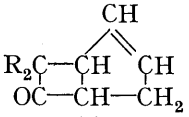
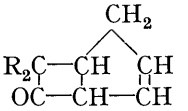
387. *The Constitution of the Condensation Product of Diphenylketen and* cyclo*Pentadiene.*

By J. R. Lewis, G. R. Ramage, J. L. Simonsen, and (in part) W. G. Wainwright.

The condensation of diphenylketen with *cyclo*pentadiene yields by 1 : 2-addition 6-*keto*-7 : 7-*diphenyl*bicyclo[3, 2, 0]*hept*-2-*ene*. This gives on oxidation with permonophthalic acid an *epoxide*, convertible by acetic–sulphuric acid into the *diacetate* of 2 : 3-*dihydroxy*-6-*keto*-7 : 7-*diphenyl*bicyclo[3, 2, 0]*heptane*, from which by the action of alkali two stereoisomeric 3 : 4-*dihydroxy*-2-*benzhydryl*cyclo*pentane*-1-*carboxylic acids* can be prepared. Oxidation of these with lead tetra-acetate, followed by potassium permanganate, gives two stereoisomeric 4 : 4-*diphenylbutane*-1 : 2 : 3-*tricarboxylic acids*, which have been prepared synthetically by the hydrolysis of the condensation product of bromodiphenylmethane and methyl sodiopropane-αααβγ-tetracarboxylate. It is suggested that the analogous condensation product from dimethylketen and *cyclo*pentadiene might provide a suitable starting material for the synthesis of caryophyllenic acid.

In the course of his well-known investigations on the reactions of the ketens (summarised in " Die Ketene," 1912), Staudinger (*Ber.*, 1906, **39**, 968; *Annalen*, 1907, **356**, 51) prepared by the condensation of dimethylketen and *cyclo*pentadiene a dicyclic unsaturated ketone, $C_9H_{12}O$, for which he suggested the alternative formulæ (I; R = Me) and (II; R = Me). It occurred to us that, if (I) correctly represented the ketone, it might prove a suitable starting point for the synthesis of caryophyllenic acid (III).


(I.)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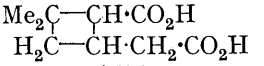
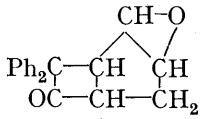

(III.)

As preliminary experiments on the degradation of this somewhat inaccessible ketone gave products which could not be characterised, we decided to investigate in the first instance the related ketone (I; R = Ph) or (II; R = Ph), which is highly crystalline and can be prepared with comparative ease from diphenylketen.

The experiments now to be described have shown the ketone to be (I; R = Ph), a result which was not anticipated, since the somewhat analogous condensations of *cyclo*pentadiene with ethyl azodicarboxylate (Diels, Blom, and Koll, *Annalen*, 1925, **443**, 242) and with maleic anhydride (Diels and Alder, *ibid.*, 1928, **460**, 98) have given 1 : 4-adducts.

By oxidation of the ketone with permonophthalic acid (Böhme, *Ber.*, 1937, **70**, 379) the *epoxide* (IV), m. p. 121—122°, was obtained in excellent yield and this on treatment with acetic–sulphuric acid formed the *diacetate* (V), m. p. 122—124°, from which the *glycol*, m. p. 178—180°, was prepared by hydrolysis with alcoholic sulphuric acid.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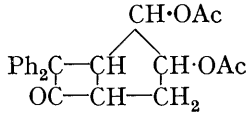
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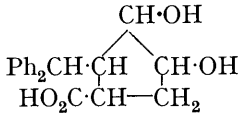
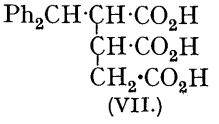

(VI.)

