THE PHOTODIMERS OF COUMARIN AND RELATED COMPOUNDS[1]

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ABSTRACT

The photodimer of coumarin is shown to have the head-to-head cis cyclobutane structure I. An isomer, obtained by the lactonization of *o*-hydroxy-*trans*-cinnamic acid, is shown to have the head-to-tail trans structure II. The photodimers of *o*-methoxy- and *o*-hydroxy-*trans*-cinnamic acids have been interrelated.

The photodimer of coumarin has been known for nearly 60 years (1). In the last 20 years, the photodimers of several substituted coumarins have also been prepared (2). These have been of interest, as the substituted coumarins, e.g., the furanocoumarins, are known to react with the skin in presence of light (3). Some of these furanocoumarins, e.g. xanthotoxin, have in fact been used for the treatment of skin depigmentation as occurs in leucoderma, in both the Middle East and in India (2, 4). The photodimers of these compounds are known (5) but the structure of the dimers have not been determined. The present work describes the elucidation of the structure and stereochemistry of the photodimer of coumarin, the parent compound in this series.

A cyclobutane-type structure was assigned to these dimers (2) by analogy with the dimerization of the cinnamic acids to 1α,3β-diphenylcyclobutane-2α,4β-dicarboxylic (α-truxillic)[2] and 1α,2α-diphenylcyclobutane-3β,4β-dicarboxylic (β-truxinic) acid (6). The similarity in ultraviolet absorption spectra of 3,4-dihydro-7-methoxycoumarin and of the photodimer of 7-methoxycoumarin (III) lent support to a cyclobutane structure in which the 3,4-double bonds of the two pyrone rings were involved (8). An incomplete X-ray diffraction study on III published in 1958 (9) confirmed the presence of a cyclobutane ring; no conclusions regarding the disposition of the rest of the molecule were drawn.[3]

On the basis of a cis fusion[4] of the cyclobutane ring to the 6-membered pyrone rings, four structures can be considered for coumarin dimers, and are represented in Fig. 1. There are two sets of structural isomers, head-to-head and head-to-tail, each of which can exist in a cis or trans form. The problems of isomerism are simpler than in the case of dimeric cinnamic acids, where 11 possible isomers can exist.

The elucidation of the structures of the cinnamic acid dimers is largely due to the extensive work of Störmer and his collaborators (for a summary see ref. 6). The German workers distinguished among the various isomers by carrying out optical resolutions on suitable derivatives. With the physical methods now available, these time-consuming procedures are no longer necessary. For example, infrared spectroscopy can be useful in distinguishing between 5- and 6-membered anhydrides, thus allowing a distinction to be

[1]*A preliminary account of this work was published in Chem. & Ind. (London), 897 (1960). Presented in part at the Annual Conference of the Chemical Institute of Canada, Ottawa, June 13–15, 1960.*
[2]*The relative stereochemistry of substituents on the cyclobutane ring is designated α and β following Fieser's convention for carbohydrate derivatives (7).*
[3]*This work is erroneously reported in the Annual Reports of the Chemical Society (London), 1958, as showing a head-to-head structure for III.*
[4]*Recently, Corse, Finkle, and Lundin (10) have postulated a transfusion of cyclobutane rings to a cyclohexane-1,4-dione ring to explain the n.m.r. spectrum of the photodimer of 1,5-dicarbomethoxy-3-ketopenta-1,4-diene.*

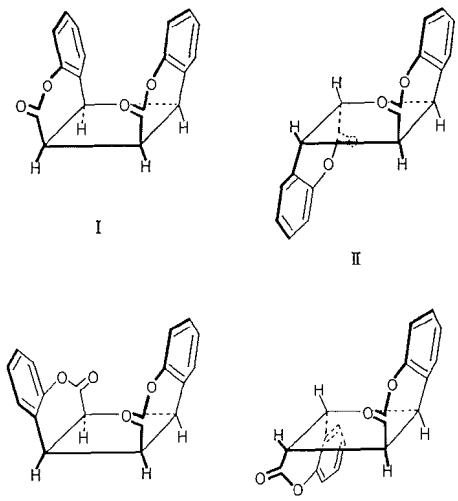


FIG. 1. Four isomeric structures for coumarin dimers. I represents the photodimer of coumarin, and II, the dilactone derived from the photodimer of *o*-hydroxy-*trans*-cinnamic acid.

made between the head-to-head (truxinic) and head-to-tail (truxillic) type dimers. Furthermore, n.m.r. spectroscopy can be a powerful tool in determining the relative stereochemistry of substituents on a cyclobutane ring, by taking advantage of the symmetry properties of these derivatives. Both these methods proved very valuable in the present work.

