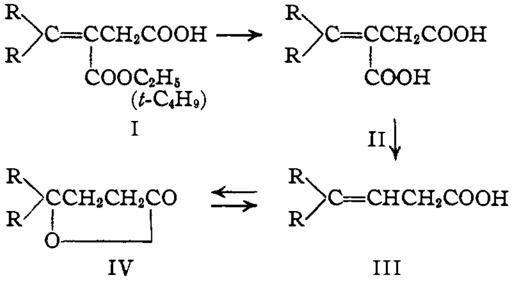
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Studies in Decarboxylation and Lacto–Enoic Tautomerism. III.[1] The Stobbe Condensation with *p,p'*-Dimethoxybenzophenone

BY WILLIAM S. JOHNSON* AND MAX W. MILLER

In the first paper of this series,[1b] it was shown that γ,γ-diphenylitaconic acid, II (R = C_6H_5), undergoes acid-catalyzed decarboxylation to give a mixture of γ,γ-diphenylvinylacetic acid, III (R = C_6H_5), and γ,γ-diphenylbutyrolactone, IV (R = C_6H_5), formed in a ratio (about 7 to 3) which proved to represent the position of a true equilibrium in an acid-catalyzed lacto–enoic tautomerism III $\rightleftarrows$ IV. The present investigation concerns a similar study with γ,γ-di-*p*-anisylitaconic acid, II (R = *p*-$CH_3OC_6H_4$), which was carried out with three main purposes in mind: (1) to test the prediction made from the β-carbonium ion mechanism of acid-catalyzed decarboxylation, that a para-methoxy substituent in the cinnamic acid system should facilitate decarboxylation.[1a] (2) According to the β-carbonium ion mechanism the β,γ-unsaturated acid III should be the precursor of the lactone IV.[1a] It was not possible to test this hypothesis in the case where R = C_6H_5,[1b] because the relative rates of the decarboxylation and the tautomerism were unfavorable and only equilibrium mixtures of unsaturated acid and lactone were obtained even under the mildest possible conditions. It was hoped that by appropriate modification of the structure the decarboxylation rate could be increased over that of tautomerism thus permitting isolation of an unequilibrated mixture of the products but this objective was not realized. (3) In the course of the preparation of II (R = *p*-$CH_3OC_6H_4$) we were interested in testing the scope of the Stobbe condensation with the relatively unreactive ketone *p,p'*-dimethoxybenzophenone.



The Stobbe condensation of benzophenone with 1.5 moles of diethyl succinate and 1.1 moles of potassium *t*-butoxide per mole of ketone has been shown to give the crystalline half-ester I (R = C_6H_5) in over 90% yield after a heating period of thirty minutes.[1b] When the same procedure was applied to the less reactive *p,p'*-dimethoxybenzophenone only a 47% yield was realized, and the remainder of the ketone was recovered. Longer reaction periods did not give an increase in the yield, thus indicating that the succinate (and consequently the butoxide) was competitively consumed by self-condensation to give diethyl 1,4-cyclohexanedione-2,5-dicarboxylate, which was shown to be present in the reaction mixture. Accordingly, when an additional charge, equivalent to the starting amounts, of ester and butoxide was introduced at the end of the usual reflux period and the heating continued for an additional thirty minutes, the yield was increased to 83%. The best yields were obtained by the use of di-*t*-butyl succinate instead of the diethyl ester. Only a single charge of reagents was necessary as the former ester undergoes self-condensation considerably slower than the latter, and thus 89% yields of the crystalline *t*-butyl acid ester, I (R = *p*-$CH_3OC_6H_4$), were realized. Saponification of the oily ethyl acid ester, I (R = *p*-$CH_3OC_6H_4$), with barium hydroxide gave the colorless crystalline itaconic acid II (R = *p*-$CH_3OC_6H_4$) which on melting at 161–161.5° loses water forming the higher-melting (210–211.5°), yellow cyclic anhydride. The acid is converted in part to the anhydride even on warming in a non-aqueous solvent, and the half-ester decomposes to this product on heating at 165°.

The effect of the methoxy groups on the rate of decarboxylation was striking, for with the 3:2:1 mixture of acetic acid, 48% hydrobromic acid and water, decarboxylation of II (R = *p*-$CH_3OC_6H_4$) was 90% complete in two minutes as compared with two hours for the parent compound II (R = C_6H_5).[1b] The decomposition of the former was indeed so rapid that satisfactory rate determinations could not be made even in the weakest of the acidic reagents for which comparative data are available with other acids.[1a] The reaction even proceeded readily in boiling 20% hydrochloric acid, 90% of the calculated amount of carbon dioxide being evolved in forty minutes. Indeed it was necessary to avoid heating with acid during the decomposition of the barium salt employed in the preparation of the dibasic acid, otherwise some decarboxylation occurred.

