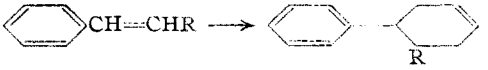
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Addition of Dienes to Coumarin and to Certain Substituted Cinnamic Acids. I.

BY ROGER ADAMS, W. D. MCPHEE, R. B. CARLIN AND Z. W. WICKS

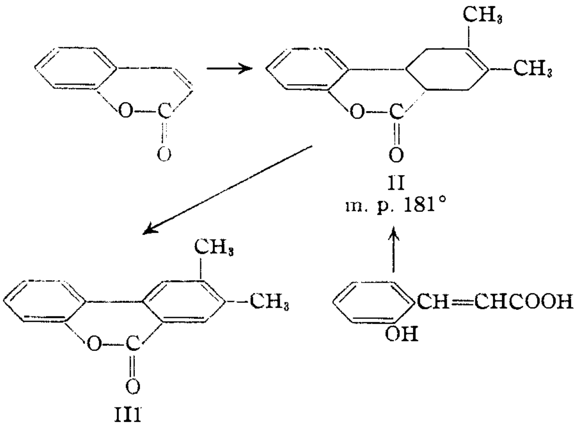
It has been demonstrated by Sugasawa, Kodama and Hara[1a] and by Fujise, Horiuchi and Takahashi[1b] that 2,3-dimethyl-1,3-butadiene will add to cinnamic acid, ethyl cinnamate, or cinnamic aldehyde to form a partially hydrogenated biphenyl carboxylic acid, its ester, or corresponding aldehyde.



I

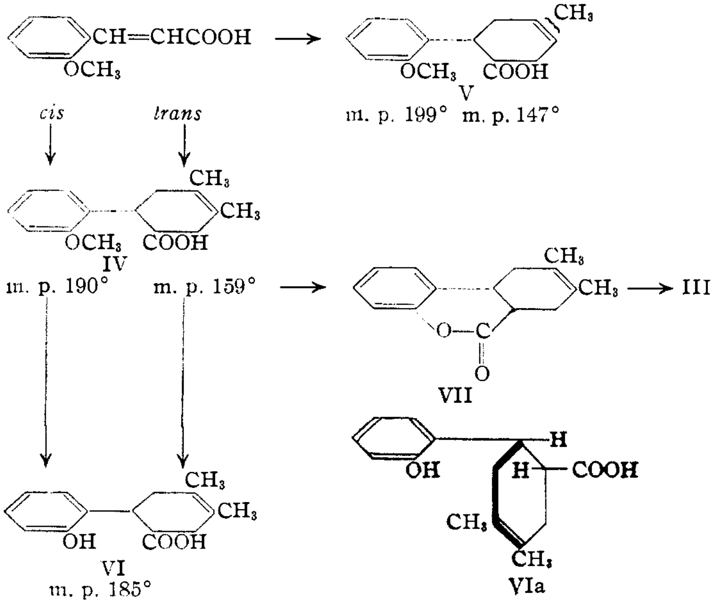
R is COOH, COOEt, or CHO

These structures were written in analogy to the earlier work of Diels and Alder.[2] The possible application of this reaction to the synthesis of partially hydrogenated dibenzopyrones required in another investigation has led to the study of the addition of dienes to coumarin, to *o*-hydroxycinnamic acid, and to several *o*-methoxycinnamic acids.



Numerous attempts to bring about the addition of dienes to coumarin, which would yield directly hydrogenated dibenzopyrones, failed under normal conditions. The reaction was finally accomplished in the case of 2,3-dimethyl-1,3-butadiene, but not with butadiene or isoprene, by using a large excess of reagent and a temperature of 260°. The pyrone (II) was formed in poor yield. *trans*-*o*-Hydroxycinnamic acid, however, reacted with dimethylbutadiene much more readily and at 185° formed directly the same pyrone (II). The pyrone was dehydrogenated to the dibenzopyrone (III), by means of palladium–charcoal.