The photodimer of coumarin was prepared according to the method of Ciamician and Silber (1), viz., irradiation of an ethanolic solution of coumarin with sunlight. The same compound was also obtained by Schönberg's method (11), irradiation of a suspension of coumarin in water.

The only meaningful work reported on the photodimer of coumarin was Schönberg's observation (11) that it dissociated to coumarin on heating. This has been confirmed in the present study. de Jong's experiments (12) on I were of little value, as the products obtained were poorly characterized; no elemental analyses were recorded. For example, alkali fusion of I was reported to give an acid, m.p. 157°, which was claimed to be a cyclobutane dicarboxylic acid. Attempted repetition gives only salicylic acid, m.p. 158°.

In the present work, I was found to give a di-*o*-hydroxyphenylcyclobutane-dicarboxylic acid (IV), $C_{18}H_{16}O_6$, by dissolution of I in hot alkali, followed by careful acidification below 0°. The acid cyclized very readily to I in presence of a trace of acid at room temperature. The cyclization also took place on heating, so that the melting point of IV was not its true melting point, but that of I. The stereochemistry of IV and I was therefore identical.

In order to obtain a dimethyl ether dimethyl ester of the same stereochemistry as I, methylation of IV was tried with diazomethane. However, even after prolonged treatment, the material was largely phenolic. Methylation with dimethyl sulphate and alkali took place slowly, but after 36 hours at room temperature, 65–75% of phenolic compound had reacted, as estimated by the change in ultraviolet absorption spectrum in going from an alkaline to an acid solution (13). As this was expected to be a mixture of epimeric, as well as partially and fully methylated, products, the crude material was treated with diazomethane. A crystalline dimethyl ether dimethyl ester, V, $C_{22}H_{24}O_6$, m.p. 110°, was obtained in 70% overall yield. It was found to be homogenous by chromatography.

The n.m.r. spectrum of V (Fig. 2) was very informative. The spectrum revealed the presence of four different[5] methoxyl groups (τ, 6.26, 6.32, 6.59, and 6.82 (15)). Thus V can

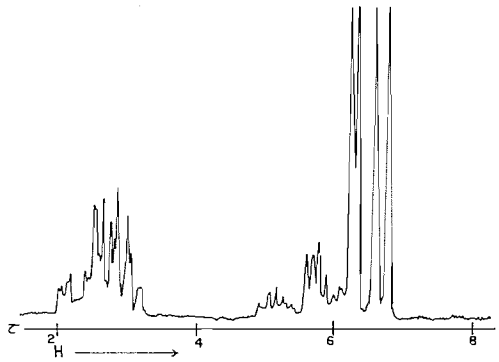


FIG. 2. The n.m.r. spectrum of V in carbon tetrachloride solution. τ values refer to tetramethylsilane as internal standard.

contain no elements of symmetry (axis, plane, or center), based on a time-average structure. This was in agreement with the unsymmetrical nature of the spectrum of the cyclobutane protons (τ, 5.0–6.3). The aromatic protons occurred at lowest field (τ, 1.98–3.6), and intensity measurements showed that the ratio of aromatic protons to methoxyl protons was 8.12.

The absence of symmetry deduced from the n.m.r. spectrum eliminated 9 of the 11 possible structures for a dimethyl ether dimethyl ester derived from the four possible structures for I (Fig. 1), taking into account the possibilities of epimerization. The 11 structures (*dl*-structures being counted as one) are shown in Fig. 3.

