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.

URBANA, ILLINOIS RECEIVED OCTOBER 31, 1942

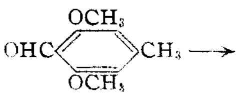
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

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

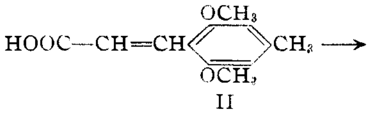
BY ROGER ADAMS AND R. B. CARLIN

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).



I



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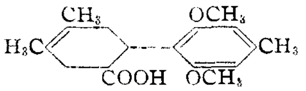
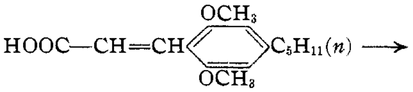
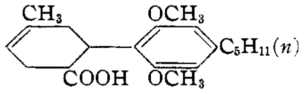


III

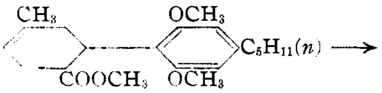
This procedure was equally successful for the preparation of 2,6-dimethoxy-4-*n*-amylcinnamic acid (IV) from the lithium derivative of olivetol dimethyl ether. To this molecule isoprene was added and, with the exception of a single experiment, the same product (V) was always isolated. In one instance 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



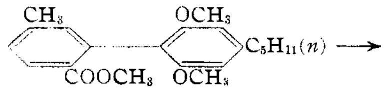
IV



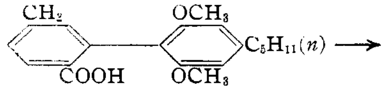
V



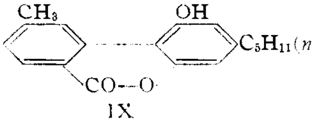
VI



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).

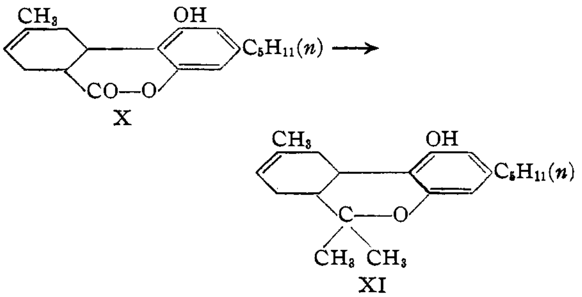
[3] Dr. A. A. Albert, private communication.

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

was then dehydrogenated to the biphenyl (VII). This latter compound was not isolated but was saponified to the corresponding acid (VIII) which was purified. Demethylation of the acid (VIII) led to the formation of the pyrone (IX) which has been synthesized previously by a method which leaves no doubt regarding its structure.[5]

It appears likely that the products of addition of isoprene to other substituted cinnamic acids, reported in a previous paper,[1] have their cyclohexenic ring methyl groups similarly located.

It is obvious that demethylation of compound V should lead to the lactone (X) and that upon treatment of this lactone with excess methylmagnesium iodide, the desired pyran (XI), identical with the postulated structure of one of the natural tetrahydrocannabinols, should be formed.



X

XI

Experimental

Orsellinaldehyde Dimethyl Ether (I).—The apparatus described by Adams, Wolff, Cain and Clark[2] was employed to prepare the lithium derivative of orcinol dimethyl ether from 1.50 g. of lithium, 9.2 g. of *n*-butyl chloride, and 15 cc. of orcinol dimethyl ether. After this reaction mixture had been allowed to stand overnight, it was treated with 15 cc. of N-methylformanilide in 35 cc. of dry ether, with shaking. The solution was added at such a rate that gentle refluxing of the reaction mixture was maintained. Shaking was continued for two hours after the N-methylformanilide solution had been added, and the solution was then refluxed for one hour. It was poured into 250 cc. of iced 10% sulfuric acid contained in a separatory funnel and the mixture thoroughly shaken. The aqueous layer was removed and twice extracted with ether. The combined ether solution was washed twice with water and dried over anhydrous magnesium sulfate. The solvent was removed and the residue distilled under reduced pressure. Approximately one-half of the total residue distilled at 90° or below (1 mm.).

The residue in the distilling flask was dissolved in boiling petroleum ether (b. p. 60–110°). On cooling, the aldehyde crystallized in long, slender needles. One recrystallization from the same solvent gave 4 g. (31% based on unrecovered orcinol dimethyl ether) of a white product melting at 91–92° (cor.). Robertson and Robinson[6] gave the melting point of this substance as 90–91°.

Unchanged orcinol dimethyl ether was recovered by refluxing the vacuum distillate with excess 10% hydrochloric acid for three hours, withdrawing the organic layer and extracting the aqueous layer with ether, washing and drying the combined organic layers, removing the solvent and distilling the residue under reduced pressure. In this way 6 g. of orcinol dimethyl ether was recovered. A more satisfactory procedure for synthesizing orsellinaldehyde dimethyl ether might be that described below for the preparation of 2,6-dimethoxy-4-*n*-amylbenzaldehyde.