The products of the decarboxylation were the expected γ,γ-di-*p*-anisylvinylacetic acid, III (R = *p*-$CH_3OC_6H_4$), and γ,γ-di-*p*-anisylbutyrolactone IV (R = *p*-$CH_3OC_6H_4$), easily separated by alkali and obtained crystalline. The ratio of these products was between 8:2 and 7:3 which represents the equilibrium mixture of a new lacto–enoic tautomerism III $\rightleftarrows$ IV (R = *p*-$CH_3OC_6H_4$). This tautomerism proved to be extremely mobile,

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* Harvard University Ph.D. 1940.

[1] (a) Paper II, Johnson and Heinz, THIS JOURNAL, **71**, 2913 (1949); (b) paper I, Johnson, Petersen and Schneider, *ibid.*, **69**, 74 (1947)

equilibrium being essentially attained from either the unsaturated acid III or the lactone IV within ten minutes at 104° in a 7:1:7.5 mixture of acetic acid, hydrochloric acid and water (see Table I). In this same reagent one and one-half hours was required to effect 90% decarboxylation of II (R = p-$CH_3OC_6H_4$) so that there was no possibility of isolating a mixture of the decarboxylated products before equilibrium was reached. That this hope was not realized is not surprising since the *p*-methoxy groups might be expected *a priori* to facilitate the tautomerism as well as the decarboxylation, although to an unknown degree. The equilibration could even be effected under conditions which gave no evident decarboxylation, *viz.*, in boiling glacial acetic acid or in acetic acid containing a trace of hydrochloric acid at room temperature. In the former, equilibrium was essentially reached after about one hour (see Table I). Any difference in the position of the equilibrium at the two temperatures was within the limits of experimental error.

TABLE I

DECARBOXYLATION AND EQUILIBRATION EXPERIMENTS IN THE γ,γ-DI-*p*-ANISYLITACONIC ACID SERIES

Substance treated[a]	Amount, mole	Reagent[b]	Heating period	Decarboxylation time[c]	Lactone IV[a] % yield	Unsatd. acid III[a] % yield
II	0.00354	C	70 min.	2 min.	29	61
II	.00354	D	80 min.	40 min.	32	69
III	.00354	B	6 hr.	.....	20	79
IV	.00354	B	6 hr.	.....	20	78
III	.00354	A	1 hr.	.....	24	74
IV	.00354	A	1 hr.	.....	26	70
III	.00354	A	10 min.	.....	23	73
IV	.00354	A	10 min.	.....	29	70
III	.00354	A	5 min.	.....	18	78
IV	.00354	A	5 min.	.....	43	54
III	.00354	E	1 hr.	.....	22	76
IV	.00354	E	1 hr.	.....	25	74
III	.00354	E	30 min.	.....	22	77
IV	.00354	E	30 min.	.....	32	68
III	.00354	E	10 min.	.....	21	77
IV	.00354	E	10 min.	.....	57	41
III	.00354	E	5 min.	.....	13	87
III	.00167	F	24 hr.	.....	30	70
IV	.00167	F	24 hr.	.....	25	75
I[d]	.00354	B	40 min.	35 min.	24	73
I[d]	.00630	A	6.5 hr.	4 hr.	32	65
II	.00354	A	2.1 hr.	1.5 hr.	22	76

[a] Roman numerals refer to formulas in flow sheet with R = p-$CH_3OC_6H_4$. [b] The reagents had the following composition by volume and attained the indicated temperatures during reaction: Reagent A (104°) = 7 acetic acid to 1 concentrated hydrochloric acid to 7.5 water; reagent B (109°) = 7 acetic acid to 3.5 concentrated hydrochloric acid to 5 water; reagent C (112°) = 3 acetic acid to 2 48% hydrobromic acid to 1 water; reagent D (112°) = 20% hydrochloric acid; reagent E (120°) = glacial acetic acid; reagent F (25°) = glacial acetic acid containing 5 drops of concentrated hydrochloric acid for each 10 ml. [c] Time required for liberation of approximately 90% of calculated amount of gas. [d] *t*-Butyl acid ester.

