Anal. Calcd. for $C_{11}H_{17}ClN_4O$: Cl, 13.81. Found: Cl, 13.79.

1,1′-Methylenebisbenzotriazole (III) and 1,2′-Methylenebisbenzotriazole.—A vigorously stirred mixture of 11.9 g. (0.1 mole) of benzotriazole and 4 g. (0.1 mole) of sodamide in 200 ml. of dry toluene was heated at reflux temperature for 4 hours. To the hot suspension, 16.7 g. (0.1 mole) of 1-chloromethylbenzotriazole (IIb) was added, and stirring and heating were continued for 19 hours. Cooling gave a solid product which was collected on a filter, washed with benzene and triturated with water to remove sodium chloride. There remained 22.5 g. of dry material, m.p. 188–191°. Concentration of the toluene and benzene solutions gave 4 g. of additional product, m.p. 180–185°. Recrystallization from toluene gave 22 g. (88%) of III, m.p. 191–192.5°. A portion was recrystallized twice from dilute alcohol, m.p. 192–193°.

Anal. Calcd. for $C_{13}H_{10}N_6$: C, 62.39; H, 4.03. Found: C, 62.20; H, 4.02.

Concentration of the original toluene filtrate to complete dryness gave a brown solid which, after recrystallization from a small volume of absolute alcohol, gave 1 g. (4% yield) of a solid; m.p. 142–145°. Two recrystallizations from alcohol and one from Skelly B produced an off-white solid, m.p. 142–146.5°.

Anal. Calcd. for $C_{13}H_{10}N_6$: C, 62.39; H, 4.03; N, 33.59. Found: C, 62.26; H, 3.89; N, 33.81.

This product has been designated as 1,2′-methylene-bis-benzotriazole. A mixed melting point with 1-hydroxybenzotriazole (IIa) was 118–145°, while one with its isomer (III) was 144–175°. It was much more soluble in benzene than III.

LAWRENCE, KANSAS

[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

Synthesis of Arylindenones and a Stereoisomer of Diisohomogenol[1]

BY E. C. HORNING[2] AND JOHN A. PARKER[3]

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An investigation of the reactions of β,β-diaryl-β-hydroxypropionic esters, obtained by the Reformatsky reaction from diaryl ketones and α-halogen esters, indicates that certain substituent groups in the aromatic ring and in the side chain determine the course of dehydration under acidic conditions. The normal product is formed in some cases; in others an indenone results. From one of these indenones, IIIA, a synthetic diisohomogenol has been prepared.

The structure of diisohomogenol has been established as IVA by degradation studies; the stereochemical arrangement of the substituents on the indane ring is not known. Studies conducted by Cartwright and Haworth[4] and Müller, Toldy, Halmi and Mészáros[5] on the synthesis of IVA indicate that the synthesized product has the same melting point as the material derived from dimerization of isohomogenol, but the two are not identical and therefore must differ in stereochemical configuration.

The key compound in these studies has been 2-methyl-3-(3′,4′-dimethoxyphenyl)-5,6-dimethoxyindenone-1, IIIA, a ketone obtained by oxidative degradation of diisohomogenol, and from which synthetic diisohomogenol has been prepared. Arylindenones of this kind have generally been almost completely inaccessible compounds, although IIIA has been identified by synthesis.[6] Since no satisfactory method has existed for the preparation by synthesis of such compounds, when IIIA is desired it is usually obtained by oxidative degradation of diisohomogenol.[4-7] In another application, difficulties in synthesis have been detailed by Feeman and Amstutz[8] who were interested in the preparation of 3-(3′,4′-dimethoxyphenyl)-5,6-dimethoxyindenone-1. The reported difficulty in finding cyclization conditions for the corresponding indanone and the failure to obtain the indenone by direct cyclization or from the indanone by dehydrogenation or bromination–dehydrobromination indicates the nature of the problem.

An examination of the reactions shown in the chart brought several rather striking facts to light. The usual Reformatsky reaction between diaryl ketones (I) and an α-bromoester results in the formation of hydroxyesters (II) of expected structure. When the hydroxyesters are subjected to dehydration under acidic conditions, the product to be expected is the corresponding β,β-diarylacrylic ester (V). While not all of the possible combinations have been explored, this normal sequence holds in the simple cases which have been investigated. When the ketone I includes an aryl group as 3,4-dimethoxyphenyl, or 3,4,5-trimethoxyphenyl, and the ester is ethyl α-bromopropionate rather than ethyl bromoacetate, the intermediate hydroxyester II is formed normally but, under apparently normal dehydration conditions, the elimination of water is accompanied by cyclization and the product observed is an indenone (III). This cyclization occurs with ease under mild acidic dehydration conditions.