cis- and *trans*-*o*-methoxycinnamic acids added dimethylbutadiene readily, each giving one diastereoisomeric form of 1,2-dimethyl-4-(*o*-methoxyphenyl)-1-cyclohexene-5-carboxylic acid (IV), or added isoprene less readily, each giving a single diastereoisomeric 1- or 2-methyl-4-(*o*-methoxyphenyl)-1-cyclohexene-5-carboxylic acid (V). Butadiene addition was not realized. The isomeric dimethylbutadiene adducts (IV) were subjected to demethylation with hydrobromic acid in acetic acid at the reflux temperature, and both yielded the same corresponding hydroxy acid (VI). This hydroxy acid was not dehydrated successfully to the pyrone although a variety of conditions was used. Therefore, it probably has the structure shown in VIa At 180°, with



hydrobromic acid in acetic acid or at 225° with ethanolic potassium hydroxide, demethylation of the *trans*-isomer (IV) occurred with simultaneous lactone formation (VII), although the yields were low. The pyrone (VII) which resulted had a melting point different from that (II) obtained by

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[1a] Sugasawa, Kodama and Hara, *J. Pharm. Soc. Japan*, **60**, 138 (1940).

[1b] Fujise, Horiuchi and Takahashi, *Ber.*, **69**, 2102 (1936).

[2] Diels and Alder, *Ann.*, **470**, 62 (1929).

direct addition of dimethylbutadiene to coumarin or *o*-hydroxycinnamic acid. These pyrones are undoubtedly diastereoisomers, for dehydrogenation resulted in the formation from both of the same dibenzopyrone (III). Dehydrogenation of the *trans*-acid (IV) always resulted in simultaneous decarboxylation.

Orcinol was converted to 5-methyl-7-hydroxycoumarin (VIII) by treatment with malic acid and sulfuric acid.[3] This pyrone was then hydrolyzed and methylated to 2-methyl-4,6-dimethoxycinnamic acid (IX). The same goal was reached by a somewhat more satisfactory procedure in which an aldehyde group was introduced into orcinol dimethyl ether (X) by means of zinc cyanide and hydrogen chloride[4] and the resulting aldehyde (XI) converted to the cinnamic acid (IX) with malonic acid in pyridine solution.[5] The cinnamic acid added dimethylbutadiene readily and butadiene rather unsatisfactorily to give 1,2-dimethyl-4-(2,4-dimethoxy-6-methylphenyl)-1-cyclohexene-5-carboxylic acid (XII) and 4-(2,4-dimethoxy-6-methylphenyl)-1-cyclohexene-5-carboxylic acid (XIII), respectively.

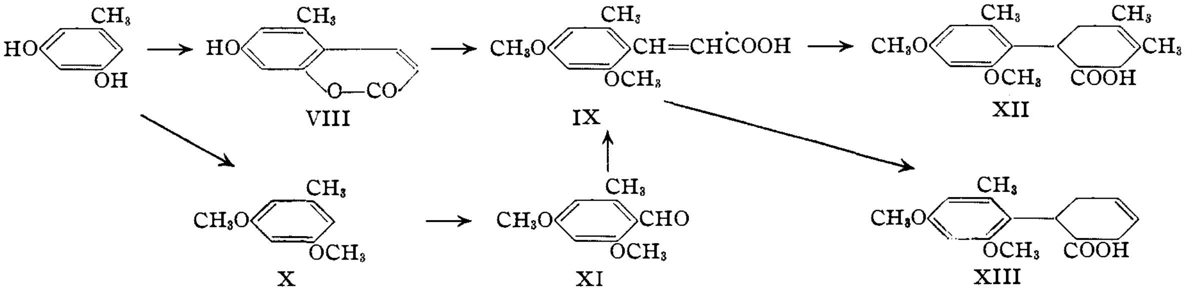
product of addition of dimethylbutadiene to coumarin showed no melting point depression.

B. From Coumarin.—A mixture of 10 cc. of dimethylbutadiene, 12 cc. of dry xylene, and 6 g. of coumarin in a glass liner was heated to 260° for forty hours. On cooling, crystals formed in the bomb jacket (having sublimed from the liner). This material weighed 2.1 g. (22%). After two recrystallizations from ethanol and three vacuum sublimations, the melting point was 181–181.5° (cor.).

