (1956).
[8] I. Roberts and G. E. Kimball, *J. Amer. Chem. Soc.* **59**, 947 (1937).
[9] M. J. S. Dewar, *Disc. Faraday Soc.* **2**, 75 (1947).
[10] P. B. D. de la Mare and J. G. Pritchard, *J. Chem. Soc.* 3910, 3990 (1954).



XVIII

paper,[1] and later by Craig[11] and by van Tamelen and Shamma[12] for different types of halolactonisations. In such a mechanism the attack by the carboxyl group should take place on the side opposite to the halogen atom, and this is now substantiated by the observed steric course of the reactions. The formation of the dibromo-acid (XII) and not of a dichloroacid as a side-product is explained by the more nucleophilic character of the bromine anion, compared to the chlorine anion, allowing the former to compete successfully with the carboxyl group in the attack on the intermediate cation.

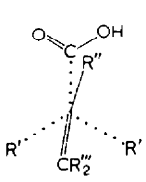
It appears that halolactonisation is the rule, when derivatives of *o*-vinylbenzoic acid are treated with halogens. Data in the literature show, that the formation of normal dihalogenated products is the usual reaction with most other types of unsaturated acids, unless the halogenation is carried out under special conditions. The best known and most widely studied example is the formation of iodolactones in the treatment of alkaline solutions of unsaturated acids with iodine,[13] recently reviewed by van Tamelen and Shamma.[12] In this case the more open nucleophilic character of the carboxyl anion facilitates the reaction so, that it can be applied to most β,γ- and γ,δ-olefinic acids. Less frequently bromo- or chlorolactones are formed directly from free acids or from esters. In addition to the reactions discussed, the following cases of monocarboxylic acids, giving halolactones directly, are reported in the literature:[14-17] Dicarboxylic acids such as diallylamalonic,[14] benzyl-allylmalonic and its esters[18] and several derivatives of itaconic[19,20,21,22] and aticonic acids[23,24] yield halolactones. It is probable that the halolactones prepared by Gaudry and Godin[25] from esters of allymalonic acid are formed from the dihalogenated esters during the distillation to which the reaction products are subjected, as it is known that γ- and δ-haloesters are easily transformed into lactones[26] and that allylmalonic acid gives a stable dibromoderivative.[14]

A common feature of most of the acids giving halolactones is the presence of two substituents, or a large one, in the α-positions. This applies to both β,γ- and

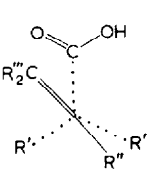
[11] P. N. Craig, *J. Amer. Chem. Soc.* **74**, 129 (1952).
[12] E. E. van Tamelen and M. Shamma, *J. Amer. Chem. Soc.* **76**, 2315 (1954).
[13] J. Bougault, *Ann. Chim. Phys.* **14**, 145 (1908); **15**, 296 (1908).
[14] R. Fittig and E. Hjelt, *Ann.* **216**, 52 (1882).
[15] W. H. Perkin and A. Smith, *J. Chem. Soc.* **85**, 155 (1904).
[16] P. N. Craig and I. H. Witt, *J. Amer. Chem. Soc.* **72**, 4925 (1950).
[17] A. Winterstein and W. Hämmerle, *Z. Physiol. Chem.* **199**, 56 (1931).
[18] R. T. Arnolds, M. de Moura Campos and K. L. Lindsay, *J. Amer. Chem. Soc.* **75**, 1044 (1953).
[19] R. Fittig, *Ann.* **226**, 366 (1884).
[20] H. Stobbe, *Ann.* **308**, 77 (1899).
[21] R. Fittig, *Ann.* **331**, 142 (1904).
[22] H. Stobbe, *Ann.* **321**, 119 (1902).
[23] R. Fittig, *Ann.* **304**, 222, 311 (1898).
[24] H. Stobbe, *Ann.* **308**, 77, 82 (1899).
[25] R. Gaudry and C. Godin, *J. Amer. Chem. Soc.* **76**, 139 (1954).
[26] V. Grignard, *Traitè de Chimie Organique* Vol. 11, p. 82. Masson, Paris (1945).

