hol (reported m. p. 238–239°),[11] was obtained as the sole product.

The hydroxamic acid is stable under the conditions of the experiment since a positive test with ferric chloride was obtained with a solution of benzhydroxamic acid (0.001 g.) in 50 ml. of water which had previously been heated on the steam-bath for one half hour.

Failure of the Ethyl Ester Derivative to Rearrange.—Benzhydroxamic acid ethyl ester, m. p. 62–63°,[6] was recovered unchanged when dissolved in sodium hydroxide as described above for bromobenzamide. No trace of aniline could be detected even with such a sensitive test for aniline as calcium hypochlorite.[12]

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[11] Young and Clark, *J. Chem. Soc.*, **73**, 367 (1898).

[12] Elvove, *Chem. Zentr.*, **89**, I, 1074 (1918).

CONTRIBUTION FROM THE
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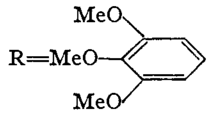
A Synthesis of β-(3,4,5-Trimethoxyphenyl)-propionic Acid[1]

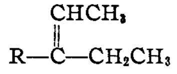
BY C. DAVID GUTSCHE AND FRIDOLIN A. HOYER

β-(3,4,5-Trimethoxyphenyl)-propionic acid, IV, a compound with possible synthetic applications in the colchicine series, has been previously synthesized in a variety of ways.[2,3,4] The best of these[4] involves the reduction of II to 3,4,5-trimethoxybenzaldehyde, condensation of the aldehyde with diethyl malonate, and catalytic hydrogenation to yield IV. The present communication describes a three-step sequence from I to IV involving conversion of II to 3,4,5-trimethoxypropiophenone, III, followed by a Willgerodt–Kindler reaction to yield IV. Although the over-all yield is lower (24–28%) than is obtained by the previously published method[4] (about 40%), the steps are simple and require neither the purification of intermediates nor the preparation of catalysts.

$$\underset{\text{I}}{RCOOH} \longrightarrow \underset{\text{II}}{RCOCl} \longrightarrow \underset{\text{III}}{RCOCH_2CH_3} \longrightarrow \underset{\text{IV}}{RCH_2CH_2COOH}$$



The over-all yield of this synthesis fell short of anticipations mainly because of an unexpected complication in the reaction of II with diethylcadmium. Numerous examples of this general reaction have been reported,[5] and in most cases the yields of ketone are excellent, further reaction of the ketone with the organocadmium reagent being almost negligible. In the present instance, however, appreciable amounts of 3-(3′,4′,5′-trimethoxyphenyl)-pentene-2, V, were formed by addition of diethylcadmium to III followed by loss of water.[6] A fairly accurate estimate of the amount of V contaminating the ketone was obtained by catalytic hydrogenation of a molecular distillate of the crude product. The much greater rate of hydrogen absorption of V as compared with III permitted a quantitative measure of the former. In one case, also, a fractional distillation gave results which correlated satisfactorily with the hydrogenation value. The amount of V contaminating III rose when the ratio of diethylcadmium to acid chloride or the reaction time was increased. Attempts to reduce the formation of V by using only a slight excess of diethylcadmium or a shortened reflux time, however, were unavailing because of the failure then of III to react completely. The conditions finally chosen as optimum resulted in almost complete consumption of II to yield 90–98% of a product containing from 15–27% of V and from which the ketone could be obtained in 43–49% yield by fractional distillation.



$$R-\overset{\overset{\displaystyle CHCH_3}{\|}}{C}-CH_2CH_3$$

V

The conversion of III to IV by the Kindler modification of the Willgerodt reaction was studied in some detail in an effort to improve the yields. Under the conditions chosen as optimum, material melting at 91–92° (reported 98°,[2] 100–102°,[3] 104°[4]) could be obtained in 35–45% yield. A small amount of impurity (probably I) may account for this low melting point and for the difficulty of further purification. The over-all yield of IV from I was about 20% when II and III were purified by distillation and about 28% when the crude intermediates were employed.

