formimidate, b.p. 147–149°, $n^{25}D$ 1.5123 was obtained, without the occurrence of the troublesome acid-catalyzed side reactions which lead to N,N'-diphenylformamidine and ortho ester.

The following experiments illustrate the methods used for all the compounds reported in Table III; experiments not described differed from these mainly in the type and size of distilling columns used and the length of time required to remove the alcohols produced by transesterification. It is necessary to use methyl N-phenylformimidate for the synthesis of isopropyl and *t*-butyl N-phenylformimidates because of the proximity of the boiling points of ethyl, isopropyl and *t*-butyl alcohols. Even when the methyl ester is used, a fairly efficient fractionating column is required; a 32-in. glass helix-packed column was found to be satisfactory. Several days of reflux with intermittent removal of the methyl alcohol produced were required in the synthesis of these two esters. By comparison, when *t*-amyl N-phenylformimidate was prepared by transesterification of *ethyl* N-phenylformimidate, only 2.5 hr. were required for the removal of the ethyl alcohol.

***sec*-Butyl N-Phenylformimidate (Method G).**—To 60 g. (0.81 mole) of *sec*-butyl alcohol was added 0.04 g. (2 m. atoms) of sodium. After the sodium had dissolved, 39.6 g. (0.27 mole) of ethyl N-phenylformimidate was added, and the mixture was heated in a flask attached to a 32-in. glass helix-packed column with a total reflux, controlled take-off distilling head. Within four hours 13 ml. of ethyl alcohol had been removed. The reaction was left on total reflux overnight and then an additional 2 ml. of ethyl alcohol was removed (a total of 15 ml. of the theoretical 15.8 ml.). The excess *sec*-butyl alcohol was distilled (b.p. 98.5°), 43 ml. of the theoretical 49 ml. being obtained. The column was allowed to drain and was then replaced by a 10-in. helix-packed column. The pressure was lowered to 40 mm., and 40.1 g. (85%) of *sec*-butyl N-phenylformimidate was obtained, b.p. 138–139° (40 mm.) (see Table III).

In the experiments with the higher-boiling alcohols, a shorter distilling column was satisfactory for the separation of the ethyl alcohol and indeed a short column was advantageous in the distillation of the product, which should be carried out at low pressure and temperature in order to avoid decomposition into phenyl isocyanide. Although the *n*-hexyl derivative was obtained by the direct fractional distillation procedure of method G, it is recommended that it and other high-boiling esters be prepared by method H, described below.

**Cyclohexyl N-Phenylformimidate (Method H).**—To 60 g. (0.60 mole) of cyclohexyl alcohol was added 0.2 g. of sodium. After the sodium had dissolved, 30 g. (0.20 mole) of ethyl N-phenylformimidate was added and the mixture was heated in a flask attached to a 10-in. Vigreux column with a total reflux, controlled take-off head. Within one hour 10.8 ml. (12 ml. theoretical) of ethyl alcohol had been collected. The column was drained and replaced by a simple distilling adapter, and the excess cyclohexyl alcohol and product were removed as rapidly as possible from the sodium alkoxide. The alcohol distilled at 64–66° (10 mm.) and the product at *ca.* 120–127° (2 mm.) (they were collected in the same flask). The mixture was then separated by distillation through a 6-in. Vigreux column; 41 ml. of cyclohexyl alcohol, b.p. 36–47° (1.4 mm.), and 35.2 g. (87%) of cyclohexyl N-phenylformimidate, b.p. 109–110° (1.4 mm.), were obtained (see Table III).

AUSTIN 12, TEXAS

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF J. T. BAKER CHEMICAL COMPANY]

# p-Methoxy-2,2-bis-(p-methoxyphenyl)-acetophenone and Some Derivatives

BY GENE SUMRELL AND GILBERT E. GOHEEN

RECEIVED JANUARY 27, 1955

The reported reactions of 2,2-diphenylacetophenone suggested that the analogous compound containing *p*-methoxy groups on the benzene rings might be converted in one step to the synthetic estrogenic substance, chlorotris-(*p*-methoxyphenyl)-ethylene. Accordingly, *p*-methoxy-2,2-bis-(*p*-methoxyphenyl)-acetophenone has been prepared and its chemistry studied. It was found to give an oxime readily and failed to give the enol derivatives reported for 2,2-diphenylacetophenone. Thus, the compound with *p*-methoxy substituents reacted more as a ketone and less as an enol than is reported for the unsubstituted compound.