The esters can be divided into two groups, five, *a* to *e*, derived from a head-to-tail (truxillic type) and six, *f* to *k*, from a head-to-head (truxinic type) acid. Structures *a* to *e* can be eliminated for V, as all of them have an element of symmetry; *a* has a center, *b* and *e* have a plane, and *c* and *d* have both a plane and an axis of symmetry. None of these compounds can give rise to four methyl bands in the n.m.r. spectrum. Whereas *a*, *c*, and *d* should give rise to only two bands corresponding to six protons each, *b* and *e* would be expected to give rise to three bands in the ratio of 3:3:6. The ester V, and therefore I, can not be derived from a head-to-tail type structure. Of the six truxinic or head-to-head types, four structures, *f*, *g*, *h*, and *i*, can be eliminated. All these will give rise to only two methyl bands, as *f* and *g* have a plane of symmetry and *h* and *i* have an axis of symmetry in the plane of the cyclobutane ring. The two remaining structures, *j* and *k*, are the only possible structures for V, as they contain no element of symmetry. Each of them is formed from a head-to-head type structure for I.

In order to distinguish between the two possible structures *j* and *k* for V, the ester was treated with sodium methoxide in methanol. An epimeric ester, VI, $C_{22}H_{24}O_6$, m.p. 138°, was obtained. The n.m.r. spectrum of VI showed only two methyl bands (τ, 6.32 and 6.46), each corresponding to six protons; an element of symmetry had been restored during this epimerization. The ester VI was shown to be a cis diester as follows. Hydrolysis of VI with alkali gave a dicarboxylic acid, VII, $C_{20}H_{20}O_6$, m.p. 202°. With acetic anhydride, VII gave an anhydride, VIII, $C_{20}H_{18}O_5$, m.p. 121°. No epimerization took

[5]*The bands at τ 6.26 and 6.32 are tentatively assigned to the methoxyl groups on the phenyl rings by comparison with the n.m.r. spectrum of the fully methylated product obtained from the photodimer of 7-methoxycoumarin (14).*

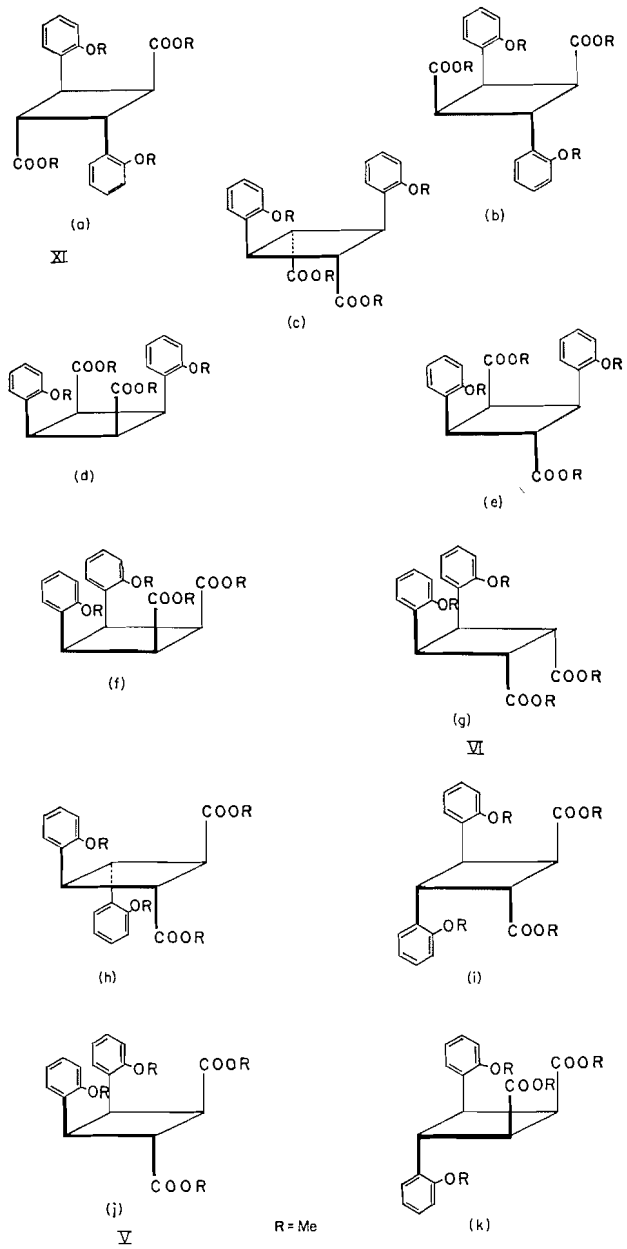


FIG. 3. The 11 isomeric structures for a dimethyl ether dimethyl ester derived from the four structures depicted in Fig. 1. V, VI, and XI are referred to in the text. Only one enantiomer of a *dl*-structure is shown.