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.91; H, 7.07. Found: C, 78.95; H, 7.25.

8,9-Dimethyldibenzopyrone (III). **(From II).**—A thorough mixture of 0.5 g. of the pyrone (II) with 50 mg. of palladium–charcoal was heated under a stream of carbon dioxide to 280°, when hydrogen began to be evolved. The hydrogen was collected and measured in a nitrometer. After nine hours of heating, during which time the temperature was gradually raised to 320°, 86% of the theoretical volume of hydrogen had been evolved.

The reaction vessel was cooled and the contents extracted with 20 cc. of ether. The palladium–charcoal was removed by filtration, and the ether evaporated from the filtrate. The residue was a yellow solid weighing 350 mg. (71%). After two recrystallizations from ethanol, one using Norite, a vacuum sublimation, and another crystallization from ethanol, long yellow needles were obtained, m. p. 175–175.5° (cor.).



These experiments with orcinol serve to demonstrate that two groups, each of which is ortho to the acrylic acid side chain, will not prevent diene addition.

Experimental

8,9-Dimethyl-6a,7,10,10a-tetrahydrodibenzopyrone (II). **A. (From *trans-o*-Hydroxycinnamic Acid).**—A mixture of 6 cc. of dimethylbutadiene, 5 cc. of dry xylene, and 3 g. of *trans-o*-hydroxycinnamic acid[6] in a glass liner was heated in a bomb at 185° for forty hours. The contents after cooling were poured into a flask and the liner rinsed with petroleum ether into this flask. After standing overnight in the ice box, the solution had deposited crystals. After two recrystallizations from ethanol and a high vacuum sublimation, the material had a m. p. of 181–181.5° (cor.); yield 0.2 g. A mixture of this material and the

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.32; H, 5.40. Found: C, 80.09; H, 5.32.

***cis-o*-Methoxycinnamic Acid.**—A solution of 10 g. of coumarin in a solution of 6 g. of sodium hydroxide in 65 cc. of water was prepared by stirring and refluxing during the course of thirty minutes. As refluxing continued, 26 g. of dimethyl sulfate was added dropwise during two hours. Occasional additions of 20% aqueous sodium hydroxide were required to maintain the reaction mixture alkaline.

After addition of the dimethyl sulfate, refluxing was continued for two hours. A solution of 8 g. of sodium hydroxide in 15 cc. of water was added and the solution refluxed for another ninety minutes. The reaction mixture was poured into 300 g. of cracked ice into which 35 cc. of concentrated sulfuric acid had been stirred. The crude solid acid was collected by filtration and dried. It weighed 12.5 g. (quantitative). After crystallization from petroleum ether (b. p. 60–110°), it melted at 91–92°; yield, 93%. Shah and Shah[7] report this same melting point.

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(3) v. Pechmann and Walsh, *Ber.*, **17**, 1646 (1884).

(4) Adams and Montgomery, THIS JOURNAL, **46**, 1518 (1924).

(5) Haworth, Perkin and Rankin, *J. Chem. Soc.*, **125**, 1693 (1924).

(6) Fittig and Ebert, *Ann.*, **226**, 351 (1884).

(7) Shah and Shah, *J. Univ. Bombay*, **7**, (3) 213 (1938).

1,2-Dimethyl-4-(*o*-methoxyphenyl)-1-cyclohexene-5-carboxylic Acid (IV). (From *trans-o*-Methoxycinnamic Acid).—A mixture of 5 cc. of dimethylbutadiene, 6 cc. of dry xylene and 2.8 g. of *trans-o*-methoxycinnamic acid[8] in a glass liner was heated in a bomb at 180° for forty hours. The product crystallized in the cooled liner. The reaction mixture was diluted with approximately twice its volume of petroleum ether (b. p. 60–110°), thoroughly stirred, and the solid collected by filtration; yield 3.3 g. (quantitative). After two recrystallizations from absolute ethanol, the material had a melting point of 159–159.5° (cor.). A mixture of this compound and that resulting from the addition of dimethylbutadiene to *cis-o*-methoxycinnamic acid (m. p. 191°) had the melting range 144–166°.