For preparative purposes the *t*-butyl acid ester could be decomposed directly in the decarboxylation reagents giving isobutylene, carbon dioxide and the equilibrium mixture of III and IV (R = p-$CH_3OC_6H_4$). The latter isomer, which is formed in unfavorable ratio for preparative purposes can be obtained in 96% yield by treatment of the unsaturated acid (or the mixture) with anhydrous hydrogen fluoride at −15°.

Experimental Part[2]

The Stobbe Condensation with *p,p'*-Dimethoxybenzophenone. (a) With Diethyl Succinate.—A mixture of 6.07 g. of the ketone,[3] m. p. 145–146°, and 6.50 g. of diethyl succinate was treated in the usual manner[1b] with a solution of 1.10 g. of potassium in 25 ml. of dry *t*-butyl alcohol. After refluxing for thirty minutes in an atmosphere of nitrogen an additional 6.50 g. of ester and 1.10 g. of potassium in 25 ml. of *t*-butyl alcohol was added and refluxing continued for another thirty minutes. The product was isolated as described in the benzophenone series[1b] except that the half-ester was extracted with saturated sodium bicarbonate. Further washing with 2% sodium hydroxide solution removed 0.94 g. of crude diethyl 1,4-cyclohexanedione-2,5-dicarboxylate, m. p. about 122–125°, giving an intense violet color with ferric chloride. The purified material melted at 126.5–127.5° and gave no m. p. depression on admixture with an authentic specimen. A total of 1.12 g. of crude ketone, m. p. 137–140°, was recovered from the remaining neutral fraction after removal of the excess diethyl succinate by saponification. Acidification of the bicarbonate extracts gave a yellow oily product which was isolated by ether extraction. The residue (9.49 g.) remaining on evaporation of the ether was treated with 24.2 g. of barium hydroxide octahydrate in 100 ml. of 50% alcohol–water. After refluxing with stirring for two and one-half hours, most of the alcohol was evaporated, and the remaining aqueous suspension of salts was cooled and acidified with cold dilute hydrochloric acid. The oil which separated was taken up in ether, washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the ether at reduced pressure gave a cream-colored crystalline product amounting to 7.12 g. (83% yield), m. p. 153–154° (dec.) with softening at 150°. An analytical sample of **γ,γ-di-*p*-anisylitaconic acid**, II (R = p-$CH_3OC_6H_4$) was prepared by repeated recrystallization from dilute alcohol giving colorless blades, which melted at 161–161.5° with evolution of gas, turning yellow and slowly resolidifying, then remelting at about 203–205° (dec.).

Anal. Calcd. for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30; neut. equiv., 171.2. Found: C, 66.65; H, 5.53; neut. equiv., 173.4.

In an experiment carried out just as described above except that the second charge of ester and butoxide as well as the additional heating was omitted, the yield of crude itaconic acid was 4.05 g. (47%), m. p. 153.5–155° (dec.) with previous softening.

(b) With Di-*t*-butyl Succinate.—A solution of 2.26 g. of potassium in 39 ml. of dry *t*-butyl alcohol was treated with 10.00 g. of *p,p'*-dimethoxybenzophenone and 13.31 g. of di-*t*-butyl succinate,[4] m. p. 36–37°, according to the general procedure for the Stobbe condensation.[1b] After refluxing in an atmosphere of nitrogen for three hours the mixture was chilled and just neutralized with 2 *N* hydrochloric acid. The acidic product, isolated as described in the benzophenone series,[1b] amounted to 14.61 g. (89% yield) of crude crystalline **β-carbo-*t*-butoxy-γ,γ-di-*p*-**

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[2] All melting points are corrected.

[3] Prepared by the procedure of Schnackenberg and Scholl, *Ber.*, **36**, 654 (1903).

[4] Prepared by the action of butoxide on diphenyl succinate; see Daub and Johnson, THIS JOURNAL, **72**, 501 (1950). The ester can also be obtained by the method indicated in footnote 20, ref. 1b

anisylvinylacetic acid, m. p. 125–127° with softening at 120°. A sample purified by repeated recrystallization from ethyl acetate was obtained as colorless prisms, m. p. 126.2–127.6° with softening at 125.5°. A less stable dimorphic modification melting at 102–103° was also occasionally encountered.

Anal. Calcd. for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58. Found: C, 69.54; H, 6.78.

From the neutral fraction in the above experiment, 1.13 g. of crude ketone, m. p. 142–145° was recovered. When a higher proportion of butoxide was employed in the condensation, yields of half-ester as high as 94% were realized, but the crude product was partly oily.