Whilst the glycol and its diacetate appear to be stable in acid solution, on treatment with alkali fission of the *cyclo*butane ring occurs with remarkable facility with the formation, depending upon the conditions used, of two stereoisomeric dihydroxy-acids or their esters. By the action of sodium methoxide on the glycol, or of cold methyl-alcoholic potassium hydroxide solution on the diacetate, *methyl* α-3 : 4-*dihydroxy*-2-*benzhydryl*cyclo*pentane*-1-*carboxylate*, m. p. 159—160°, is obtained, yielding on alkaline hydrolysis in the cold the α-*acid*, m. p. 170—171°. If, however, the diacetate, the glycol or the α-methyl ester is digested with an excess of methyl-alcoholic potassium hydroxide solution, an isomeric acid, β-3 : 4-*dihydroxy*-2-*benzhydryl*cyclo*pentane*-1-*carboxylic acid*, m. p. 177—180° (*methyl*

ester, m. p. 126—128°), is obtained. The ease of esterification of the acids and of hydrolysis of their esters suggests that the structure (VI) represents the two isomeric acids and this was proved by their oxidation with lead tetra-acetate, followed by potassium permanganate, to two isomeric α- and β-4 : 4-*diphenylbutane*-1 : 2 : 3-*tricarboxylic acids* (VII), m. p. 185—187° and 208—209° respectively. These acids were prepared synthetically by the hydrolysis of the condensation product of bromodiphenylmethane and methyl sodiopropane-ααβγ-tetracarboxylate, one of the carboxyl groups being eliminated.

The facility with which ring fission occurs in the dihydroxy-ketone is somewhat remarkable, but it finds an approximate parallel in the fission of fenchone (VIII) with potassium hydroxide (Wallach and Wienhaus, *Annalen*, 1909, **369**, 72) or sodamide (Semmler, *Ber.*, 1906, **39**, 2578) to fencholic acid (IX) or its amide.



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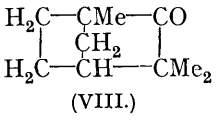
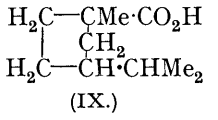
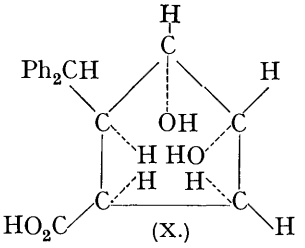


(VIII.)

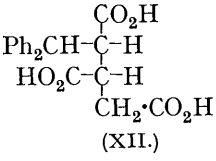


(IX.)

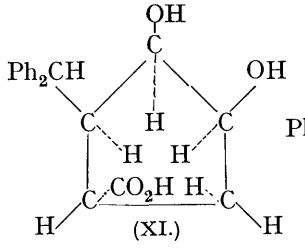
Although it has not proved possible to determine the configurations of the two isomeric hydroxy-acids and the related tricarboxylic acids, certain points of interest have emerged. The fact that neither of the hydroxy-acids lactonises necessitates both the hydroxy-groups in the two acids having the *trans*-configuration with respect to the carboxyl group; the hydroxy-groups must therefore be *cis* to one another. This configuration for the hydroxy-groups is supported by the equally facile oxidation of the methyl esters of the α- and the β-dihydroxy-acid with lead tetra-acetate (Criegee, *Ber.*, 1932, **65**, 1771) and, although as a general rule the hydration of an epoxide gives exclusively the *trans*-glycol, it has been observed by Böeseken (*Rec. trav. chim.*, 1928, **47**, 683) that the *cis*-form may predominate in certain cases if the hydration is carried out in acid solution. It follows, therefore, that the most probable representations of the two hydroxy-acids are (X) and (XI), which would on oxidation give the isomeric tricarboxylic acids (XII) and (XIII). It has not, however, proved possible to assign a definite configuration to the acids.



(X.)



(XII.)



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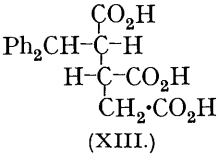
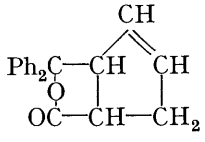
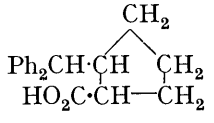


(XIII.)