place in this sequence of reactions, as VIII could be converted to VII with alkali at room temperature and further to VI with diazomethane. The carbonyl frequencies of the anhydride (1854 and 1768 cm^{-1}) were characteristic of a 5-membered anhydride (16) and were identical with those of the model compound 1α,2α-diphenylcyclobutane-3β,4β-dicarboxylic (β-truxinic) anhydride (6). The formation of a 5-membered anhydride from VI, via the reaction sequence described above, confirmed the head-to-head type

structure for VI, and therefore for V. The application of symmetry principles to the interpretation of the n.m.r. spectrum of V was correct.

Of the two structures for V, viz., *j* and *k*, only the former can give rise to an epimeric cis diester. The latter, *k*, which is itself a cis diester, can not epimerize to a new cis ester, but can only give rise to a trans ester. The structure *k* is therefore excluded for V, which must be 1α,2α-di-*o*-methoxyphenylcyclobutane-3α,4β-dicarboxylate *j*. Epimerization of this ester can lead to two possible cis esters, the all-cis 1α,2α-di-*o*-methoxyphenylcyclobutane-3α,4α-dicarboxylate (*f*) or 1α,2α-di-*o*-methoxyphenylcyclobutane-3β,4β-dicarboxylate (*g*). Of these, the former can be ruled out as it is unlikely that V, with three eclipsed interactions, would epimerize to an ester with four eclipsed interactions, and the ester VI must be 1α,2α-di-*o*-methoxyphenylcyclobutane-3β,4β-dicarboxylate (*g*).

The structure for V establishes the stereochemistry of the two aryl groups. These are 1:2-cis in V and VI, and must also be cis in their precursors, IV and I, as no epimerization of aryl groups is likely under the reaction conditions employed. Since the dicarboxylic acid IV cyclizes so readily to the dilactone I, the two carboxyl groups must be cis to the *o*-hydroxyphenyl groups. The complete structure and stereochemistry of IV and I is therefore 1α,2α-di-*o*-hydroxyphenylcyclobutane-3α,4α-dicarboxylic acid for IV, and the corresponding dilactone for I. These compounds therefore represent the hitherto unknown ω-truxinic acid type.[6]

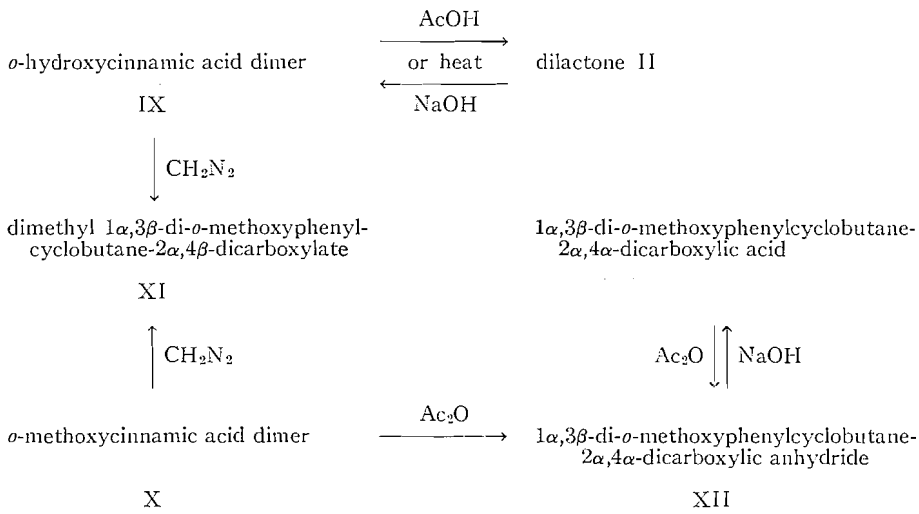
Having established the structure for the photodimer of coumarin, the structures of the photodimers of two related compounds, viz., *o*-hydroxy-*trans*-cinnamic acid and *o*-methoxy-*trans*-cinnamic acid, can be considered. These are of interest, as the photodimer of *o*-hydroxy-*trans*-cinnamic acid has been reported to cyclize to a dilactone, II, m.p. 320° (19, 20), which is isomeric with the photodimer of coumarin.