Anal. Calcd. for $C_{16}H_{20}O_3$: C. 73.82; H. 7.75. Found: C, 73.77; H, 7.78.

1,2-Dimethyl-4-(*o*-methoxyphenyl)-1-cyclohexene-5-carboxylic Acid (IV). (From *cis-o*-Methoxycinnamic Acid).—A mixture of 3.5 cc. of dimethylbutadiene, 5 cc. of dry xylene, and 3.1 g. of *cis-o*-methoxycinnamic acid in a glass liner was heated in a bomb at 170° for twenty-eight hours. The reaction mixture was poured into a beaker and allowed to stand until crystallization occurred. The solid was collected by filtration and dried. After one recrystallization from absolute ethanol, the product melted at 191° (cor.); yield 2.2 g. (48%).

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H. 7.75. Found: C, 73.87, 73.99; H, 8.06, 7.96.

(2)- or 1-Methyl-4-(*o*-methoxyphenyl)-1-cyclohexene-5-carboxylic Acid (V). (From *cis-o*-Methoxycinnamic Acid).—Isoprene used in this and succeeding experiments was supplied by United Gas Improvement Company at Philadelphia. This material is 80% isoprene and contains about 0.1% hydroquinone. It was found that purification of this isoprene mixture to approximately 100% isoprene effected no improvement in the yields of product from reactions in which it was employed.

A mixture of 15 cc. of isoprene, 12 cc. of dry xylene, and 7 g. of *cis-o*-methoxycinnamic acid in a glass liner was heated in a bomb at 170° for thirty hours. The cooled reaction mixture was dissolved in ether and the ether solution extracted three times with saturated aqueous sodium bicarbonate solution. On acidification, the bicarbonate extract deposited a mixture of *cis*- and *trans-o*-methoxycinnamic acids; weight 4.1 g.

The ether solution was then extracted three times with 10% aqueous sodium hydroxide. Acidification of this extract gave a pasty material weighing 2.0 g. This material was dissolved in ether, the solution dried over anhydrous magnesium sulfate, and the ether replaced by benzene. The benzene was removed until the volume of the solution was 10 cc. and 5 drops of absolute ethanol added. On cooling a crystalline solid deposited. Recrystallizations from benzene–absolute ethanol gave fine, white needles, m. p. 199–199.5° (cor.); yield, 0.5 g.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.36. Found: C, 73.30; H, 7.52.

(2)- or 1-Methyl-4-(*o*-methoxyphenyl)-1-cyclohexene-5-carboxylic Acid (V). (From *trans-o*-Methoxycinnamic Acid).—A mixture of 5 cc. of isoprene, 6 cc. of dry xylene and 3.1 g. of *trans-o*-methoxycinnamic acid in a glass liner was heated in a bomb at 185° for forty hours. The cooled reaction mixture was poured into a beaker and allowed to stand in air until crystals formed. These were collected by filtration and dried. A second crop was obtained on standing; yield 2.1 g. (49%).

The crude product was treated several times with Norite in ethanol and recrystallized to constant m. p. The compound formed white needles, m. p. 147–147.5° (cor.).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.36. Found: C, 73.45; H, 7.33.

1,2-Dimethyl-4-(*o*-hydroxyphenyl)-1-cyclohexene-5-carboxylic Acid (VI). A. From High-melting Form of IV.—A mixture of 0.25 g. of the methoxy acid (IV) (m. p. 186–190°), 2.5 cc. of glacial acetic acid, and 2 cc. of 48% hydrobromic acid was refluxed for eight hours and then poured into 250 cc. of water. The salmon-pink paste which settled out was dissolved in ether and the solution extracted several times with saturated aqueous sodium bicarbonate solution. On acidification of this extract, a pink solid was formed, which was collected by filtration and dried; yield 0.1 g. (42%).