Experimental[7,8]

3,4,5-Trimethoxypropiophenone (III): (a) Optimum Reaction Conditions.—A solution of diethylcadmium was prepared according to standard procedures[5] from 47.2 g. (0.433 mole) of ethyl bromide in 470 cc. of dry, thiophene-free benzene. To this was added a solution of 50.0 g. (0.217 mole) of 3,4,5-trimethoxybenzoyl chloride (prepared in 91% yield from I and thionyl chloride; b. p. 174–176° at 15 mm.) in 120 cc. of dry, thiophene-free benzene. The mixture was stirred at room temperature for twenty minutes, refluxed for two and one-half hours, and then chilled and treated with water and dilute sulfuric acid. The organic material was extracted into benzene, the benzene washed several times with sodium bicarbonate solution (which removed 0.61 g. of I) and water, and the benzene then evaporated to leave 47.9 g. (98.5%) of an oil which slowly changed to a semi-crystalline mass. Fractional distillation through a thirty-four inch glass-

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[1] This investigation was supported in part by a research grant from the National Cancer Institute, U. S. Public Health Service.

[2] Slotta and Heller, *Ber.*, **63**, 3029 (1930).

[3] Cook, Graham, Cohen, Lapsley and Lawrence, *J. Chem. Soc.*, **322** (1944).

[4] Frank, Fanta and Tarbell, THIS JOURNAL, **70**, 2314 (1948).

[5] Cason, *Chem. Rev.*, **40**, 15 (1947).

[6] The addition of a dialkylcadmium to carbonyl groups has been reported in several instances [Gilman and Nelson, *Rec. trav. chim.*, **55**, 518 (1936); Christensen, *et al.*, THIS JOURNAL, **69**, 1909 (1947); Baker and Squire, *ibid.*, **70**, 1487 (1948)] and has been thought to be due to the activating influence of an electron withdrawing group adjacent to the carbonyl group.

[7] All melting points are corrected.

[8] We are indebted to Dorothy Kuenne for performing the microanalyses.

helix packed column yielded 21.4 g. (44%) of material; b. p. 181–182° (10 mm.), m. p. 44–48°. Several recrystallizations from benzene–petroleum ether (30–60°) yielded colorless needles; m. p. 51.5–52.5° (reported 51–2°,[10] 53.5°[9]).

The **p-nitrophenylhydrazone of III**, prepared by the method of Mauthner[10] was obtained as orange needles; m. p. 184–184.5° (reported[10] 182–183°).

The **2,4-dinitrophenylhydrazone of III**, prepared in the usual manner, was recrystallized from chloroform to yield small, dark-red prisms; m. p. 203–205°.

Anal. Calcd. for $C_{18}H_{20}N_4O_7$: C, 53.46; H, 4.99. Found: C, 53.50; H, 5.10.

The **semicarbazone of III** was prepared by standard methods and obtained as a colorless powder by recrystallization from ethanol; m. p. 174.5–175.5°.

Anal. Calcd. for $C_{13}H_{19}N_3O_4$: C, 55.50; H, 6.81. Found: C, 55.60; H, 6.75.

(b) **Effect of Reaction Conditions.**—The effects of the amount of diethylcadmium and the time of reflux are shown in Table I.

TABLE I

Moles of EtBr per mole of II	Reflux time, hr.	Crude III, %	V in crude III, %	Unreacted II, %
6	2	. .	40.0	1
2	2.5	98.5	27.5	1
1.5	2.5	91.5	18.0	7
2	1	22	2.0	76
2	2	77[a]	5.0	2

[a] This product was obtained from an "inverse" reaction in which the diethylcadmium was added to II. The yield shown in the table is of distilled material.

(c) **Olefin Assay by Hydrogenation.**—A 1.00-g. sample of the crude product was purified by molecular distillation at 0.01 mm., dissolved in ethyl acetate, and added to an equilibrated suspension of 0.200 g. of 10% palladium on charcoal in ethyl acetate. The fast hydrogen uptake, complete within three to five minutes, was taken as a direct index of the amount of V in the product since III under the same conditions absorbed hydrogen extremely slowly.

(d) **Olefin Assay by Fractional Distillation.**—A careful fractional distillation of a sample of crude ketone through a Piros–Glover column yielded 12% of V. An assay by hydrogenation on the same crude sample indicated 14% of olefin.

(e) **Isolation of V from the Product.**—A benzene solution containing 3.17 g. of the product from run 1, Table I was adsorbed on a column of alumina. Elution with benzene produced in the first three fractions 1.5 g. (47%) of a pale yellow oil with $n^{20}D$ of 1.5344, 1.5360 and 1.5362, respectively (reported[9] 1.5360). The middle fraction did not form a p-nitrophenylhydrazone or 2,4-dinitrophenylhydrazone. Hydrogenation in the presence of 10% palladium on charcoal resulted in an uptake of 104% of the amount calculated for one double bond.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.12; H, 8.14.