The photodimers of the substituted cinnamic acids were prepared by irradiation of the crystalline acids with sunlight (19, 21), or with ultraviolet light (20). The photodimer of the *o*-hydroxy acid IX was reported to melt at 320°, which is undoubtedly not its true melting point, but the melting point of the cyclized dilactone II. The photodimer of the *o*-methoxy acid was reported to melt at 264°. These dimers were assigned a head-to-tail trans cyclobutane structure by Stobbe and Bremer (22) by analogy with the dimerization of *trans*-cinnamic acid to 1α,3β-diphenylcyclobutane-2α,4β-dicarboxylic acid (α-truxillic acid). However, this analogy is not strictly valid, as Bernstein and Quimby (23) demonstrated that different crystalline forms of *trans*-cinnamic acid give structurally different acids, i.e. head-to-tail (α-truxillic) or head-to-head (β-truxinic acid). The structures of IX and X could not be considered as established.

In the present work, IX and X were prepared by irradiation of the crystalline acids with ultraviolet light. In the case of the *o*-methoxy acid, the dimer obtained by this method had the same melting point (264°) as that reported in the literature (21). The structures of these compounds were investigated, by essentially the same approach as followed for I. However, as both the *o*-hydroxy and *o*-methoxy compounds were available in this series, the stereochemistry was established by making use of the interrelationships shown in the scheme below.

The dimers IX and X were shown to have the same stereochemistry at all the centers, by preparing the same dimethyl ether dimethyl ester XI, m.p. 132°, from each acid with diazomethane in ether. No epimerization seemed likely under the conditions employed.

[6]*Although all 11 dimeric cinnamic acids have been reported (6), the preparation of 1α,2α-diphenylcyclobutane-3α,4α-dicarboxylic (ω-truxinic) and 1α,2β-diphenylcyclobutane-3β,4α-dicarboxylic (μ-truxinic) acids by Shemyakin (17) is doubtful. Ettlinger (18) has suggested that these are lactonic acids, but the evidence has not been published.*



Treatment of X with boiling acetic anhydride containing a trace of *p*-toluenesulphonic acid gave an anhydride, $C_{20}H_{18}O_5$, m.p. 188° (XII), in good yield. The same anhydride could be obtained if the toluene sulphonic acid was omitted, but the yield of XII was very poor. The anhydride was shown to be intramolecular from its molecular weight (323) and 6-membered from its infrared spectrum (carbonyl bands at 1814 and 1762 cm^{-1}) (16). The model compound 1α,3β-diphenylcyclobutane-2α,4α-dicarboxylic anhydride (γ-truxillic anhydride) (6) showed the same frequencies, and these were slightly higher than those of glutaric anhydride (1802 and 1761 cm^{-1}) (16). This may reflect the strain involved in fusing a 6-membered anhydride 1:3 on a cyclobutane ring. The n.m.r. spectrum of XII, measured in pyridine (24), showed two methoxyl bands (τ, 6.87, 6.93); the two aryl groups were in different stereochemical environment, i.e., one group was cis and the other trans to the anhydride ring. Thus the aryl groups were situated 1:3-trans on the cyclobutane ring.

The stereochemistry of the two carboxyl groups relative to the aryl groups was shown as follows. The dilactone II was easily hydrolyzed to IX and the latter relactonized to give II. The stereochemistry of II and IX was identical. The easy interconversions of II and IX implied a cis relationship of the carboxyl and *o*-hydroxyphenyl substituents. The carboxyl groups were therefore 1:3-trans, and each of them was cis to one of the aryl substituents. That the lactonization of IX to give II involved the formation of 6-membered dihydropyrones was shown by the thermal decomposition of II to give coumarin. The compounds IX and X were indeed derivatives of 1α,3β-diphenylcyclobutane-2α,4β-dicarboxylic (α-truxillic) acid, and the isomer II was the head-to-tail trans compound.