The extracted ether solution was washed with water, dried over anhydrous magnesium sulfate, and the ether removed. A very small quantity of a very high-melting solid remained, which had the characteristics of a polymer.

The bicarbonate-soluble solid was recrystallized several times from petroleum ether (b. p. 60–110°); brilliant white needles, m. p. 183--185° (cor.).

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 73.14; H, 7.36. Found: C, 73.41; H, 7.37.

B. From Low-melting Form of IV.—A mixture of 3.6 g. of the methoxy acid (IV) (m. p. 158–159°), 30 cc. of glacial acetic acid, and 12 cc. of 48% hydrobromic acid was treated as just described; yield 3 g. (91%). After two recrystallizations from petroleum ether (b. p. 60–110°), a product identical with that obtained from the high-melting form was isolated.

8,9-Dimethyl-6a,7,10,10a-tetrahydrodibenzopyrone (VII). A. Hydrobromic Acid Method.—A mixture of 1 g. of the methoxy acid (IV) (m. p. 158–159°), 10 cc. of glacial acetic acid and 2 cc. of 48% hydrobromic acid was heated in a sealed glass tube at 180° for eight hours. The reaction mixture was then cooled and poured onto ice. The gummy, dark material which collected was removed and dissolved in ether. The ether solution was extracted three times with saturated aqueous sodium bicarbonate solution. Acidification of this extract gave a small quantity of dark-colored material which could not be characterized.

The residual ether solution was washed with water, dried over anhydrous magnesium sulfate, and the solvent removed. The brown, solid residue was dissolved in 2 cc. of hot ethanol. On cooling, a white solid separated. Recrystallization from ethanol gave brilliant white threads, m. p. 154–155° (cor.); yield 0.2 g. The phenol test (Folin) was negative, and the substance was insoluble in sodium carbonate solution.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.91; H, 7.07. Found: C, 79.08; H, 7.22.

B. Potassium Hydroxide Method.—A mixture of 1 g. of the methoxy acid (IV) (m. p. 158–159°) and a solution

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(8) Reychler, *Bull. soc. chim.*, [4] **3**, 552 (1908).

of 3 g. of potassium hydroxide in 10 cc. of ethanol was heated in a steel bomb at 225° for twenty-four hours. The reaction mixture was poured into a beaker, the bomb rinsed with water into the beaker, and the contents acidified. A greyish solid formed which was collected by filtration and dissolved in ether. The ether solution was twice extracted with 10% aqueous potassium hydroxide solution. The alkaline extract formed a very small quantity of oil on acidification. This material was not further examined.

The residual ether solution was washed with water, dried over magnesium sulfate, and the solvent removed. The residue was crystallized from ethanol, m. p. 153–154°; yield 250 mg. A mixture of this substance and that obtained in part A showed no melting point depression.

8,9-Dimethyldibenzopyrone (III) from the Pyrone (VII).—A sample of 150 mg. of the pyrone (VII) was dehydrogenated over palladium–charcoal in the same manner as described for the dehydrogenation of the pyrone (II). The hydrogen evolved was quantitative. The product, isolated as in the previous case, melted at 175°; yield, 125 mg. A mixture of this material and that obtained from the pyrone (II) showed no melting point depression.

2-Methyl-4,6-dimethoxycinnamic Acid (IX). A. From 5-Methyl-7-hydroxycoumarin.—A solution of 23 g. of 5-methyl-7-hydroxycoumarin (VIII)[8] in a solution of 16 g. of sodium hydroxide in 150 cc. of water was prepared by refluxing for one hour. As refluxing continued, 100 cc. of dimethyl sulfate was added dropwise over the course of two hours, accompanied by enough 20% aqueous sodium hydroxide to keep the solution alkaline. After addition of the dimethyl sulfate, refluxing was continued for two hours, after which 20 g. of sodium hydroxide was added and the solution refluxed two hours longer. The solution was cooled and acidified with iced dilute hydrochloric acid. The solid was collected by filtration and dried. After four recrystallizations from dilute ethanol, with Norite and Darco, the compound was obtained as nearly colorless needles, m. p. 190° (cor.): yield, 5.2 g. (18%).