The fact that there are no known conditions for the cyclization of β,β-di-(3,4-dimethoxyphenyl)-acrylic acid or the corresponding β-hydroxyester to the indenone[8] is in sharp contrast to the behavior of the β-hydroxyesters IIA and IIB found here. The substitution of a methyl group in the structure now makes cyclization the exclusive reaction under the conditions indicated. The effect of polyphosphoric acid, a reagent recently introduced by Snyder and Werber[9] in cyclizations, is evidently nonspecific, since phosphorous oxychloride in boiling

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[2] National Heart Institute, Bethesda, Maryland.

[3] National Institutes of Health Predoctorate Fellow, 1950–1951. This paper is from the doctoral thesis of J. A. Parker, submitted to the Graduate School of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[4] N. J. Cartwright and R. D. Haworth, *J. Chem. Soc.*, 948 (1947).

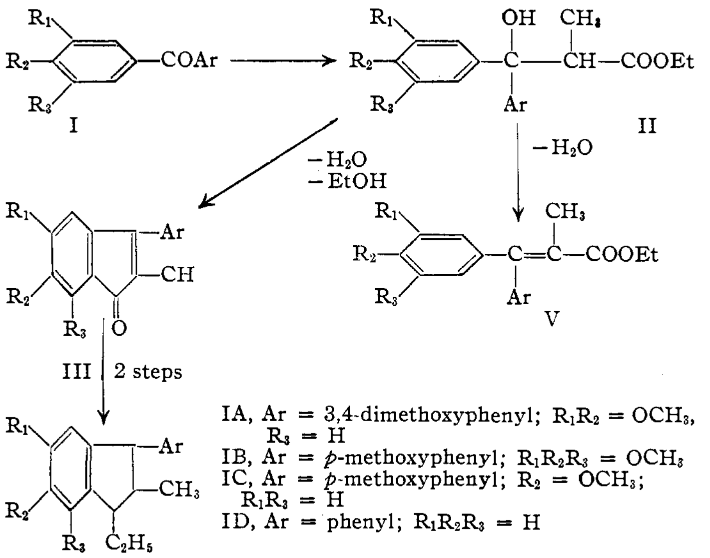
[5] A. Müller, L. Toldy, G. Halmi and M. Mészáros, *J. Org. Chem.*, **16**, 481 (1951).

[6] A. Müller and E. Gal, *Ber.*, **77**, 343 (1944).

[7] W. Doering and J. A. Berson, THIS JOURNAL, **72**, 1118 (1950).

[8] J. F. Feeman and E. D. Amstutz, *ibid.*, **72**, 1526 (1950).

[9] H. R. Snyder and F. X. Werber, *ibid.*, **72**, 2962, 2965 (1950).



IA, Ar = 3,4-dimethoxyphenyl; $R_1R_2 = OCH_3$, $R_3 = H$
IB, Ar = p-methoxyphenyl; $R_1R_2R_3 = OCH_3$
IC, Ar = p-methoxyphenyl; $R_2 = OCH_3$; $R_1R_3 = H$
ID, Ar = phenyl; $R_1R_2R_3 = H$

CHART I

benzene also brings about the dehydration-cyclization. An early example cited by deFazi[10] in which ethyl α-ethyl-β,β-diphenyl-β-hydroxypropionate was converted to 2-ethyl-3-phenylindenone-1 by cold concentrated sulfuric acid probably is a reaction in the same class. The effects described here are being investigated further, but as a result of this unusual reversal of reactivity under moderate conditions, certain indenones including IIIA can now be obtained easily from the parent ketones (I).

Through a Grignard reaction, followed by catalytic hydrogenation, the indenone IIIA was converted to a synthetic diisohomogenol, and our results in this respect paralleled the recent work of Müller.[5] The stereochemical configuration of our compound is unknown but is under investigation.

The experimental section includes a description of the catalytic hydrogenation of three diaryl ketones (IA, B, C) to the corresponding diarylmethanes. We have been interested in the structure and reactions of antimitotic agents, and our general investigation has been extended to substituted diarylmethanes including the compounds described in this paper.