β-(3,4,5-Trimethoxyphenyl)-propionic Acid (IV): (a) **Optimum Reaction Conditions.**—The method employed was patterned after one described by Schwenk and Papa.[11] A 5.00-g. (0.0223 mole) sample of 3,4,5-trimethoxypropiophenone (m. p. 44–48°) was heated for four hours at 110° in an atmosphere of nitrogen with 5.83 g. (0.067 mole) of morpholine and 1.79 g. (0.056 mole) of sulfur. The mixture was cooled, the organic material extracted into chloroform, and the chloroform solution washed with dilute hydrochloric acid and water and then evaporated to leave the crude, oily thiomorpholide. This could not be purified by distillation or crystallization and was saponified directly by refluxing for thirty-six hours with 60 cc. of ethanol containing 12 g. of potassium hydroxide. Although the reaction mixture after this process was still very alkaline, a resaponification was found, in almost every case, to markedly increase the amount of acidic product obtained. The crude acid, obtained by working up in the usual way, was separated into 1.10 g. of bicarbonate-insoluble material and 3.47 g. (65%) of bicarbonate-soluble material. The latter was molecularly distilled at 0.02 mm. and the sublimate recrystallized from benzene–Skellysolve C to yield 2.39 g. (45%) of a light tan powder; m. p. 91–92°. Three recrystallizations from water yielded small, colorless plates, m. p. 96.5–97°, which showed no depression in m. p. when admixed with a sample of IV prepared by an alternate method as described below.

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59.98; H, 6.71. Found: C, 59.66; H, 6.45.

The **p-toluidide of IV** was prepared in the usual fashion and obtained, after recrystallization from aqueous ethanol, as almost colorless needles; m. p. 101.5–102°.

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.27; H, 7.04. Found: C, 69.41; H, 7.02.

(b) **Effect of Reaction Conditions.**—The reaction proved to be quite insensitive to changes in the ketone to sulfur ratio (1/1.25 to 1/2.5), the temperature (110 to 147°), and the time of heating (two to four hours). The crude yields, which in these cases were 57–65%, dropped significantly only when the time of heating was reduced to one hour (45%), when piperidine instead of morpholine was used (33%), or when the original Willgerodt sealed tube reaction conditions were employed (no product).

(c) **Alternate Preparation of IV.**—β-(3,4,5-Trimethoxyphenyl)-propionic acid was prepared according to a previously described method[3,4] and was obtained as a crystalline product melting, in one experiment, at 97–97.5° and, in another experiment, at 103–103.5°.

Over-all Reaction without Purification of Intermediates.—A 20.0-g. sample of I was converted to II which, without distillation, was subjected to reaction with diethylcadmium as described above to yield 19.0 g. (90%) of crude III. The Willgerodt–Kindler reaction was carried out with 5.00 g. of this material to yield 1.6 g. of once-recrystallized IV (m. p. 91–92°), bringing the over-all yield of IV from I to 28%.

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[9] Bogert and Isham, THIS JOURNAL, **36**, 514 (1914).

[10] Mauthner, *J. prakt. Chem.*, [2] **112**, 268 (1926).

[11] Schwenk and Papa, *J. Org. Chem.*, **11**, 798 (1946).

The Inertness of Crystalline Ovalbumin in Systems Containing α-Chymotrypsin and Hydrolyzable Substrates

BY H. T. HUANG AND CARL NIEMANN[1]

The observation that native crystalline ovalbumin is not hydrolyzed and heat denatured ovalbumin is hydrolyzed by α-chymotrypsin at 25° and pH 7.9 may be regarded as a confirmation of earlier reports in respect to the lack of digestability of certain native proteins by the so-called tryptic enzymes.[2] However in view of the fact that the above phenomenon has been interpreted in terms of the non-availability of certain peptide bonds in the native protein which become available when the protein is denatured[2] we believe it important to call attention to the hitherto undisclosed fact that native ovalbumin also has no demonstrable inhibitory properties

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[1] To whom inquiries regarding this article should be sent.

[2] For a review of the literature see H. Neurath, J. P. Greenstein, F. W. Putnam and J. O. Erickson, *Chem. Revs.*, **34**, 157 (1944).