γ,δ-unsaturated acids; thus, while 3-pentenoic[27] and 4-pentenoic acids[28] give normal dibromoderivatives with bromine, 2:2-dimethyl-3-pentenoic and 2:2-diphenyl-4-pentenoic acids, yield bromolactones. These are examples of the so-called "*gem* group effect", which facilitates cyclisations. There can be little doubt that this difference in behaviour is entirely due to steric effects, as the size of the groups seems to be more important than their type. Only if in the intermediate cation the carboxyl group and the positive centre are near enough to enter rapidly into the transition state leading to the lactone ring, formation of the halolactone can take place; otherwise, the cation is attacked by a halogen anion and a dihalogenated compound is formed.

It can be assumed that the most stable conformation for β,γ-unsaturated acids, having no substituents α to the carboxyl group (R′ = H) and with R″ small, is (XIX);



XIX



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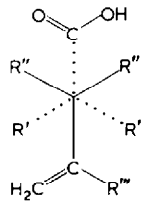
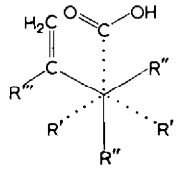


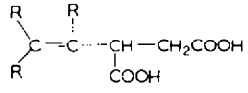
XXI



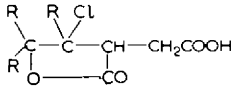
XXII

as, however, the R′ groups become radicals of increasing steric requirements, configuration (XX) should be favoured, unless R″ also increases. Only in the latter conformation the carboxyl group and double bond are near enough to allow cyclisation of the intermediate ion to occur rapidly enough to avoid reaction with the halogen anion. A similar explanation also holds for γ,δ-unsaturated acids, as shown by the conformations (XXI) and (XXII). If one of the R′ groups is a carboxyl group or a second unsaturated group, cyclisation is again facilitated, since in any of the possible conformations a carboxyl group and a double bond are near enough to produce cyclisation; this explains the higher tendency to halolactonisation of derivatives of malonic and of diallylacetic acid. A particular case in favour of the above hypothesis is that of the derivatives of aticonic acid (XXIII), in which lactonisation can take place through two different carboxyl groups; in all cases described in the literature[23,24] only the lactones of type (XXIV) are formed, that is, those involving the carboxyl group attached to the most heavily substituted carbon atom.

The analysis made does not take into account the sizes of the groups R″ and R‴, but the line of reasoning can be extended to foresee their effects. Too few cases are known to allow of a more general theory. The effect of *gem*-groups, favouring



XXIII



XXIV

other cyclisation reactions, is explained in a somewhat similar way by Hammond.[29]

Derivatives of *o*-vinylbenzoic acid, (I) and (II) have a particular tendency to give

[27] R. Fittig and J. E. Mackenzie, *Ann.* **283**, 97 (1894).
[28] R. Fittig and A. Messerschmidt, *Ann.* **208**, 92 (1881).
[29] M. S. Newman (Editor), *Steric Effects in Organic Chemistry* p. 468. Wiley, New York (1956).

halolactones, as the carboxyl and vinyl groups are forced in the *cis*-position by the benzene ring to which they are attached. This should lead to a very rapid interaction between the carboxyl group and the positive centre and may account for the observed stereospecificity. The great tendency towards formation of the lactone ring is confirmed by the fact that the methyl esters of (I) and (II) give only the halolactones, when treated with halogens. Until it is established that all types of halolactonisations proceed by the same mechanism, no general conclusions can be drawn. No kinetic data is available, nor are there any other stereochemical studies.*

EXPERIMENTAL

Melting points were determined on the Kofler block.

trans-*Stilbene-2-carboxylic acid* (I) was prepared from 3-benzylphthalide with potassium hydroxide;[30] *cis*-stilbene-2-carboxylic acid (II) by isomerisation in sunlight of the *trans*-acid.[2]