The formation of the anhydride XII had involved the epimerization of one of the carboxyl groups. This was confirmed by treating XII with alkali at room temperature, which gave a new acid, $C_{20}H_{20}O_6$, m.p. 225–226° (XIII), mixed m.p. with X, 199–220°. The acid XIII was readily converted into its anhydride, and was therefore 1α,3β-di-*o*-methoxyphenylcyclobutane-2α,4α-dicarboxylic acid. Treatment of XIII with diazomethane gave a low-melting ester which readily epimerized to XI. The ester was not obtained crystalline, but its n.m.r. spectrum did show three methyl bands in the ratio of 1:1:2. The pattern changed rapidly to that given by dimethyl 1α,3β-di-*o*-methoxyphenyl-2α,4β-dicarboxylate (XI), if traces of acid or alkali were added.

The assignment of the cis structure for the photodimer of coumarin (I) has now received full confirmation by Professor Griffin, Yale University (private communication). Ozonolysis of I gives 1α,2α,3α,4α-tetracarboxycyclobutane identical with the one prepared by Griffin and Veber (25).

It is of interest that Schenck has recently reported (26) that irradiation of coumarin in presence of benzophenone gives a new dimer. A head-to-head trans structure has been suggested for it.

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were determined on a Perkin–Elmer 'Infracord' instrument except those of anhydrides, which were measured on a Perkin–Elmer single-beam double pass instrument. The n.m.r. spectra were recorded on a Varian V-4302 60 Mc/s instrument.

1α,2α-Di-o-hydroxyphenyl-3α,4α-dicarboxylic Acid Dilactone: the Photodimer of Coumarin (I)

Coumarin (300 g) was dissolved in 3 l. ethanol and exposed to sunlight in eight stoppered pyrex flasks (500 ml) for 4 weeks (May–June). After 1 week, the solution turned pale yellow and started depositing crystals. These were removed periodically, and a total of 4.5 g was collected in 4 weeks. Two crystallizations from glacial acetic acid gave 4 g of I, m.p. 260–262° (decomp.) (lit. m.p. 260° (1)). The ethanolic mother liquors were once again irradiated; after a further 6 weeks, 1 g of I was collected. No crystalline material apart from coumarin was isolated from the deep red solution.

The same compound was also obtained when a suspension of 20 g coumarin in 300 ml water was irradiated with sunlight. The yield of I was 185 mg, which was isolated by extraction of unchanged coumarin with ether.

Alkali Fusion of I: Formation of Salicyclic Acid

One hundred milligrams of I was heated with 0.5 g solid potassium hydroxide at 275° for 10 minutes. The melt was cooled, 5 ml water added, and the mixture acidified with hydrochloric acid. Extraction with ethyl acetate gave a gum from which 22 mg salicylic acid was isolated by extraction with hot petroleum ether (b.p. 80–100°). Recrystallization from the same solvent gave a sample, m.p. 158°, undepressed with an authentic sample. The infrared spectra (nujol mull) of the two samples were superposable.

Hydrolysis of I: 1α,2α-Di-o-hydroxyphenylcyclobutane-3α,4α-dicarboxylic Acid (IV)

Three hundred milligrams of I were dissolved in 5 ml of hot 10% potassium hydroxide. The solution was filtered and cooled to 0°. An ice-cold solution of 2% hydrochloric acid was added gradually with strong cooling, taking care to keep the temperature at 0–5°. The addition of acid was stopped when the solution turned milky. This was then allowed to stand at 0° for 15 minutes. The precipitated acid was filtered off and washed with 10 ml of a citrate–phosphate buffer of pH 7, and then with 5 ml water, followed by 20 ml pentane. The solid was taken up in acetone and filtered. The acetone solution gave 127 mg of the cyclobutane acid IV on evaporation of the solvent below 10°. (Found: C, 66.0; H, 4.7. Calc. for $C_{18}H_{16}O_6$: C, 65.8; H, 4.9%.)