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.93; H, 6.51.

B. From Orcylaldehyde Dimethyl Ether.—The method used here is essentially that of Haworth, Perkin and Rankin.[5]

To a solution of 1.1 g. of orcylaldehyde dimethyl ether[9,10,4] in 3 cc. of dry pyridine and 0.5 cc. of piperidine, 1.5 g. of malonic acid was added and the mixture warmed on the steam-bath until carbon dioxide began to be evolved (about fifteen minutes) and then for another hour. The solution was then refluxed for five minutes and poured into excess iced 10% hydrochloric acid. The resulting solid was collected by filtration and dried. After one recrystallization from dilute ethanol, the compound formed nearly colorless needles, m. p. 188–190°; yield, 1.2 g. (quantitative).

4-(2-Methyl-4,6-dimethoxyphenyl)-1-cyclohexene-5-carboxylic Acid (XIII).—A mixture of 2 g. of 2-methyl-4,6-dimethoxycinnamic acid, 6 cc. of liquid butadiene, and 6 cc. of dry xylene in a glass liner was heated in a bomb at 170° for forty-eight hours. The cooled reaction mixture was thoroughly extracted with ether and the ether solution extracted three times with 5% aqueous sodium hydroxide solution. The alkaline extract was washed with ether, filtered, and acidified with dilute sulfuric acid. The resulting solid was collected by filtration and dried. This material was a mixture from which starting compound could be isolated by fractional crystallization from ethanol. The ethanol mother liquors were combined and the solvent removed. The residue was crystallized from petroleum ether (b. p. 60–110°). This compound had a m. p. of 140–141° (cor.); yield, 0.2 g.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.52; H, 7.31. Found: C, 69.33; H, 7.23.

1,2-Dimethyl-4-(2-methyl-4,6-dimethoxyphenyl)-1-cyclohexene-5-carboxylic Acid (XII).—A mixture of 1.5 g. of 2-methyl-4,6-dimethoxycinnamic acid, 3 cc. of dimethylbutadiene, and 4 cc. of dry xylene in a glass liner was heated in a bomb at 170° for forty-eight hours. The cooled reaction mixture was dissolved in petroleum ether (b. p. 60–110°) and the solution extracted with a solution of 10% potassium hydroxide in 50% methanol until acidification of the extract no longer caused precipitation to occur. The precipitated solid was collected by filtration and dried; yield 1.2 g. (58%). After several alternate crystallizations from dilute ethanol and from petroleum ether (b. p. 60–110°), the compound formed small white needles, m. p. 174–175° (cor.).

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.00; H, 7.96. Found: C, 71.16; H, 7.82.

Summary

1. 2,3-Dimethylbutadiene was added to coumarin with formation of the pyrone, 8,9-dimethyl-6a,7,10,10a-tetrahydrodibenzopyrone, in poor yield. *trans-o*-Hydroxycinnamic acid added 2,3-dimethylbutadiene more readily to give the same pyrone.

2. *cis*- and *trans-o*-methoxycinnamic acids added dimethylbutadiene readily, each giving one diastereoisomeric form of 1,2-dimethyl-4-(*o*-methoxyphenyl)-1-cyclohexene-5-carboxylic acid. Isoprene added similarly to give the corresponding diastereoisomeric 1- or 2-methyl derivatives.

3. The isomeric dimethylbutadiene addition products mentioned in 2 were demethylated to the same hydroxy acid which could not be dehydrated to the pyrone. The *trans*-form also was demethylated under conditions which gave directly a pyrone stereoisomeric with that obtained from coumarin and dimethylbutadiene. Dehydrogenation of the two pyrones gave the same dibenzopyrone.

4. 2-Methyl-4,6-dimethoxycinnamic acid added dimethylbutadiene or butadiene in a similar manner to give 1,2-dimethyl-4-(2,4-di-

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(9) Adams, Pease, Cain and Clark, THIS JOURNAL, **62**, 2402 (1940).