Methyl trans-*stilbene-2-carboxylate*. Acid (I, 3·5 g) and thionyl chloride (10 ml) were heated at 60° for 2 hr, the excess chloride was distilled off under reduced pressure, the residue treated with anhydrous methanol (15 ml) and dimethyl-aniline (3 ml) and refluxed for 1 hr. The methanol was distilled off, the residue poured into water, extracted with ether, washed with hydrochloric acid, water and sodium carbonate solution, dried on magnesium sulphate and distilled; an oil, b.p. 168–170°/0,5 mm, was obtained (Found: C, 80·15; H, 5·64. $C_{16}H_{14}O_2$ requires C 80·64; H, 5·92%). *Methyl* cis-*stilbene-2-carboxylate* was prepared in a similar manner.[31]

trans-3-*Phenyl*-4-*chlorodihydro*iso*coumarin* (III a). Dry chlorine was passed through a solution of *trans*-stilbene-2-carboxylic acid (2·0 g) in chloroform (30 ml) for 20 min; much hydrogen chloride was evolved. After washing with sodium carbonate solution (the alkaline layer did not precipitate on acidification) and drying on magnesium sulphate, the solvent was evaporated. Crystallisation of the residue from benzene-ligroin yielded needles (1·85 g), m.p. 108–110° (Found: C, 69·70; H, 4·46; Cl, 13·46. $C_{15}H_{11}O_2Cl$ requires C, 69·64; H, 4·29; Cl, 13·70%). Also when the reaction was repeated under different conditions (low temperature, avoiding excess of chlorine, using acetic acid or carbon tetrachloride as solvents, etc.) the only product was (III a), and in no case was it possible to isolate a dichloro-acid. Only the chlorolactones (III a) was also obtained in the chlorination of the methyl ester of the acid (I) in chloroform solution.

cis-3-*Phenyl*-4-*chlorodihydro*iso*coumarin* (IV a). The chlorination of *cis*-stilbene-2-carboxylic acid (3 g), as described for the *trans*-acid, yielded a neutral product (3·1 g) which crystallised from ethanol in stout needles, m.p. 146–147° (Found: C, 69·44; H, 4·55. $C_{15}H_{11}O_2Cl$ requires C, 69·64; H, 4·29%). The same product was obtained from the chlorination of the methyl ester of the acid (II).

trans-3-*Phenyl*-4-*bromodihydro*iso*coumarin* (III b). A solution of the acid (I, 1·0 g) in acetic acid (20 ml), cooled with ice, was treated with bromine (0·8 g) in acetic

* Only one other case has been found in the literature, in which the halolactonisation reaction has been applied to a couple of *cis-trans* isomers: of the two forms of γ-methyl-γ-phenylitaconic acid each gives a different diastereoisomeric lactone.[24] This is a further proof of the stereospecificity of the reaction, even if the configurations given by Stobbe to the two lactones probably are wrong, as he supposes that they were formed as secondary products from the cyclisation of the dibromoacids.

[30] S. Gabriel and T. Posner, *Ber. Dtsch. Chem. Ges.* **27**, 2506 (1894).
[31] D. F. DeTar and L. A. Carpino, *J. Amer. Chem. Soc.* **78**, 475 (1956).

acid (5 ml), rapidly and with stirring. After 15 min the mixture was filtered, allowing the acetic acid to melt on the filter. The dibromoacid (XII, 0·45 g), m.p. 180°, was thus obtained. The filtrate, on dilution with water, separated an oil, which solidified on standing. Recrystallisation from light petroleum, containing a little benzene, yielded needles, m.p. 90–92° (0·7 g). (Found: Br, 26·31. $C_{15}H_{11}O_2Br$ requires Br, 26·36%). When the bromination was carried out in carbon tetrachloride at −10°, the acid (I, 0·5 g) yielded (XII, 0·7 g) and (III b, 0·1 g). When chloroform was used as the solvent, (XII, 0·15 g) and (IV b, 0·4 g) were obtained from (I, 0·4 g).

cis-3-*Phenyl*-4-*bromodihydroisocoumarin* (IV b). A solution of *cis*-stilbene-2-carboxylic acid (II, 2 g) in chloroform (20 ml) was treated with bromine (1·6 g) in chloroform (5 ml). A small amount of the dibromoacid (XII) separated out and was filtered off. The solution, after elimination of the solvent, gave a residue, which, taken up in light petroleum, yielded 1·85 g of a product, m.p. 136–138°, which had been previously described by Leupold,[3] who obtained it on refluxing an acetic solution of (XII). Using carbon tetrachloride as the solvent for the bromination, (II, 0·5 g) yielded (XII, 0·45 g) and only traces of the lactone (IV b). Refluxing the dibromoacid (XII) for one hr in acetone or chloroform, left it unchanged.