A further example of the facility with which ring fission occurs in the adduct was provided by its oxidation with hydrogen peroxide to an unsaturated *lactone*, $C_{19}H_{16}O_2$, m. p. 116—117°, probably (XIV), which gives on catalytic hydrogenation an acid, $C_{19}H_{20}O_2$, m. p. 125—127°, probably 2-*benzhydryl*cyclo*pentane*-1-*carboxylic acid* (XV).

(XIV.)





(XV.)

The ring fission occurring here is analogous to that observed in the oxidation of cyclic ketones with Caro's reagent (compare Robinson and Smith, this vol., p. 371).

Experimental.

6-*Keto*-2 : 3-*epoxy*-7 : 7-*diphenyl*bicyclo[3, 2, 0]*heptane*.—Diphenylketen (from diphenylchloroacetyl chloride, 28 g.) and *cyclo*pentadiene (10 g.) in ligroin (b. p. 40—60°) were kept for 2 days in a carbon dioxide atmosphere. The solvent was removed, and the solid residue crystallised

from methyl alcohol (yield 23 g.; m. p. 86—88°). The condensation product (5 g.) in ether was mixed with an ethereal solution of permonophthalic acid and kept at room temperature for 12—15 days, titration of 2 c.c. portions with N/20-sodium thiosulphate, compared with blank per-acid solution, indicating the completion of the oxidation. The ethereal solution, washed with potassium iodide solution, followed by sodium hydroxide solution, was dried, and the ether removed, leaving the *oxide* (5 g.), which crystallised from *cyclo*hexane and then from methyl alcohol in fine needles, m. p. 121—122° (Found: C, 82·8; H, 5·8. $C_{19}H_{16}O_2$ requires C, 82·6; H, 5·8%).

2 : 3-*Dihydroxy*-6-*keto*-7 : 7-*diphenyl*bicyclo[3, 2, 0]*heptane*.—The oxide (6·4 g.), dissolved in acetic acid (120 c.c.) containing concentrated sulphuric acid (0·5 c.c.), was kept overnight and then poured on ice. The separated solid was dissolved in ether, and the ethereal extract washed with sodium carbonate solution and dried over potassium carbonate. Removal of the solvent left a gum (7·8 g.), which was dissolved in hot methyl alcohol; on cooling, the *diacetate* crystallised in large prismatic needles, m. p. 122°, raised to 122—124° by two further crystallisations from the same solvent [Found: C, 72·6; H, 5·6; OAc, 22·3. $C_{19}H_{16}O(OAc)_2$ requires C, 73·0; H, 5·8; OAc, 22·8%]. The diacetate (0·2 g.), mixed with ethyl alcohol (5 c.c.) and sulphuric acid (0·5 c.c.), was heated on the water-bath for 3 hours. Addition of water to the cooled solution precipitated the *glycol*, which was sparingly soluble in ether and benzene, but crystallised from dilute methyl alcohol or ethyl acetate in balls of needles, m. p. 178—180° (Found: C, 77·8; H, 6·3. $C_{19}H_{18}O_3$ requires C, 77·5; H, 6·1%). The glycol can also be prepared by allowing the diacetate to stand overnight with very dilute methyl-alcoholic potassium hydroxide solution.

α-3 : 4-*Dihydroxy*-2-*benzhydryl*cyclo*pentane*-1-*carboxylic Acid*.—*Methyl ester*. (a) To a well-cooled solution of the diacetate (1 g.) in methyl alcohol (8 c.c.), a cold methyl-alcoholic potassium hydroxide solution (KOH, 0·4 g.; MeOH, 2 c.c.) was added. After keeping overnight, the addition of water precipitated the α-*methyl* ester (0·7 g.), which crystallised from benzene in fine needles, m. p. 159—160° [Found: C, 73·5; H, 6·3; OMe, 9·2. $C_{19}H_{19}O_3(OMe)$ requires C, 73·6; H, 6·7; OMe, 9·5%], sparingly soluble in ether.