2,6-Dimethoxy-4-methylcinnamic Acid (II).—A mixture of 2.6 g. of orsellinaldehyde dimethyl ether, 9 cc. of pyridine, 0.5 cc. of piperidine, and 4.0 g. of malonic acid was warmed on the steam-bath for one hour. Another gram of malonic acid was added and heating continued for a half hour. The solution was then refluxed for thirty minutes and poured into excess iced 10% hydrochloric acid, where the crude solid acid which formed was allowed to stand for two hours, with occasional stirring. The dried crude acid weighed 3.0 g. (98%). After several recrystallizations from ethanol, using Norite and Raney nickel, the acid formed very pale yellow platelets, m. p. 202° (cor.) with decomposition.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.04; H, 6.45.

1,2-Dimethyl-4-(2,6-dimethoxy-4-methylphenyl)-1-cyclohexene-5-carboxylic Acid (III).—A mixture of 1.5 g. of 2,6-dimethoxy-4-methylcinnamic acid, 3 cc. of dimethylbutadiene and 3 cc. of xylene in a glass liner was heated in a bomb at 170° for thirty hours. After the contents of the liner were cooled, 10 cc. of petroleum ether (b. p. 60–110°) was added and the mixture stirred until the gummy material was resolved into a granular solid. It was collected by filtration, dissolved in ether and the ether solution thoroughly extracted with saturated aqueous sodium bicarbonate to remove unchanged cinnamic acid. The alkaline extract was acidified and cinnamic acid contaminated with a small amount of reaction product was obtained. The residual ether solution was dried over anhydrous magnesium sulfate, and the solvent removed. The solid residue was recrystallized from petroleum ether (b. p. 60–110°) to constant melting point. The compound weighed 0.5 g. and formed white needles, m. p. 178–180° (cor.).

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.00; H, 7.96. Found: C, 71.21; H, 7.86.

2,6-Dimethoxy-4-*n*-amylbenzaldehyde.—A 200-cc. 3-necked round-bottomed flask was provided with a Hershberg wire stirrer with a mercury seal, a reflux condenser, a dropping funnel, and a nitrogen inlet tube. A rapid stream of dry, oxygen-free nitrogen was introduced and allowed to issue from the central neck, and in this stream 1.5 g. of lithium was cut into about seventy pieces and allowed to drop into the flask, which contained 25 cc. of dry ether. The stirrer, condenser and dropping funnel were then set in position, the nitrogen stream was slowed, and about one-fourth of a solution of 9.2 g. of *n*-butyl chloride in 25 cc. of dry ether was added at once. Stirring was

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(5) Adams, Baker and Wearn, THIS JOURNAL, **62**, 2204 (1940).

(6) Robertson and Robinson, *J. Chem. Soc.*, 2196 (1927).

started, and the reaction began immediately. The remainder of the *n*-butyl chloride solution was added at such a rate that gentle refluxing was maintained throughout the addition. Stirring was continued and the solution refluxed for two more hours, when essentially all the lithium had disappeared. To this mixture was added a solution of 15 cc. of olivetol dimethyl ether[7] in 25 cc. of dry ether. The resulting suspension was stirred for two hours and then permitted to stand overnight under a gentle nitrogen stream.

A solution of 15 cc. of N-methylformanilide in 25 cc. of dry ether was added dropwise with stirring, sufficient heat being evolved to cause refluxing. The mixture became thick with suspended solids, and stirring was continued for one hour after all the N-methylformanilide had been added. The mixture was then treated with 3% sulfuric acid until any small scraps of lithium were destroyed, before pouring into an excess of this acid. The upper layer was removed, and the aqueous layer extracted twice with ether. The ether extract and upper layer were washed once with dilute aqueous sodium bicarbonate and once with water. The ether solution was dried over anhydrous magnesium sulfate and the solvent removed. The fraction boiling at 148–152° (0.3 mm.) was 2,6-dimethoxy-4-*n*-amylbenzaldehyde. It was a straw-yellow, sirupy liquid; $n^{20}\text{D}$ 1.5407; yield, 12 g. (78% based on unrecovered olivetol dimethyl ether).

By a procedure analogous to that used to recover orcinol dimethyl ether from the orsellinaldehyde dimethyl ether reaction mixture, 1.5 g. of olivetol dimethyl ether was recovered.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.13; H, 8.55. Found: C, 71.07; H, 8.53.