γ,γ-Di-*p*-anisylitaconic anhydride was prepared from the dibasic acid (1.0 g.) and 5.0 g. of acetyl chloride. As the mixture was refluxed (one hour) the acid dissolved and the yellow anhydride separated. The mixture was evaporated at reduced pressure and the residue washed with water, and then sodium bicarbonate solution. The crude anhydride amounted to 0.92 g. (97% yield), m. p. 203–205° (soft at 190°). Repeated recrystallizations from chloroform gave a yellow powdery product, m. p. 210–211.5° (soft at 200°).

Anal. Calcd. for $C_{19}H_{16}O_5$: C, 70.36; H, 4.97. Found: C, 70.20; H, 5.02.

Decarboxylation Experiments.—These experiments were conducted according to the general technique described in paper II of this series.[1a] About 25–30 ml. of decarboxylation reagent was employed with the quantities of organic acid and heating periods specified in Table I. At the termination of the heating period, the product was isolated by pouring the hot reaction mixture quickly onto a slurry of ice and sodium carbonate in excess of that required to neutralize all acid. In this way tautomerism was "frozen" as demonstrated by control experiments with the lactone and unsaturated acid. The cold mixture was extracted with ether, and the ether solution then washed repeatedly with 10% sodium carbonate solution. The combined alkaline extracts were washed once with ether, then added to dilute hydrochloric acid. The colorless oil which separated usually crystallized within a few minutes, and was then separated by filtration and dried. The yields of the products thus prepared and melting between 85 and 86.5° or 88 and 92° depending on the form isolated (see below) are reported in column 7 of Table I. This substance, **γ,γ-di-*p*-anisylvinylacetic acid, III** (R = *p*-$CH_3OC_6H_4$) exists in two dimorphic forms, one melting at 85.5–86°, and the other at 93–94° after recrystallization from ether. The latter agrees with the melting point (94–95°) reported by Borsche and Kühn[5] for this compound prepared from anisole, succinyl chloride and aluminum chloride.

The ether solution from which the above acid was extracted, was washed with saturated salt solutions and dried over anhydrous sodium sulfate. Evaporation of the ether left colorless crystals of **γ,γ-di-*p*-anisylbutyrolactone, IV** (R = *p*-$CH_3OC_6H_4$) which was dried to constant weight *in vacuo*. The yields of these products, m. ps. ranging between 105 and 107.5°, appear in column 6 of Table I. A sample of the lactone purified by repeated recrystallization from ether was obtained as colorless needles, m. p. 107.8–108.5°.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.58; H, 6.23.

Equilibration Experiments.—These experiments were conducted in a 50-ml. flask fitted with a thermometer and a condenser (ground-glass joints). The sample of pure unsaturated acid or lactone was placed in the flask, then 15.5 ml. of reagent (see Table I) was added and (when heating was used) the flask immediately immersed in an oil-bath at 140°. The temperature of the reaction mixture thus became stabilized within two minutes. At the end of the heating period (see Table I) the product was worked up just as described above for the decarboxylation experiments. The m. ps. of the products corresponding to the yields recorded in columns 6 and 7 (Table I) were within the ranges specified above for the decarboxylation products.

Lactonization of γ,γ-Di-*p*-anisylvinylacetic Acid.—A 1.43-g. sample of the pure acid, m. p. 85.5–86.2°, was treated with about 100 ml. of anhydrous hydrogen fluoride in a chloropolythene vessel cooled in an ice-salt-bath. After two hours at −10°, the reagent was evaporated in a stream of air, the residue treated with ice and sodium carbonate, and the product isolated as described above. The crude lactone amounted to 1.37 g. (96% yield) and melted at 104–106° with softening at 100°.

Summary

The condensation of *p,p'*-dimethoxybenzophenone with both diethyl and di-*t*-butyl succinate has been studied. γ,γ-Di-*p*-anisylitaconic acid, thus produced, was found to be extremely susceptible to acid-catalyzed decarboxylation, a behavior which is compatible with a mechanism previously advanced. The products of decarboxylation were γ,γ-di-*p*-anisylvinylacetic acid and γ,γ-di-*p*-anisylbutyrolactone which were formed in a ratio which proved to represent the position of a true equilibrium in an extremely labile lacto-enoic tautomerism.

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[5] Borsche and Kühn, *Ann.*, **526**, 19 (1936).