(b) To a solution of the glycol (0·5 g.) in methyl alcohol (2 c.c.), sodium methoxide (Na, 0·05 g.) was added. The solution was boiled for 1 minute, kept for an hour, water added, and the separated solid (0·3 g.) collected and crystallised from benzene; m. p. 159—160°, both alone and in admixture with the above ester.

The methyl ester (0·2 g.), when digested with dilute sulphuric acid (conc. acid, 1 c.c.; water, 10 c.c.) for 3 hours, was converted into a gum. This was dissolved in ether, and the ethereal extract washed with sodium carbonate solution, dried, and evaporated. The residue (0·05 g.) crystallised when triturated with benzene and had m. p. 150—170°; it was not further examined. Acidification of the carbonate solution gave the α-*dihydroxy-acid*, which crystallised from ethyl acetate in hard prismatic needles, m. p. 170—171° (Found: C, 72·8; H, 6·5; *M*, 315. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·4%; *M*, 312). The *ethyl* ester, prepared by treatment of the glycol with sodium ethoxide or by digestion of the methyl ester with ethyl alcohol and sulphuric acid, crystallised from *cyclo*hexane in soft prismatic needles, m. p. 140—141° (Found: C, 74·2; H, 7·2. $C_{21}H_{24}O_4$ requires C, 74·1; H, 7·1%). The *dibenzoate* of the ethyl ester, prepared in pyridine solution, crystallised from ethyl alcohol in soft needles, m. p. 138—139° (Found: C, 77·0; H, 5·6. $C_{35}H_{32}O_6$ requires C, 76·6; H, 5·8%). The p-*bromophenacyl* ester crystallised from dilute acetone in fine needles, m. p. 128—129° (Found: C, 63·7; H, 5·1. $C_{27}H_{25}O_5Br$ requires C, 63·6; H, 4·9%).

β-3 : 4-*Dihydroxy*-2-*benzhydryl*cyclo*pentane*-1-*carboxylic Acid*.—The α-methyl ester (3 g.) was digested with methyl-alcoholic potassium hydroxide solution for 1 hour on the water-bath. After removal of the alcohol, water was added, the solution washed with ether and acidified, and the acid extracted with ether. Removal of the solvent left the β-*dihydroxy-acid* (2·8 g.), m. p. about 155°, raised to 177—180° after several recrystallisations from benzene–acetone (Found: C, 73·0; H, 6·4. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·4%). The m. p. was somewhat dependent on the rate of heating and the mixed m. p. with the α-dihydroxy-acid was 154° with previous softening. The β-dihydroxy-acid was very sparingly soluble in benzene, toluene and chloroform, somewhat more readily in ether and ethyl acetate, very readily in alcohol and acetone. The acid was obtained also by digestion of the diacetate with methyl-alcoholic potassium hydroxide solution (6 mols.) or by the hydrolysis of the ethyl ester of the α-dihydroxy-acid, but always as a mixture consisting mainly of the β-acid. The *methyl* ester crystallised from *cyclo*hexane in fine needles, m. p. 126—128° (Found: C, 73·6; H, 6·8. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·7%). The p-*bromophenacyl* ester crystallised from dilute acetone in fine needles, m. p. 154—155° (Found: C, 63·3; H, 4·7. $C_{27}H_{25}O_5Br$ requires C, 63·6; H, 4·9%).