2,6-Dimethoxy-4-*n*-amylcinnamic Acid (IV).—This acid was prepared from 6.5 g. of 2,6-dimethoxy-4-*n*-amylbenzaldehyde, 20 cc. of pyridine, 1 cc. of piperidine, and 10 g. of malonic acid by the same procedure as that described for the preparation of 2,6-dimethoxy-4-methylcinnamic acid (II). After one recrystallization from ethanol, the acid weighed 6.6 g. (86%). After several recrystallizations from ethanol (Darco), the compound was obtained in the form of small white needles, m. p. 179° (cor.) with decomposition.

Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.02; H, 7.98. Found: C, 69.28; H, 8.06.

2-Methyl-5-(2,6-dimethoxy-4-*n*-amylphenyl)-1-cyclohexene-4-carboxylic Acid.—A mixture of 6.6 g. of 2,6-dimethoxy-4-*n*-amylcinnamic acid, 12 cc. of 80% isoprene, and 12 cc. of dry xylene in a glass liner was heated in a bomb at 185° for forty hours. After cooling, the viscous reaction mixture was treated with twice its own volume of petroleum ether (b. p. 60–110°). The solid which formed quickly weighed 1.0 g. and was unchanged starting material.

The mother liquors were concentrated, and a white granular solid separated; yield 3 g. The mother liquors gave no more solid material on further concentration. The product was recrystallized from ethanol; glistening white threads, m. p. 133–134° (cor.); yield, 43%.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.79; H. 8.72. Found: C, 73.05; H, 8.83.

This was a single, isolated experiment which never could be repeated successfully.

1-Methyl-5-(2,6-dimethoxy-4-*n*-amylphenyl)-1-cyclohexene-4-carboxylic Acid (V).—A mixture of 10 g. of 2,6-dimethoxy-4-*n*-amylcinnamic acid, 40 cc. of 80% isoprene and 40 cc. of dry xylene was heated in a steel bomb at 185° for forty hours. The mixture was cooled and diluted with twice its own volume of petroleum ether (b. p. 60–110°) and thoroughly shaken with 100 cc. of saturated aqueous sodium carbonate. On settling, the liquid resolved itself into three phases, the middle of which was the sodium salt of the product, insoluble in both the aqueous and petroleum ether layers. This material was separated and washed with a mixture of petroleum ether and dilute aqueous sodium carbonate, again separated from the ternary mixture, and treated with 75 cc. of 10% hydrochloric acid and 75 cc. of ether. The mixture was shaken vigorously, and the aqueous layer withdrawn. The ether layer was washed three times with water and the solvent replaced by 30 cc. of petroleum ether (b. p. 60–110°). On standing for ten minutes, the solution deposited 1 g. of solid which was unchanged starting material.

The mother liquor was placed in the ice box overnight, during which time a crystalline solid deposited; yield 6.2 g. Another 0.8 g. was obtained by concentrating the filtrate. The total yield, corrected for recovered starting material, was 62%. A sample was crystallized from petroleum ether and from dilute ethanol (Darco), vacuum sublimed three times, and again recrystallized from petroleum ether. It formed very fine white needles, m. p. 115–115.5° (cor.).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.79; H, 8.72. Found: C, 72.98; H, 8.72.

Methyl 1-Methyl-5-(2,6-dimethoxy-4-*n*-amylphenyl)-1-cyclohexene-4-carboxylate.—A solution of 6.0 g. of the acid in 75 cc. of 5% methanolic hydrogen chloride was allowed to stand overnight and then poured into 200 cc. of water. The resulting mixture was extracted four times with petroleum ether (b. p. 60–110°). The petroleum ether solution was extracted with saturated aqueous sodium carbonate, and the slight interphase removed. The organic layer was dried over anhydrous magnesium sulfate, the solvent removed, and the residue distilled under reduced pressure. The ester was a clear, water-white liquid, b. p. 170° (0.1 mm.); $n^{20}\text{D}$ 1.5220; Yield 6.0 g. (96%).

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.29; H, 8.94. Found: C, 73.45; H, 8.92.

2,6-Dimethoxy-4-*n*-amyl-5′-methyl-2′-carboxybiphenyl.—A mixture of 3.0 g. of methyl 1-methyl-5-(2,6-dimethoxy-4-*n*-amylphenyl)-1-cyclohexene-4-methyl carboxylate and 0.65 g. of sulfur was heated at 240–250° for forty-five minutes, when hydrogen sulfide was no longer being evolved. The mixture was cooled to about 150° and the contents of the reaction vessel were distilled under reduced pressure onto a cold finger. The distillate was collected until the bath temperature reached 225°. The combined distillate was saponified with 75 cc. of a 3% aqueous solution of sodium hydroxide in 80% ethanol for three hours. The alkaline solution was poured into excess iced 10% hydrochloric acid. The acid mixture was extracted thoroughly with ether, and the ether solution washed with dilute aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. The solvent was re-

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(7) Suter and Weston, THIS JOURNAL, **61**, 232 (1939).

moved and the residual viscous red oil treated with 5 cc. of boiling petroleum ether (b. p. 60–110°). The insoluble dark gum was removed from the solution by decantation of the latter. On cooling, the petroleum ether deposited an orange-colored solid which weighed 235 mg. By concentrating the mother liquors, carefully discarding the red gum which formed regularly, another 540 mg. of this solid was obtained. The total yield was 775 mg. (26%). A sample was recrystallized from petroleum ether (Darco) to constant melting point; tiny needles, m. p. 146° (cor.).

