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Cyclizations of Benzylsuccinic Acids

BY E. C. HORNING AND G. N. WALKER

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The effect of polyphosphoric acid in cyclizations of compounds of the benzylsuccinic acid type has been investigated. Polyphosphoric acid is an effective cyclization agent, and the resulting compounds are substituted tetralones. This indicates that the general conclusion that six-membered cyclic ketones are formed in preference to five-membered ketones in intramolecular cyclizations holds for polyphosphoric acid cyclizations as well as the usual Friedel–Crafts cyclizations. Certain reactions of the intermediates are described, including an interesting acylation and cyclization leading to a naphthoic acid.

The general conclusion that six-membered cyclic ketones are formed in preference to five-membered ketones in intramolecular cyclizations is based upon several examples in which cyclization was carried out by the usual Friedel–Crafts procedure.[1] These examples include the cyclization of α-benzyl-γ-phenylbutyric acid to 2-benzyltetralone-1, and of benzylsuccinic acid to 3-carboxytetralone-1. This paper reports the result of a study carried out to determine (a) whether the polyphosphoric acid reagent of Snyder and Werber,[2] which has been found to be the reagent of choice for a variety of reactions,[3] is generally useful in intramolecular cyclizations of dibasic acids, and (b) whether, if cyclization occurs, six-membered rings are always formed in preference to five-membered rings in this procedure and the comparable sulfuric acid cyclization as well as in the Friedel–Crafts method.

Four arylitaconic acids were prepared by the condensation of the appropriate aromatic aldehyde with diethyl succinate or diethyl α-methylsuccinate, using the general method of Cornforth, Hughes and Lions.[4] The initial condensation product, which by analogy with the products of the usual Stobbe condensation should be the ester-acid corresponding to IX, may usually be isolated in high yield; the details of one such experiment are recorded here, and since subsequent steps including hydrogenation and cyclization yielded the corresponding tetralone (VI) this structure for the product may be assumed to be correct. If the initial condensation reaction is continued through a hydrolysis step, the products are the corresponding arylitaconic acids, and the yields are then lowered (Table I).

TABLE I

ARYLITACONIC ACIDS

Compound, acid	Yield, %	M.p., °C. (dec.)	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Phenylitaconic	50	185–188 (from aq. EtOH)				
α'-Methyl-α-benzylidenesuccinic	20	186.5–189 (from aq. EtOH)	65.44	5.50	65.60	5.67
3,4-Dimethoxyphenylitaconic	52	169–171.5 (from EtOAc)	58.64	5.30	58.72	5.45
o-Methoxyphenylitaconic	72	208.5–211 (from EtOH)	61.01	5.12	60.87	5.16

The itaconic acids were hydrogenated with a palladium–carbon catalyst to the corresponding benzylsuccinic acids. The cyclization of an acid of this type should give either a 3-carboxytetralone-1 or a 2-substituted hydrindone-1. Both polyphosphoric acid and sulfuric acid were examined for their effectiveness as cyclization agents; it was found that the yields of cyclic ketone with the two agents were approximately the same when the possibility for sulfonation was low, as in the case of benzylsuccinic acid or anhydride (69% yield with polyphosphoric acid, 64% yield with sulfuric acid; the anhydride cyclization reported here was designed to follow the experiments of Attwood, Stevenson and Thorpe[5]), but with a methoxy-substituted acid it was found that polyphosphoric acid gave good results while sulfuric acid gave low and variable yields. This result parallels our observations in studies of glyoxylate cyclizations, and probably is due to loss of material by sulfonation.

The cyclization of benzylsuccinic acid or anhydride gave 3-carboxytetralone-1, a compound of known structure. In the case of 3,4-dimethoxybenzylsuccinic acid, the identity of the product as 3-carboxy-6,7-dimethoxytetralone-1 (II) was confirmed in the following way. The ester-acid IX was hydrogenated and cyclized to VI; the keto-ester obtained in this way was identical to that obtained by esterification of II. This is in agreement with the expected structure for IX, but also assumes that ester-exchange did not occur during the sequence. By dehydrogenation over a palladium–charcoal catalyst, II was converted to a naphthalene derivative III. This dehydrogenation was difficult, and required heating for several hours in boiling biphenyl. The keto group of II was eliminated by esterification of II to yield VI, followed by catalytic hydrogenation to VII; the latter compound was dehydrogenated readily in boiling cymene in quantitative yield to the naphthoic acid VIII.