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Experimental

3,4,3',4'-Tetramethoxybenzophenone (IA).—A solution of 27.0 g. of veratroyl chloride in 150 ml. of carbon disulfide (prepared by warming the mixture) containing 18.3 g. of veratrole was chilled in ice, and 26.0 g. of anhydrous aluminum chloride was added in 5.0-g. portions, with good stirring. The mixture was allowed to stand for 12 hours at room temperature, and was then heated under reflux for 30 minutes. After decomposition with ice water and 200 ml. of concentrated hydrochloric acid, the product was extracted with 1:1 benzene–ether. The aqueous solution was extracted once with 1:1 ether–ethyl acetate, and the combined organic extracts were washed well with 10% sodium hydroxide solution, with water, and with 2% aqueous acetic acid. A residue of 30.2 g. of crude ketone was obtained after drying and removal of the solvents; this was recrystallized from aqueous ethanol to provide 26.0 g. (60%) of product, m.p. 144–146° (reported[7] m.p. 146–147.2°).

3,4,5,4'-Tetramethoxybenzophenone (IB).—The mixture resulting from the addition of 50 g. of anhydrous aluminum chloride to a solution of 60 g. of 3,4,5-trimethoxybenzoyl chloride and 48 ml. of anisole in 300 ml. of carbon disulfide was heated under reflux for one hour. After treatment with ice, water and diluted hydrochloric acid, the organic solvent was evaporated, and the mixture was made alkaline with 10% sodium hydroxide solution. The product was extracted with 1:1 ether–ethyl acetate, and the precipitated yellow sodium salt which separated was removed by filtration. From the organic extracts there was obtained a crude product yielding 31 g. (40%) of the ketone, m.p. 76–77° (reported[11] m.p. 76–77°) after recrystallization from aqueous ethanol.

From the sodium salt there was obtained 36 g. (48%) of 4-hydroxy-3,5,4'-trimethoxybenzophenone, m.p. 163–164°, as reported by Frank and Tarbell.[11] This material could be converted into 3,4,5,4'-tetramethoxybenzophenone in 87% yield by methylation with methyl sulfate in hot sodium hydroxide solution, using portionwise addition of both reagents.

4,4'-Dimethoxybenzophenone (IC).—This compound was prepared in the usual way from anisoyl chloride and anisole; m.p. 144–145° (reported m.p. 143–144°).

3,4,3',4'-Tetramethoxydiphenylmethane.—A 2.0-g. sample of 3,4,3',4'-tetramethoxybenzophenone was hydrogenated at 60–65° in 100 ml. of acetic acid with 1.5 g. of 5% palladium–carbon catalyst, over a two-hour period. The catalyst was removed by filtration and washed with ethyl acetate; the organic solvents were evaporated and the residue was crystallized from methanol to yield 1.7 g. (89%) of colorless product, m.p. 69–71°.

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.83; H, 6.98. Found: C, 70.57; H, 7.15.

3,4,5,4'-Tetramethoxydiphenylmethane.—A solution of 15.0 g. of 3,4,5,4'-tetramethoxybenzophenone in 30 ml. of acetic acid was hydrogenated at 60–65° with 4.0 g. of 5% palladium–carbon catalyst. The catalyst was removed and the acetic acid solution was diluted with 200 ml. of water. The crude product was crystallized from aqueous ethanol to yield 13.5 g. (92%) of product, m.p. 66–67°.

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.83; H, 6.98. Found: C, 71.08; H, 7.14.

4,4'-Dimethoxydiphenylmethane.—Hydrogenation of 10.0 g. of 4,4'-dimethoxybenzophenone at 60–65° in 40 ml. of acetic acid with 4.0 g. of 5% palladium–carbon catalyst yielded 7.1 g. (74%) of 4,4'-dimethoxydiphenylmethane, m.p. 55–56°, after recrystallization from cyclohexane (reported m.p. 51–52°).

2-Methyl-3-(3',4'-dimethoxyphenyl-5,6-dimethoxyindenone (IIIA).—A Reformatsky reaction was carried out in the usual way with 10.0 g. of 3,4,3',4'-tetramethoxybenzophenone, 9.5 g. of ethyl α-bromopropionate, and 30 g. of 20-mesh zinc in 100 ml. of dry benzene, using an additional 50 ml. of dry benzene for addition of the bromoester. A second portion of zinc (15 g.) was added at the end of the initial reaction, and after 30 minutes 4 ml. of acetic acid was added dropwise. The neutral reaction products were separated (12.9 g. of nearly colorless oil) and dissolved in 50 ml. of dry ether. After chilling for 12 hours, the mixture was filtered to yield 5.5 g. of recovered 3,4,3',4'-tetramethoxybenzophenone, m.p. 140–146°, which was purified for further use by recrystallization from aqueous alcohol. Evaporation of the ether gave 5.0 g. of colorless, viscous oil which showed normal hydroxyl absorption in the infrared. This material was crude ethyl α-methyl-β-hydroxy-β,β-di-(3,4-dimethoxyphenyl)-propionate, and it was used without further purification.