Methylation of I: Dimethyl 1α,2α-Di-o-methoxyphenylcyclobutane-3α,4β-dicarboxylate (V)

A solution of 1 g of I in 10% potassium hydroxide was stirred with dimethyl sulphate (1 ml added at intervals) for 36 hours. The solution was kept strongly alkaline, more potassium hydroxide was added as necessary. After acidification with hydrochloric acid, the product was extracted with ethyl acetate when a gum (0.98 g) was obtained. Attempts to obtain a crystalline material did not succeed. The gum was therefore treated with excess ethereal diazomethane at room temperature. After 2 hours, the excess diazomethane was destroyed by cautious addition of acetic acid and the ether extracted with 1% alkali (twice) and then with water till neutral. The ether extract was dried over anhydrous sodium sulphate and the ether removed under reduced pressure. The residue (0.78 g) crystallized on treatment with a little ethyl acetate followed by petroleum ether (b.p. 30–60°). The crystals, m.p. 104–108°, were chromatographed over alumina, and benzene–ether (9:1) eluted 0.75 g of the dimethyl ether dimethyl ester V, m.p. 110°. (Found: C, 68.7; H, 6.2. Calc. for $C_{22}H_{24}O_6$: C, 68.7; H, 6.3%.)

Epimerization of V: Dimethyl 1α,2α-Di-o-methoxyphenylcyclobutane-3β,4β-dicarboxylate (VI)

The dimethyl ester V (200 mg) was refluxed under nitrogen with a solution of 100 mg of sodium in 25 ml methanol. After 6 hours the methanol was removed, and the residue treated with dilute hydrochloric acid and extracted with ethyl acetate (3×20 ml). The organic layer was washed with dilute alkali and dried (sodium sulphate). Removal of ethyl acetate gave 171 mg of VI, crystallizing from ethyl acetate – petrol ether in colorless plates, m.p. 138°. (Found: C, 68.5; H, 6.2. Calc. for $C_{22}H_{24}O_6$: C, 68.7; H, 6.3%.)

Hydrolysis of VI: 1α,2α-Di-o-methoxyphenylcyclobutane-3β,4β-dicarboxylic Acid (VII)

The ester VI (100 mg) was refluxed with 10% potassium hydroxide (8 ml) containing a few drops of dioxane for 8 hours. The alkaline solution was extracted with ethyl acetate to remove unchanged ester VI,

and the aqueous layer acidified with hydrochloric acid. Extraction with ethyl acetate gave 60 mg of VII, which after crystallization from the same solvent melted at 202° with decomposition. (Found: C, 67.2; H, 5.5. Calc. for $C_{20}H_{20}O_6$: C, 67.4; H, 5.9%.)

Methylation of VII

The acid VII (20 mg) was treated with diazomethane in ether. After 1 hour at room temperature, the ether was evaporated to give 20 mg of VI, m.p. 137–138°, mixed m.p. with VI 138°. The infrared spectra of the two samples (nujol mull) were superposable.

Anhydride from VII: 1α,2α-Di-o-methoxyphenylcyclobutane-3β,4β-dicarboxylic Anhydride (VIII)

The acid VII (40 mg) was refluxed with acetic anhydride (3 ml) for 1 hour. The acetic anhydride was removed under reduced pressure, and the residue dissolved in chloroform. The chloroform solution was washed with aqueous sodium carbonate, and the chloroform layer dried over anhydrous sodium sulphate. Evaporation of the solvent followed by crystallization from acetone – petrol ether gave 28 mg of the anhydride VIII, m.p. 121° after three crystallizations. (Found: C, 70.8; H, 5.5. Calc. for $C_{20}H_{16}O_5$: C, 71.0; H, 5.6%.)

Hydrolysis of VIII

The anhydride VIII (20 mg) was stirred with 5% aqueous sodium hydroxide at room temperature for 10 hours. The aqueous layer was extracted with chloroform to remove unchanged anhydride (2 mg). Acidification of the aqueous layer followed by extraction with ethyl acetate gave 15 mg of an acid, m.p. 202° (decomp.). Mixed melting point with a sample of VII was undepressed, and the infrared spectra (nujol mull) were superposable.

Photodimer of o-Hydroxy-trans-cinnamic Acid: 1α,3β-Di-o-hydroxyphenylcyclobutane-2α,4β-dicarboxylic Acid (IX)

Two grams of *o*-hydroxy-*trans*-cinnamic acid prepared from coumarin (27) was irradiated with ultraviolet light (Hanovia, Type 306). From time to time, the solid was stirred. After 48 hours the solid was extracted with hot chloroform, in which the monomer is insoluble. Evaporation of VIII gave 0.4 g of VIII. The melting point of VIII reported in the literature (320°) was the same as that of the dilactone II, into which it is converted on heating.