While absorption spectral data[1] indicate that 2,2-diphenylacetophenone (I) exists in the keto form in the liquid state, many of its chemical reactions suggest the enol form. For example, it was only with great difficulty and in low yield that Kohler[2] succeeded in converting it to the oxime after previous investigators[3] had failed. Attempts to cause reaction between I and hydrazine, phenylhydrazine or aniline also failed. However, I was readily converted to the acetate of the enol form with acetic anhydride, and was benzoylated when heated with benzoyl chloride and pyridine.[3] The reaction of I and phosphorus pentachloride is reported to give a 59% yield of chlorotriphenylethylene (II).[4]

A convenient method of preparing chlorotris-(*p*-methoxyphenyl)-ethylene (VII)[5] was desired in this Laboratory. The reported reactions of I suggested that VII might be prepared in suitable yield by the reaction of phosphorus pentachloride with *p*-methoxy-2,2-bis-(*p*-methoxyphenyl)-acetophenone (IV). The only reported preparation found for this latter material involved the condensation of anisoin and anisole using sulfuric acid, and yielded a mixture from which pure IV could not be obtained.[6] In the present work it was found that the use of sirupy phosphoric acid as the condensing agent gave much better results. Furthermore, the presence of an extra mole of anisole in the reaction mixture gave a solid complex V of anisole and IV which could be purified by recrystallization. The anisole was then readily removed from V by heating on the steam-bath at reduced pressure, leaving unchanged IV as a residue.

An alternate method of preparing IV involving the reaction of *p*-methoxyphenylmagnesium bromide with nitrile III was investigated. Though IV was obtained in 40% yield by this method, its separation from unreacted nitrile and high-melting material of unknown structure was difficult. Thus, the condensation of anisoin and anisole in the presence of phosphoric acid is the preferable method.

(1) H. Ley and W. Manecke, *Ber.*, **56**, 777 (1923).

(2) E. P. Kohler, *Amer. Chem. J.*, **36**, 194 (1906).

(3) (a) H. Biltz, *Ber.*, **32**, 650 (1899); (b) M. Delacre, *Bull. soc. chim. France*, [3] **13**, 857 (1895).

(4) E. Bergmann and A. Bondi, *Ber.*, **64**, 1467 (1931).

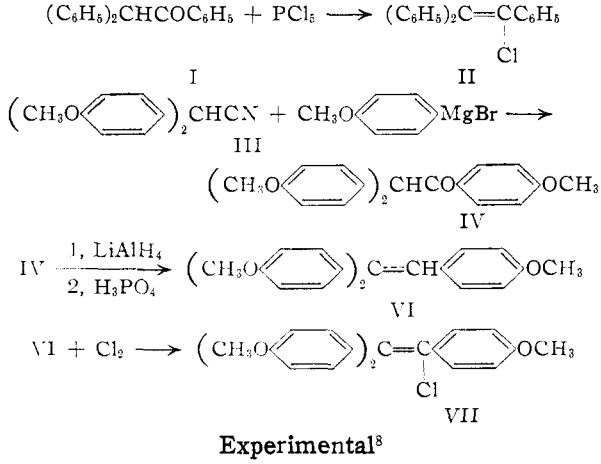
(5) This substance is known commercially as Tace and is marketed by the Wm. S. Merrell Company.

(6) E. C. Dodds, *et al.*, *Proc. Roy. Soc. (London)*, **132B**, 83 (1944); *C. A.*, **38**, 3639 (1944).

When IV was treated with phosphorus pentachloride a lively reaction occurred even at room temperature, with the evolution of hydrogen chloride, but a pure product could not be obtained from such runs If the mixture was heated with an excess of the pentachloride several chlorines could be introduced, judging from analyses of the crude material. The only pure product isolated from these runs was a solid melting at 180–182° and analyzing for $C_{23}H_{20}O_4Cl_2$. Thus, the keto oxygen was not replaced. The positions of the chlorines were not established, but it seems fairly clear that the main course of the reaction of IV with phosphorus pentachloride is different than that reported for I, in which an enolic hydroxy group is apparently replaced by a chlorine atom.[4]

IV was recovered unchanged after extended heating periods with phosphorus trichloride, phosphorus oxychloride or acetic anhydride. In contrast to the difficulty reported[2,3] with I, IV gave an oxime fairly readily. Attempts to reduce the keto group in IV by methods employing sodium and ethanol, heating with sodium isopropoxide, or with zinc and glacial acetic acid all failed. This reduction was successfully carried out with lithium aluminum hydride, but much dehydration evidently occurred during the working up of the reaction mixture and pure hydroxy compound could not be obtained. Treatment of the crude material with sirupy phosphoric acid, however, gave an excellent yield of the dehydrated compound, VI.[7]

The reduced tendency of IV to react as an enol, as compared to I, might be explained by the electron releasing ability of the methoxy groups. The effect would be transmitted through the benzene rings and effectively increase the electron density of the carbon alpha to the keto group, thus reducing the ability of the attached hydrogen to escape and allow the enol form of IV to exist.