(10) Gattermann, *Ann.*, **357**, 372 (1907).

methoxy-6-methylphenyl)-1-cyclohexene-5-carboxylic acid or 4-(2,4-dimethoxy-6-methylphenyl)-1-cyclohexene-5-carboxylic acid, thus demonstrating that two ortho groups will not prevent diene addition to a cinnamic acid.

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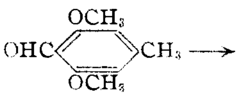
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Addition of Dienes to Certain Di-*o*-methoxy-substituted Cinnamic Acids. II

BY ROGER ADAMS AND R. B. CARLIN

In a previous paper,[1] the addition of 2,3-dimethyl-1,3-butadiene or isoprene to coumarin, *trans-o*-hydroxycinnamic acid, *cis*- and *trans-o*-methoxycinnamic acids, and 2-methyl-4,6-dimethoxycinnamic acid to form pyrones or partially hydrogenated biphenyl derivatives was described. Application of a similar reaction provides an approach to the synthesis of a tetrahydrocannabinol with a double bond in a position postulated for the natural tetrahydrocannabinol obtained by rearrangement of cannabidiol with toluenesulfonic acid.

As a type compound, 2,6-dimethoxy-4-methylcinnamic acid was selected and prepared for preliminary study. An aldehyde group, when introduced into orcinol dimethyl ether by any of the usual procedures, enters between the methyl and the methoxyl groups. Advantage was, therefore, taken of the fact that orcinol dimethyl ether reacts with butyl lithium to give a molecule with the lithium attached to the carbon between the two methoxyls.[2] Replacement of the lithium atom by an aldehyde group by treatment with orthoformic ester[3] or ethoxymethylene aniline failed, but N-methylformanilide[4] reacted readily with the formation of the desired aldehyde (I) By means of malonic acid and pyridine this aldehyde was converted to 2,6-dimethoxy-4-methylcinnamic acid (II), which added 2,3-dimethyl-1,3-butadiene to form the partially hydrogenated biphenyl (III).



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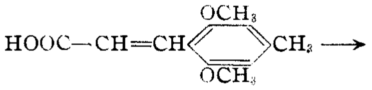

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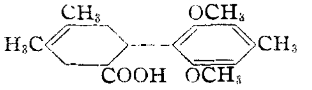
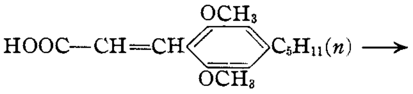
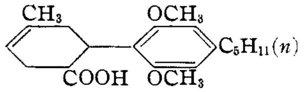


III

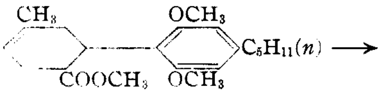
This procedure was equally successful for the preparation of 2,6-dimethoxy-4-*n*-amylcinnamic acid (IV) from the lithium derivative of olivetol dimethyl ether. To this molecule isoprene was added and, with the exception of a single experiment, the same product (V) was always isolated. In one instance which could not be repeated, an addition product with a different melting point resulted. This substance may have been the isomer of V with the methyl group in the other possible position. The position of the methyl group in compound V was proved by converting it to a compound of known configuration. The acid (V) was esterified to the methyl ester (VI) which



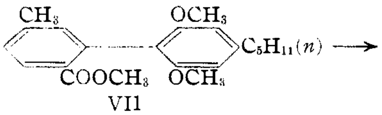
IV



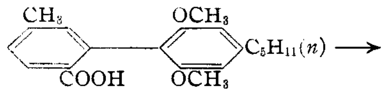
V



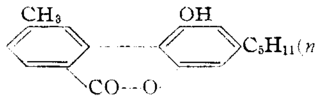
VI



VII



VIII



IX

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[1] Adams, McPhee, Carlin and Wicks, THIS JOURNAL, **65**, 35 (1943).

[2] Adams, Wolff, Cain and Clark, *ibid.*, **62**, 1770 (1940).

[3] Dr. A. A. Albert, private communication.

[4] Wittig, *Z. angew. Chem.* **53**, 243 (1940).