Oxidation of Methyl α-**3** : **4**-*Dihydroxy*-**2**-*benzhydryl*cyclo*pentane*-**1**-*carboxylate. Formation of* α-**4** : **4**-*Diphenylbutane*-**1** : **2** : **3**-*tricarboxylic Acid.*—A standard acetic acid solution of lead tetra-acetate (107 c.c., 1·39N/10) was added to the α-methyl ester (2·2 g.) dissolved in acetic acid (20 c.c., distilled over chromic acid). Titration of 2 c.c. portions showed that the reaction was practically complete in 2—4 minutes. After standing for 1 hour, the acetic acid solution was poured into water and extracted with ether, the extract being washed with sodium carbonate solution and dried. Removal of the solvent left an oil (2 g.), which gave amorphous derivatives with carbonyl reagents. It was dissolved in dry acetone (30 c.c., distilled from potassium permanganate), and finely powdered potassium permanganate (1·4 g.) added slowly. The precipitate was collected and washed with acetone, and sulphur dioxide passed into a suspension of it until the manganese dioxide was in solution. The acid (1·8 g.), isolated by ether extraction, was dissolved in sodium hydroxide solution (20 c.c., 8%) and warmed on the water-bath for 15 minutes. The acidified solution was extracted with ether, removal of the solvent giving the *α-tricarboxylic acid*, which crystallised from formic acid in small prismatic needles, decomp. 187—188° (Found : C, 66·4; H, 5·2. $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·2%). The acid was very readily soluble in alcohol, acetone and hot water, sparingly so in benzene. On heating above its m. p. it gave a gum, probably the acid anhydride. The barium salt was very sparingly soluble, and the calcium salt was sparingly soluble in hot water, readily in cold. The *methyl* ester, prepared by means of diazomethane, crystallised from methyl alcohol in prisms, m. p. 117—119° (Found : C, 68·6; H, 6·1. $C_{22}H_{24}O_6$ requires C, 68·8; H, 6·2%).

Oxidation of Methyl β-**3** : **4**-*Dihydroxy*-**2**-*benzhydryl*cyclo*pentane*-**1**-*carboxylate. Formation of* β-**4** : **4**-*Diphenylbutane*-**1** : **2** : **3**-*tricarboxylic Acid.*—The pure β-methyl ester (0·67 g.) was oxidised with lead tetra-acetate (30 c.c., 1·67N/10), and the neutral product (0·6 g.) further oxidised with potassium permanganate as described above, giving an acid converted by diazomethane into the methyl ester, m. p. 121—122·5°, described below.

A similar oxidation of the crude β-methyl ester (3·7 g.) gave the tricarboxylic acid as a yellow oil, which crystallised after trituration with formic acid and then had m. p. 173—203°. The acid (0·5 g.) was heated with hydrochloric acid (concentrated acid, 5 c.c.; water, 5 c.c.) at 200° for 24 hours; the product was dissolved in ether and, after removal of the solvent, crystallised from formic acid. The solid which separated, m. p. 180—192°, was dissolved in hot water, and the solution filtered from a little tar and kept in the ice-box overnight. The *β-tricarboxylic acid*, which was deposited, decomp. 203—205°, crystallised twice from formic acid (charcoal), separated in fine needles, decomp. 208—209° (Found : C, 66·7; H, 5·7. $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·2%). The *β-methyl* ester, prepared by means of diazomethane, crystallised from methyl alcohol in rosettes of prisms, m. p. 121—122·5°, depressed to 110° on admixture with the methyl ester of the α-tricarboxylic acid (Found : C, 68·4; H, 6·1. $C_{22}H_{24}O_6$ requires C, 68·8; H, 6·2%).