## Experimental[8]

**Bis-(*p*-methoxyphenyl)-acetonitrile** (I).—I was prepared by a procedure similar to that described in the literature.[9] The anisaldehyde cyanohydrin was not recrystallized before condensation with anisole, and 85% sulfuric acid was used for the condensation. The molar ratio of anisole to the cyanohydrin was 1.5:1 instead of 2.5:1. This cyanohydrin was found to decompose rather rapidly and was used immediately after preparation without drying. These modifications gave a crude yield of 67% of I, compared to the 46% reported in the literature. The crude material melted at 154–158°. Recrystallization of 140 g. from 700 ml. of glacial acetic acid yielded 135 g. of material melting at 156–158.5°, a value unchanged by further recrystallization (literature,[9] m.p. 154°).

**The Reaction of *p*-Methoxyphenylmagnesium Bromide with I.**—To a stirred solution of the Grignard reagent prepared from 300 g. (1.6 moles) of *p*-methoxyphenyl bromide in 800 ml. of ether was added a solution of 101.2 g. (0.4 mole) of I in 1 l. of hot benzene. The reaction mixture was refluxed for 17 hours, hydrolyzed with 6 *N* sulfuric acid, and the resulting two-phase mixture boiled for 2 hours. The reaction mixture was filtered hot to yield 42 g. of material with m.p. 230–240°. The two-phase filtrate was worked up in the usual fashion, and the crude product was dissolved in 200 ml. of ether. After cooling this solution at 0° for several hours, a total of 93.5 g. of solid was obtained; m.p. 63–95°. Several recrystallizations from ether during which the insoluble material was removed by filtration and the filtrate was treated with small amounts of anisole yielded 12.2 g. of recovered starting material (ether-insoluble fraction) and 75 g. (40%) of the complex of IV with anisole (ether-soluble fraction); m.p. 77–79°. This complex showed no depression in m.p. when admixed with a sample prepared by an alternate route (*cf.* below).[10]

**The Condensation of Anisole and Anisoin.**—A mixture of 50 g. (0.184 mole) of anisoin and 40 g. (0.37 mole) of anisole, in a flask fitted with a reflux condenser, mechanical stirrer and thermometer, was heated to 100°. With stirring, 40 ml. of 85% phosphoric acid was added down the condenser in small portions, followed by heating at 120° for 2 hours. After standing overnight, the crystalline mass was filtered, washed with water, dried and dissolved in 150 ml. of ether. Then 10 ml. of anisole was added and the solution cooled to 0° for several hours, yielding 63 g. (73%) of material of m.p. 73–78°. A second recrystallization gave 58.3 g. of pure ***p*-methoxy-2,2-bis-(*p*-methoxyphenyl)-acetophenone anisolate** (V); m.p. 77–79°.

*Anal.* Calcd. for $C_{30}H_{30}O_5$: C, 76.57; H, 6.43. Found: C, 76.42; H, 6.49.

When a sample of 20 g. of V was heated at reduced pressure, 4.5 g. (98% of theory) of anisole was readily removed and collected in a cold trap. On further heating, 13.7 g. (95% from V) of IV distilled without decomposition at 265° (0.2 mm.), $n^{30}D$ 1.6182.

*Anal.* Calcd. for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12. Found: C, 76.21; H, 6.25.

IV was a viscous yellow liquid which became brittle and glass-like at −80° but did not crystallize. When IV was stirred with an equimolar quantity of anisole, the mixture became warm and quickly changed to a white powder of m.p. 77–79°. This powder was stable in a closed bottle but slowly lost anisole in the open.

**The Oxime of IV.**—The anisole was removed from 15 g. (0.0319 mole) of V by heating at reduced pressure. To the residue was added 25 ml. of 95% ethanol, 4.5 g. (0.64 mole) of hydroxylamine hydrochloride and 5 ml. of pyridine. The mixture was refluxed 3 hours and allowed to stand overnight. The mother liquor was decanted and the solid was washed with ether and recrystallized several times from ethanol–acetone, yielding needles of m.p. 159–161°.