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 72.85; H, 7.89. Found: C, 73.55; H, 7.82.

1-Hydroxy-3-*n*-amyl-9-methyl-6-dibenzopyrone.—A mixture of 235 mg. of 2,6-dimethoxy-4-*n*-amyl-5′-methyl-2′-carboxybiphenyl, 0.6 cc. of 48% hydrobromic acid, 1 cc. of glacial acetic acid, and 0.5 cc. of acetic anhydride was heated to reflux to dissolve the solid acid, and heating continued for four hours. After pouring into 20 cc. of water, the reaction mixture was extracted three times with ether and the organic layer washed thoroughly with saturated aqueous sodium bicarbonate and dried over magnesium sulfate. The solvent was removed and the oily residue was treated with boiling petroleum ether (b. p. 60–110°) for five minutes. The solid material insoluble in this boiling solvent weighed 50 mg. After recrystallization from ethyl acetate, it melted at 183–185° (cor.), and a mixture of this material and an authentic specimen of 1-hydroxy-3-*n*-amyl-9-methyl-6-dibenzopyrone[8] showed no melting point depression.

The petroleum ether extract deposited another 50 mg. of the dibenzopyrone on standing. Concentration of the mother liquors showed that the remainder of the starting material had been essentially unchanged in the reaction.

Summary

1. Treatment of the lithium derivative of orcinol dimethyl ether with N-methylformanilide produced orsellinaldehyde dimethyl ether, which was converted to the corresponding 2,6-dimethoxy-4-methylcinnamic acid by means of malonic acid and pyridine. Addition to this acid of 2,3-dimethyl-1,3-butadiene gave 1,2-dimethyl-4-(2,6-dimethoxy-4-methylphenyl)-1-cyclohexene-5-carboxylic acid.

2. In a similar manner, 2,6-dimethoxy-4-*n*-amylcinnamic acid was synthesized from olivetol dimethyl ether. This cinnamic acid added isoprene to give 1-methyl-5-(2,6-dimethoxy-4-*n*-amylphenyl)-1-cyclohexene-4-carboxylic acid. In one instance, which could not be repeated, an isomer of this latter compound was formed.

3. That the adduct mentioned in 2 had a methyl group in the 1- rather than the 2-position, was proved by converting it to 1-hydroxy-3-*n*-amyl-9-methyl-6-dibenzopyrone, which had been synthesized by a method leaving no doubt of its structure. This was accomplished by conversion of the adduct to its methyl ester, dehydrogenation of the ester to 2,6-dimethoxy-4-*n*-amyl-5′-methyl-2′-carbomethoxybiphenyl which was saponified to the corresponding acid. Demethylation of this acid gave the pyrone.

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[8] Adams and Baker, THIS JOURNAL, 62, 2401 (1940).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF TRINITY COLLEGE]

A New Modification of the Ullmann Synthesis of Fluorene Derivatives

BY WARREN C. LOTHROP AND PAUL A. GOODWIN

The present paper describes preliminary investigation of a previously unexplored modification of the method of arriving at substituted *o*-aminobenzophenones, which as Ullmann[1] discovered react with nitrous acid to yield the corresponding fluorenones. The new method avoids the necessity of using *p*-toluenesulfonyl chloride to protect the amino group of anthranilic acid from the subsequent reactions with thionyl chloride and aluminum chloride, and therefore the frequent difficulty met with in removing this large and relatively inert group by hydrolysis afterwards.

The simplest illustration of this method is given below in which anthranilic acid is refluxed with acetic anhydride and thus converted into 2-methyl-3,1,4-benzoxaz-4-one (I). The latter when treated with phenylmagnesium bromide by the inverse method yields the acetyl derivative of *o*-aminobenzophenone into which it can be readily converted by hydrolysis with dilute hydrochloric acid, as shown in the equations

The importance of carrying out the reaction by the inverse procedure was made evident when an experiment was performed adding I to a solution of the Grignard reagent. In this case none of the desired product resulted and only 2-acetamidophenyldiphenylcarbinol (II) was formed, even when equimolecular quantities were employed.

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[1] Ullmann and Mallet, *Ber.*, 31, 1694 (1898).