*Condensation of Methyl Propane-*αα*β*γ*-tetracarboxylate* and *Bromodiphenylmethane.*—To a solution of methyl sodiopropane-ααβγ-tetracarboxylate (from the ester, 10 g.) in benzene (50 c.c.), bromodiphenylmethane (9 g.) was added, and the mixture boiled for 24 hours. After addition of water to the cooled solution, the benzene layer was separated and dried, and the solvent removed. Distillation of the residual oil at 5 mm. gave, after a low-boiling fraction, the condensation product (8 g.), b. p. 258°, as a very viscid oil which set to a hard glass. This was dissolved in methyl alcohol and hydrolysed with methyl-alcoholic potassium hydroxide solution (KOH 8 g.). After removal of the alcohol, the solution was acidified, the gummy acid collected in ether, the solvent removed, and the residue digested with hydrochloric acid for 4 hours. The acid was again recovered by ether extraction and, after removal of the solvent, dissolved in aqueous ammonia, and the sparingly soluble barium salt precipitated in three fractions. The acid (1·9 g.) from the most sparingly soluble fraction was repeatedly crystallised from formic acid (charcoal), α-**4** : **4**-diphenylbutane-**1** : **2** : **3**-tricarboxylic acid being ultimately obtained in prismatic needles, decomp. 185°, both alone and in admixture with the α-tricarboxylic acid described above (Found: C, 66·4; H, 5·4%). The acids (1 g. and 3 g.) separated from the remaining fractions of the barium salt were somewhat gummy and after crystallisation from formic acid each had m. p. 150—170°. They were combined and heated at 200° for 24 hours with hydrochloric acid (concentrated acid, 10 c.c.; water, 10 c.c.). The acid, isolated by means of ether, was dissolved in formic acid and, on cooling, the solution deposited a fraction, m. p. 170—185°, consisting of the nearly pure α-tricarboxylic acid; the filtrate (*A*) was reserved. The acid was dissolved in hot water and filtered from a little tar and the solid which separated on cooling was crystallised twice from formic acid, the α-tricarboxylic acid, decomp. 185°, being obtained. The identity was confirmed by the preparation of the methyl ester, m. p. 117—118°

both alone and in admixture with the methyl ester of the α-tricarboxylic acid described on p. 1840.

The formic acid filtrate (*A*) was evaporated on the water-bath until free from the solvent, and the gummy residue digested with hot water, which left undissolved a red tar. The aqueous solution, kept overnight in the ice-box, deposited a solid which after three crystallisations from formic acid (charcoal) gave the pure β-4 : 4-diphenylbutane-1 : 2 : 3-tricarboxylic acid, decomp. 208—209° both alone and in admixture with the β-tricarboxylic acid described on p. 1840 (Found : C, 66·4; H, 5·5%). The methyl ester, prepared by digestion of the acid with methyl alcohol and sulphuric acid for 8 hours, crystallised from methyl alcohol in rosettes of prisms, m. p. 124—125°, which in admixture with the methyl ester of the β-tricarboxylic acid, m. p. 121—122·5° (p. 1840), had m. p. 122—124° (Found : C, 68·6; H, 6·0%).

Oxidation of 6-*Keto*-7 : 7-*diphenyl*bicyclo[3, 2, 0]*hept*-2-*ene with Hydrogen Peroxide*.—To a solution of the dicyclic ketone (5 g.) in methyl alcohol (150 c.c.) cooled to − 10°, a mixture of methyl-alcoholic potassium hydroxide solution (KOH, 1 g.) and hydrogen peroxide (8·5 c.c.; 15%) was slowly added; the whole was kept for 1 hour in the freezing mixture and for 2 hours at room temperature. Water (600 c.c.) was then added, and the *lactone* taken up in ether. The residue (5 g.) after removal of the solvent crystallised from *cyclo*hexane or methyl alcohol in prisms, m. p. 116—117° (Found : C, 82·5; H, 6·2. $C_{19}H_{16}O_2$ requires C, 82·5; H, 5·8%). The lactone was soluble in hot alkali solution and precipitated on acidification.

2-*Benzhydryl*cyclo*pentane*-1-*carboxylic Acid* (XV ?).—The lactone (1 g.) was reduced in alcoholic solution with hydrogen and a palladium-norit catalyst, the hydrogen absorption corresponding to two molecules. The viscid oil obtained on evaporation of the alcohol was dissolved in sodium carbonate solution; this was washed with ether and acidified, and the acid extracted with ether. Removal of the solvent gave the cyclo*pentane acid* (0·8 g.), which crystallised from ligroin (b. p. 40—60°) in large cubes with bevelled edges, m. p. 125—127°, sintering at 117° (Found : C, 81·3; H, 7·1. $C_{19}H_{20}O_4$ requires C, 81·4; H, 7·1%).

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