Proofs of structure of the lactones (III) *and* (IV). All four halolactones (III a and b, IV a and b) were subjected to pyrolysis and yielded 3-phenyl*iso*coumarin (VII). The method followed for (III a) was the following: the compound was heated in an open vessel at 220–250° until foaming ceased and the residue was recrystallised from ethanol, and then from light petroleum. A product, m.p. 89–90°, was thus obtained, which did not depress the melting point of an authentic sample of (VII). The same result was obtained with the other lactones, the bromo lactones requiring a lower temperature (180–200°) for pyrolysis. The transformation of (IV B) into (VII) has been described by Leupold.[3]

The bromolactone (IV b) was transformed into 3-phenyl*iso*coumarin as follows: a solution of (IV b 0·2 g) and potassium acetate (0·2 g) in ethanol (5 ml) was refluxed during 30 min. Potassium bromide separated out. On dilution with water a product, containing only traces of bromine was obtained, which after one crystallisation from light petroleum-benzene, gave (VII), m.p. 89–90°. On the other hand the bromolactone (III b) was recovered unchanged from such a treatment.

The chlorolactones (III a) and (IV a) were also transformed into 3-phenyl-3:4-dihydro*iso*coumarin (VIII) in the following way: a solution of (III A, 0·6 g) in ethanol (20 ml) was hydrogenated at atmospheric pressure, in the presence of 5% palladiated carbon (0·15 g). The hydrogenation was stopped when a 30% excess of the equimolar quantity of hydrogen had been absorbed. (It is not convenient to stop the hydrogenation after absorption of the equimolar quantity, as at this stage a substantial amount of the starting material, which is difficult to separate from (VIII), is still present). The catalyst was filtered off, the solvent eliminated on a steam-bath, the residue treated with sodium carbonate solution and filtered. The product was crystallised twice from aqueous ethanol, yielding 0·2 g of a product, m.p. and mixed m.p. with (VIII), 89–90°. The alkaline solution, an acidification and crystallisation of the precipitate from benzene-light petroleum, yielded 0·2 g of dibenzyl-*o*-carboxylic acid, m.p. 130–131°, formed by hydrogenolysis of the lactone ring of (VIII). The same results were obtained in the reduction of (IV a).

The dibromoacid (XII, 0·1 g), dissolved in acetone, was treated with a 15%

solution of sodium iodide in acetone and refluxed for 30 min. After dilution with water a product precipitated, which was crystallised from ethanol, yielding needles, m.p. 158–160°, of *trans*-stilbene-2-carboxylic acid (I).

erythro-3-(α-*Hydroxybenzyl*)*phthalide* (V). A solution of the lactone (III a, 3·0 g) in 10% alcoholic potassium hydroxide (30 ml) was refluxed for 30 min, then diluted with water and acidified with sulphuric acid. The precipitate, which was insoluble in cold sodium hydroxide, was crystallised from benzene-petroleum ether, yielding needles, m.p. 148–149° (2·6 g). (Found: C, 74·86; H, 5·30. $C_{15}H_{12}O_3$ requires C, 74·99; H, 5·04%). The same product was obtained from the lactone (III B) in a similar way.

Compound (V) was also obtained as follows: a solution of the methyl ester of the acid (II, 0·1 g) and pyridine (0·2 ml) in anhydrous ether (3 ml) was treated with a solution of osmium tetroxide (0·1 g) in ether (3 ml). A yellow colour appeared immediately, and after a few minutes a precipitate started to separate. After 48 hr at room temperature, the light brown precipitate was collected, washed with ether, dissolved in dichloromethane (5 ml) and treated with a solution of sodium hydroxide (0·2 g) and mannitol (0·5 g) in water (8 ml). After shaking until it was decolourised, the organic layer was dried with magnesium sulphate, evaporated to dryness and the residue crystallised from benzene-petroleum ether, yielding a product, m.p. 148–149°, identical with the one described above. A further quantity of the same compound was obtained on acidification of the aqueous layer and extraction with ether. The same result was also obtained with the Milas method.[6] To a solution of hydrogen peroxide in tertiary butanol, prepared in the usual way[32] from the alcohol (10 ml) and peroxide (3 ml, 30%), *cis*-stilbene-2-carboxylic acid (3·5 g) and osmium tetraoxide (10 mg) were added, the mixture was heated to 50° until solution was complete and left at room temperature during 48 hr. Water was added, the solution extracted with benzene, the benzene layer washed with sodium carbonate solution and evaporated. Addition of ligroin to the residue gave product (V, 2·2 g).