Dilactone of IX: 1α,3β-Di-o-hydroxyphenylcyclobutane-2α,4β-dicarboxylic Acid Dilactone (II)

The acid IX (200 mg) was heated with acetic anhydride for 5 minutes. The anhydride was removed under reduced pressure and the residue treated with aqueous sodium carbonate. The insoluble dilactone (163 mg) was collected and crystallized from glacial acetic acid, m.p. 324° (decomp.).

Hydrolysis of II

The dilactone II (100 mg) was dissolved in 5% aqueous potassium hydroxide on heating. The solution was filtered, cooled to 0°, and acidified cautiously with hydrochloric acid till neutral. After standing for 15 minutes, the precipitated acid was collected (40 mg) and found to be identical with IX (infrared spectra).

Decomposition of II: Formation of Coumarin

The dilactone II (50 mg) was heated at 300° for 10 minutes in a test tube. An oily distillate collected at the top of the tube and was treated with a little ether when it crystallized. The crystals, m.p. 68°, were found to be identical with coumarin (mixed m.p.).

Methylation of IX: Dimethyl 1α,3β-Di-o-methoxyphenylcyclobutane-2α,4β-dicarboxylate (XI)

The acid IX (100 mg) was suspended in 30 ml ether containing a few drops of methanol. An excess of diazomethane in ether was added and the mixture allowed to stand at room temperature for 3 hours. It was worked up in the usual manner to give 25 mg of the dimethyl ether dimethyl ester XI, m.p. 132° after crystallization from ether. (Found: C, 68.4; H, 6.4. Calc. for $C_{22}H_{24}O_6$: C, 68.7; H, 6.3%.)

Photodimer of o-Methoxycinnamic Acid: 1α,3β-Di-o-methoxyphenylcyclobutane-2α,4β-dicarboxylic Acid (X)

An acetone solution of *o*-methoxy-*trans*-cinnamic acid prepared by the methylation of coumarin (28) was evaporated on two watchglasses (7-cm diameter) by a fast stream of air. The small crystals thus deposited were irradiated by a Hanovia lamp for 36 hours. From time to time the solid was taken up in cold acetone to remove the sparingly soluble dimer X, and the acetone solution recycled. X (1.8 g) as collected from 4 g of the monomer, and crystallized from chloroform–methanol, m.p. 264° (lit. (21) m.p. 264°).

Methylation of X: Dimethyl 1α,3β-Di-o-methoxyphenylcyclobutane-2α,4β-dicarboxylate (XI)

The acid (120 mg) was esterified with diazomethane as described above to give the same diester (130 mg), XI, m.p. 132°. Mixed melting point with a sample prepared from IX was undepressed and the infrared spectra (nujol mull) were superposable.

Anhydride from X: 1α,3β-Di-o-methoxyphenylcyclobutane-2α,4α-dicarboxylic Acid Anhydride (XII)

The acid X (200 mg) was refluxed with 7 ml acetic anhydride containing 5 mg *p*-toluenesulphonic acid for 6 hours. The acetic anhydride was removed under reduced pressure and the residue taken up in chloroform. The chloroform extract was washed with alkali and dried over anhydrous sodium sulphate. Concentration of the chloroform solution followed by addition of petrol ether (b.p. 30–60°) gave a crystalline anhydride

(154 mg) which, after three crystallizations from chloroform – petrol ether, melted at 188°. (Found: C, 70.9; H, 5.6; mol. wt. (Rast), 323. Calc. for $C_{20}H_{18}O_5$: C, 71.0; H, 5.6; mol. wt., 338.) The infrared spectrum (CCl_4) showed carbonyl bands at 1814 and 1762 cm^{-1}.

Hydrolysis of XII: 1α,3β-Di-o-methoxyphenylcyclobutane-2α,4α-dicarboxylic Acid (XIII)

The anhydride XII (170 mg) was treated with 10% aqueous sodium hydroxide at room temperature for 18 hours. The aqueous layer was extracted once with chloroform to remove unchanged anhydride, and the aqueous layer acidified. Ethyl acetate extraction gave the acid XII (104 mg), which after crystallization from acetone – petrol ether melted at 225–226°. Mixed melting point with X was 199–220°. (Found: C, 67.2; H, 5.9. Calc. for $C_{20}H_{20}O_6$: C, 67.4; H, 5.9%.)

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