*Anal.* Calcd. for $C_{23}H_{23}O_4N$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.17; H, 6.18; N, 3.64.

(7) R. S. Shelton, THIS JOURNAL, **75**, 5491 (1953), and co-workers have reported the conversion of VI to VII in 70% yield. These results have been duplicated in this Laboratory.

(8) Melting points and boiling points are uncorrected. Unless otherwise indicated, the reagents were the best obtainable commercial grades and were not purified further before use. The analyses were performed by Mr. R. Gordon Goodin of the Microanalytical Laboratory of the J. T. Baker Chemical Company.

(9) A. Bistrzycki, J. Paulus and R. Perrin, *Ber.*, **44**, 2596 (1911).

(10) The structure of the material of m.p. 230–240° is uncertain. The use of a lower ratio of Grignard reagent to I and/or a shorter reflux time gave smaller amounts of it, but the purification of IV was more difficult due to the presence of more unreacted I. Attempts to purify the high-melting material failed due to its very slight solubility in most organic solvents. It was soluble in glacial acetic acid or concd. sulfuric acid, but was evidently decomposed in either case, as dilution with water yielded an oil. The solid was insoluble in dilute acid or base. Analysis of the crude material showed the absence of nitrogen and gave values of 82.8% carbon and 6.43% hydrogen. It is not clear how the reactants employed could give a product containing as little oxygen as this analysis indicates.

**The Reaction of IV with Phosphorus Pentachloride.**—Varying amounts of a white solid melting at 180–182° after purification were obtained from all runs involving heating IV with an excess of phosphorus pentachloride, either with or without the presence of phosphorus oxychloride as a solvent. The run giving the largest amount of this solid is described here. A sample of 17.7 g. (0.049 mole) of IV was heated under reflux with 20 ml. of phosphorus oxychloride and 10.2 g. (0.049 mole) of phosphorus pentachloride for one hour. Then, at hourly intervals, 10.2 g. of the pentachloride was added and refluxing continued for 4 hours. After standing overnight, the mixture was poured into ice and ether. The solid was filtered from the two-phase mixture and rinsed with water and cold ether. After drying it amounted to 9 g.; m.p. 173–180°. Recrystallization from benzene raised the m.p. to 180–182°.

*Anal.* Calcd. for $C_{23}H_{20}O_4Cl_2$: C, 64.05; H, 4.67; Cl, 16.44. Found: C, 64.0; H, 4.30; Cl, 16.1.

**The Reduction and Dehydration of IV.**—A solution of 23.5 g. (0.065 mole) of IV in 100 ml. of anhydrous ether was added dropwise to a stirred suspension of 2.8 g. (0.073 mole) of lithium aluminum hydride in 100 ml. of ether. The mixture was heated under reflux with stirring for 24 hours. After standing an additional 38 hours, it was hydrolyzed in the usual manner with 6 *N*, sulfuric acid. Filtration of the two-phase mixture yielded 19.7 g. of gray solid; m.p. 80–106°. An additional 3 g. of solid melting at 90–99° was obtained by removal of the solvent from the organic phase. This material was combined and heated at 100° with 45 ml. of 85% phosphoric acid for 5 hours. After cooling, the acid was decanted and the viscous, glue-like organic phase was washed with water, dried, and recrystallized from acetone–methanol. It yielded 19.1 g. (85%) of solid melting at 100–102° (literature[7] for tris-(*p*-methoxyphenyl)-ethylene (VI), m.p. 100–101°).

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[CONTRIBUTION FROM THE WM. H. NICHOLS CHEMICAL LABORATORY, NEW YORK UNIVERSITY]

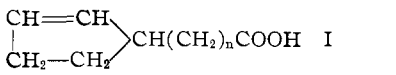
# The Synthesis and Stereochemistry of Chaulmoogric Acid

BY KURT MISLOW AND I. V. STEINBERG

RECEIVED DECEMBER 9, 1954

Electrolysis of a mixture of (+)-2-cyclopentene-1-acetic acid and ethyl hydrogen brassylate has yielded, after saponification of the product mixture, chaulmoogric acid identical with the natural product. Oxidation of (+)-2-cyclopentene-1-acetic acid to (−)-3-carboxyadipic acid, whose configuration is known, and, separately, reduction of (−)-2-cyclopentene-1-acetic acid to (−)-3-ethylcyclopentene, followed by oxidation to (+)-α-ethylglutaric acid, whose configuration is also known, establishes the configuration of the chaulmoogra oil acids by two independent paths.