Threo-3-(α-*hydroxybenzyl*) *phthalide* (VI). A solution of the chlorolactone (IV a, 1·5 g) in alcoholic potassium hydroxide (10 ml, 10%) was refluxed 5 min, then diluted with water and acidified. The precipitate was collected and treated with sodium carbonate solution. The residue (0·7 g), after crystallisation from benzene-ligroin, had m.p. 102–103° (Found: C, 74·63; H, 5·48. $C_{15}H_{12}O_3$ requires C, 74·99; H, 5·04%). Acidification of the alkaline solution yielded needles (0·3 g), which, after crystallisation from benzene, had m.p. 160° with decomposition; they were identified as *o*-phenacylbenzoic acid (XVII) by the mixed m.p. with an authentic sample.[33] When the reaction was repeated with bromolactone (IV, b, 0·5 g) only (VI, 0·1 g) was obtained, together with (XVII, 0·23 g).

Compound (VI) was further obtained when a solution of *trans*-stilbene-2-carboxylic acid (0·05 g) in anhydrous ether (1·5 ml), containing pyridine (0·1 ml), was treated with a solution of osmium tetroxide (0·05 g) in ether (1·5 ml). An amorphous brown precipitate was formed at once, which, after 48 hr at room temperature, had become crystalline. The osmic ester was decomposed as described above. The aqueous layer, after acidification and extraction with ether, gave a product, melting at 102–103°, identical with the one described above. The same product was also

[32] A. I. Vogel, *Practical Organic Chemistry* p. 895. Longmans, London (1956).
[33] S. Gabriel, *Ber. Dtsch. Chem. Ges.* **18**, 2446 (1885).

obtained from (I), using hydrogen peroxide and trace amounts of osmium tetroxide.

Transformation of (V) *and* (VI) *into phthalide and benzaldehyde.* The lactone (V, 1 g) was heated rapidly in an alloy bath with a small distillation flask. When the bath temperature reached 280° decomposition became evident and a liquid, having all the characteristics of benzaldehyde (0·4 g, yielding a DNP, m.p. 237–238°) distilled. When the temperature reached 360°, another fraction distilled, which solidified on scratching, yielding a compound (0·3 g), melting, after recrystallisation from water, at 72° (phthalide). The isomeric hydroxylactone (VI) gave pthalide and benzaldehyde too, but decomposition started only at 300° and the yields were lower.

threo-3-(α-*Chlorobenzyl*) *phthalide* (IX). A solution of the lactone (V, 0·5 g) in thionyl chloride (2 ml) was refluxed for 30 min, then poured on ice. The precipitate was extracted with ether, dried on magnesium sulphate, and the ether was distilled off; the residue was taken up in benzene and fractionally precipitated with petroleum ether. After decantation from a first oily fraction, needles (0·2 g) were obtained, which, after a second crystallisation from the same solvent mixture, had m.p. 106–107° (a mixture with the chlorolactone (III a) had m.p. 85–90°) (Found: C, 69·83; H, 4·35; Cl, 14·0. $C_{15}H_{11}O_2Cl$ requires C, 69·64; H, 4·29; Cl, 13·7%).

erythro-3-(α-*Chlorobenzyl*) *phthalide* (X). It was obtained from the hydroxylactone (VI, 0·5 g), on refluxing with thionyl chloride (3 ml) for 10 min, evaporating under reduced pressure at room temperature and recrystallising the residue from a little methanol: 0·3 g, m.p. 147–148° (mixed m.p. with (IV a, 115–120°). (Found: C, 69·46; H, 4·60; Cl, 13·4. $C_{15}H_{11}O_2Cl$ requires C, 69·64; H, 4·29; Cl, 13·7%).

Both (IX) and (X) were reduced with palladium on carbon, as described above, yielding 3-benzylphthalide, m.p. 60–61°.