A 3.6-g. sample of the hydroxyester was mixed with 40 g. of polyphosphoric acid[9] and heated to 65–75° for 30 minutes. The resulting deeply colored mixture was treated with water, and the phosphoric acid was neutralized with

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(10) M. deFazi, *Atti. accad. Lincei*, **24**, II, 150 (1915); *Gazz. chim. ital.*, **45**, 143 (1915).

(11) H. R. Frank and D. S. Tarbell, THIS JOURNAL, **70**, 1276 (1948).

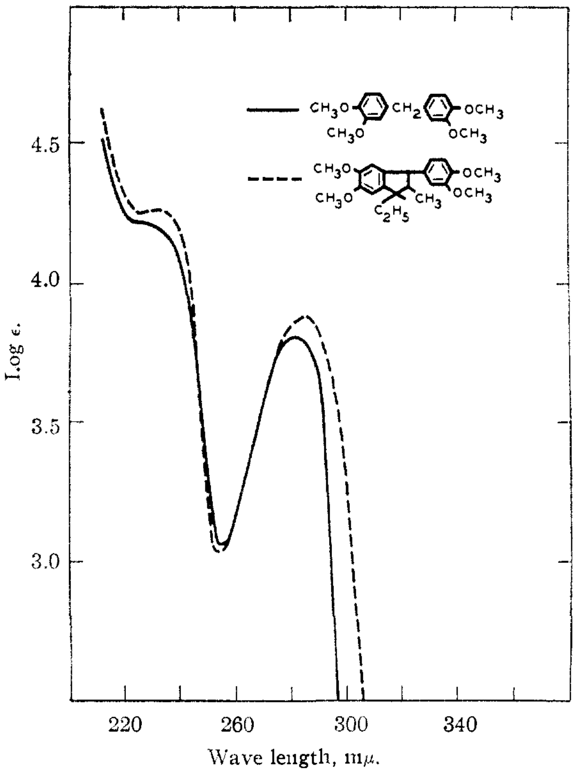

Fig. 1.—Ultraviolet absorption spectra of synthetic diisohomogenol and 3,4,3′,4′-tetramethoxydiphenylmethane (in ethanol).

solid sodium bicarbonate. The organic products were extracted with 4:1 benzene–ethyl acetate, and after the usual washes the neutral products were isolated, giving 3.4 g. of material. This was separated into its components by chromatography on alumina. Elution with benzene containing 10% hexane gave 2.1 g. of red crystalline ketone, m.p. 196–198° (cor.) which by analysis and melting point was identified as 2-methyl-3-(3′,4′-dimethoxyphenyl)-5,6-dimethoxyindenone-1 (reported[7] m.p. 196–198°).

Anal. Calcd. for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.52; H, 6.26.

The separation was continued with 50% hexane in benzene, yielding 0.2 g. of recovered 3,4,3′,4′-tetramethoxybenzophenone.

In some experiments an orange substance was eluted with 10% ethyl acetate in benzene to provide orange needles, m.p. 132–134° after recrystallization from methanol; this material is still under investigation.

2-Methyl-3-(4′-methoxyphenyl)-5,6,7-trimethoxyindenone-1 (IIIB).—A Reformatsky reaction was carried out in the usual way with 10.0 g. of 3,4,5,4′-tetramethoxybenzophenone, 12.7 g. of ethyl α-bromopropionate, and 30 g. of 20-mesh zinc in 100 ml. of dry benzene. The neutral products were isolated as usual to yield 12.1 g. of crude ethyl α-methyl-β-hydroxy-β-(3,4,5-trimethoxyphenyl)-β-(4-methoxyphenyl)-propionate as a colorless oil, containing a small amount of unchanged ketone.

The crude ester was dissolved in 60 ml. of dry benzene and treated with 3 ml. of phosphorus oxychloride. The solution, which turned red immediately, was heated (steam) for 30 minutes, and the neutral products were isolated as usual. The product was crystallized from ethanol to yield 8.2 g. of orange needles, m.p. 100–102.5°.

Anal. Calcd. for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.24; H, 5.91.

This ketone was assumed to be the product resulting from cyclization to the trimethoxyphenyl ring, since a corresponding ketone was not obtained from a similar reaction sequence with 4,4′-dimethoxybenzophenone.

The yellow **semicarbazone** was obtained in the usual way; m.p. 213–214°.

Anal. Calcd. for $C_{21}H_{23}O_5N_3$: C, 63.46; H, 5.83. Found: C, 63.21; H, 5.89.