The chaulmoogra oil acids, with the single exception of gorlic acid, are dextrorotatory members of a homologous series I. Interest in their



chemistry derives as much from their ancient renown in the chemotherapy of leprosy[1] as from the uniqueness of their structure: among seed fat acids, they are alone in having the cyclopentene system; further, together with sterculic acid,[2] they share the distinction of possessing a cycloalkene system, and at that a dissymmetric one.

The structure proof of I was initiated with extensive degradative work.[3] These investigations eventually led to a synthesis of dihydrochaulmoogric acid,[4] a synthesis[5] of chaulmoogric acid (I, $n = 12$) from hydnocarpic acid (I, $n = 10$), and the total synthesis of *dl*-chaulmoogric acid[6] and of *dl*-hydnocarpic acid.[7] Chaulmoogric acid, in turn, has been racemized to *dl*-chaulmoogric acid.[8]

The present investigation had as its first objective the realization of a total synthesis of naturally occurring, optically active chaulmoogric acid. In order to make our synthetic scheme adaptable to a feasible elucidation of the stereochemistry of the chaulmoogra oil acids, as well as to avoid laborious syntheses[6,7] followed by attempts at resolution of doubtful promise and of unavoidable tediousness, we resorted to anodic Kolbe coupling of a mixture of (+)-2-cyclopentene-1-acetic acid (II) and of ethyl hydrogen brassylate. In the design of this scheme, it had to be borne in mind that II is a β-substituted, γ,δ-unsaturated carboxylic acid with a center of asymmetry at the β-position, and that consequently[9] normal coupling could be expected, unattended by racemization.

Approximately eight recrystallizations from acetone–water of the brucine salt of 2-cyclopentene-1-acetic acid gave a pure diastereomer, from which optically pure (+)-II could be isolated. Electrolysis of a 3:1 mole ratio mixture of ethyl hydrogen brassylate and of freshly distilled (+)-II[10] gave a 30% yield of crude ethyl chaulmoograte, which was saponified to crude chaulmoogric acid. Recrystallization of the acid from ethanol yielded material substantially identical in melting point, rotation and infrared spectrum with the natural product. The total synthesis of chaulmoogric acid also represents a total synthesis of hydnocarpic acid and of alepric acid, the last two having been previously prepared[11] by degradation of chaulmoogric acid.

The remaining problem concerned the choice

(1) L. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," The Macmillan Co., New York, N. Y., 1941, p. 943.

(2) J. R. Nunn, *J. Chem. Soc.*, 313 (1952).

(3) (a) F. B. Power and F. H. Gornall, *ibid.*, 838 (1904); (b) F. B. Power and F. H. Gornall, *ibid.*, 851 (1904); (c) F. B. Power and M. Barrowcliff, *ibid.*, 884 (1905); (d) F. B. Power and M. Barrowcliff, *ibid.*, 557 (1907); (e) R. L. Shriner and R. Adams, THIS JOURNAL, **47**, 2727 (1925); (f) G. Stefanovic and I. Pejkovic, *Compt. rend.*, **238**, 697 (1954).

(4) C. R. Noller and R. Adams, THIS JOURNAL, **48**, 1080 (1926).

(5) W. M. Stanley and R. Adams, *ibid.*, **51**, 1515 (1929).

(6) G. A. Perkins and A. O. Cruz, *ibid.*, **49**, 1070 (1927).

(7) K. V. Bokil and K. S. Nargund, *Proc. Indian Acad. Sci.*, **13A**, 233 (1941); D. G. M. Diaper and J. C. Smith, *Biochem. J.*, **42**, 581 (1948).

(8) W. S. Hinegardner, THIS JOURNAL, **55**, 2831 (1933).

(9) B. C. L. Weedon, *Quart. Revs.*, **6**, 380 (1952).

(10) In common with chaulmoogric acid (P. Baranger and R. Maréchal, *Compt. rend.*, **231**, 661 (1950)), 2-cyclopentene-1-acetic acid undergoes slow air oxidation; undeteriorated acid may be recovered from the oxidation mixture by distillation.

(11) N. P. Buu-Hoï, *Ann. chim.*, **19**, 446 (1944).