β,β-Di-(3,4-dimethoxyphenyl)-acrylic Acid.—A Reformatsky reaction was carried out with 4.0 g. of 3,4,3′,4′-tetramethoxybenzophenone, 8.0 ml. of ethyl bromoacetate and 20 g. of 20-mesh zinc, in 200 ml. of dry benzene. The yield of crude ethyl β-hydroxy-β,β-di-(3,4-dimethoxyphenyl)-propionate (4.2 g., colorless oil) was dissolved in 75 ml. of benzene, to which 4 ml. of phosphorus oxychloride was added. The mixture was heated (steam) for one hour, but the deep red color characteristic of indenone cyclization did not develop. The cooled mixture was treated in the usual way to isolate the neutral products, and 3.2 g. of colorless oil was obtained. This was hydrolyzed in 200 ml. of 1:1 methanol-water containing 10 g. of sodium hydroxide, with heating under reflux for three hours. The alcohol was removed (distillation) and the aqueous solution was acidified with diluted hydrochloric acid. The acidic products were removed by extraction with 1:1 ether–ethyl acetate, and isolated as usual to yield 2.7 g. of colorless β,β-di-(3,4-dimethoxyphenyl)-acrylic acid, m.p. 155–157°. Recrystallization from hexane–ethyl acetate provided an analytical sample without change in melting point.

Anal. Calcd. for $C_{19}H_{20}O_6$: C, 66.24; H, 5.85. Found: C, 66.18; H, 5.69.

Ethyl β-(3,4,5-Trimethoxyphenyl)-β-(4-methoxyphenyl)-acrylate.—A Reformatsky reaction was carried out with 4.4 g. of 3,4,5,4′-tetramethoxybenzophenone, 8 ml. of ethyl bromoacetate and 20 g. of zinc, in 200 ml. of dry benzene. The yield of crude ethyl β-hydroxy-β-(3,4,5-trimethoxyphenyl)-β-(4-methoxyphenyl)-propionate (4.0 g., colorless oil) was dissolved in 30 ml. of dry benzene and treated with 4.0 ml. of phosphorus oxychloride. The mixture was heated (steam) for five minutes; it slowly became dark but did not develop a deep red color characteristic of indenone formation. The neutral product, 3.6 g. of crude discolored material, was purified by chromatography on alumina. Elution with 1:1 cyclohexane–benzene gave 2.1 g. of colorless crystalline material. Recrystallization from aqueous methanol provided an analytical sample, m.p. 102–103°.

Anal. Calcd. for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50. Found: C, 67.41; H, 6.52.

Synthetic Diisohomogenol: 1-Ethyl-2-methyl-3-(3,4-dimethoxyphenyl)-5,6-dimethoxyindane (IVA).—A Grignard solution was prepared from 7.0 g. of ethyl iodide and 1.0 g. of magnesium turnings in 150 ml. of dry ether. The ether was replaced (distillation) with 75 ml. of dry benzene, and a solution of 0.51 g. of 2-methyl-3-(3′,4′-dimethoxyphenyl)-5,6-dimethoxyindenone-1 in 60 ml. of dry benzene was added with good stirring. After heating under reflux for 1.5 hours, the mixture was treated with ice and diluted hydrochloric acid. The ether-benzene extract of the product was light yellow at first, but gradually turned red. The neutral products were separated as usual, giving 0.50 g. of oil. This neutral material was hydrogenated in 60 ml. of acetic acid with 2.0 g. of 5% palladium–carbon catalyst, first at room temperature (one hour) and then at 60–65° (two hours). The colorless product, 0.42 g., was isolated in the usual way and purified by chromatography on alumina. Elution with 1:1 hexane–benzene gave a colorless fraction which was crystallized from hexane; m.p. 102–105°. Recrystallization from hexane–ethyl acetate provided an analytical sample, m.p. 103–105°.

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.98; H, 7.84.

The ultraviolet absorption spectrum (in ethanol) of synthetic diisohomogenol is compared in Fig. 1 with the spectrum for the corresponding diphenylmethane, 3,4,3′,4′-dimethoxydiphenylmethane.

From the work of Müller[5] it is now known that the procedure described here yields a synthetic product (reported m.p. 105–106°) which is a stereoisomer of the material obtained by dimerization of isohomogenol, and that this general relationship holds in other cases as well.

Additional Reactions.—Reformatsky reactions were carried out with ethyl α-bromopropionate and 4,4′-dimethoxybenzophenone (IC) and benzophenone (ID); the neutral products were subjected to dehydration with phosphorus oxychloride in benzene, but indenone formation was not observed.

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