An attempt was made to obtain the corresponding hydrindone-1 by cyclization of an ester-acid. The itaconic acid I was converted to its anhydride II, and on treatment with ethanol an ester-acid,

(1) W. S. Johnson, "Organic Reactions," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 116.

(2) H. R. Snyder and F. X. Werber, THIS JOURNAL, **72**, 2962, 2965 (1950).

(3) E. C. Horning, J. Koo and G. N. Walker, *ibid.*, **73**, 5826 (1951); E. C. Horning and V. L. Stromberg, *ibid.*, **74**, 2680 (1952); E. C. Horning, G. N. Walker and D. B. Reisner, to be published.

(4) J. W. Cornforth, G. K. Hughes and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 228 (1939).

(5) A. J. Attwood, A. Stevenson and J. F. Thorpe, *J. Chem. Soc.*, 1755 (1923).

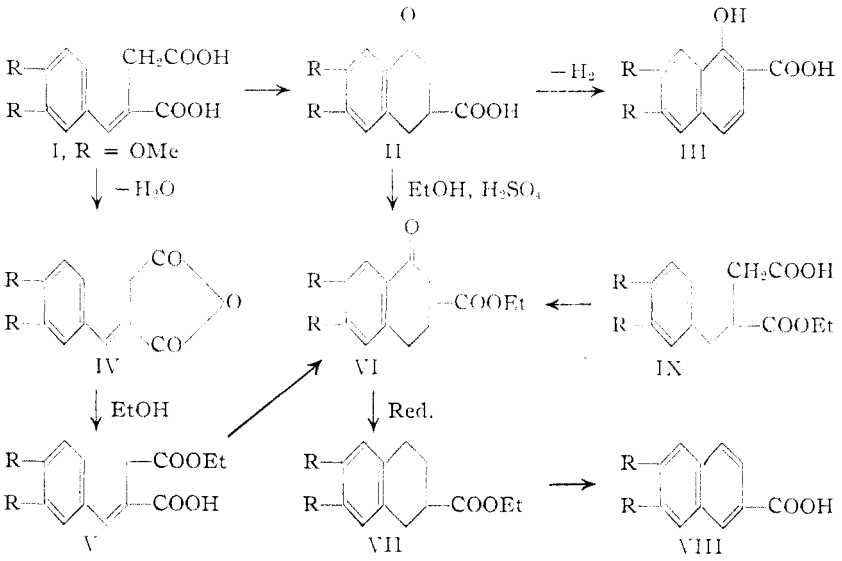

Fig. 1.

presumably V, was obtained in crystalline form. The stereochemical configuration of this product is unknown, but it is highly unlikely that the acid and ester groups of V are wrongly assigned. The product was not the same as IX, but products corresponding to IX are often non-crystalline owing to the presence of *cis–trans* isomers, and this comparison is therefore not exact. The ester-acid V, after reduction and cyclization with polyphosphoric acid, gave the keto-ester VI, indicating that ester-exchange occurred during the sequence, or that the ester-acid V is indeed an isomer with ester and acid groups interchanged.

From this it may be concluded that polyphosphoric acid is an effective agent for cyclizations of dibasic acids of the substituted succinic acid variety, and that its action, like that found for Friedel–Crafts conditions, is such as to lead to the six-membered cyclic ketone rather than to the five-membered ketone. Unlike the Friedel–Crafts method, with polyphosphoric acid it is possible to cyclize the ester-acid obtained by hydrogenation of the Stobbe condensation product IX, and this provides a direct and very good means of obtaining substituted tetralones corresponding to VI. From benzaldehyde and diethyl α-methylsuccinate, by the method described in the experimental section, there was prepared 2-methyl-3-carboxytetralone-1. Tests for vitamin K activity of this compound are not complete.

If the stereochemical structure of the substituted cinnamic acids resulting from the Stobbe condensation is indeed that represented by I, it might be expected that cyclization to a naphthol would represent a competitive reaction to itaconic anhydride formation, under circumstances where a mixed anhydride with sulfuric or phosphoric acids is probably involved as an intermediate. It was found, however, that anhydride formation was the only reaction observed when the acid I (R, R = OMe or R, R = H) was treated with polyphosphoric acid.

Certain reactions of the anhydride IV were also investigated. On heating with acetic anhydride in the presence of pyridine, a low yield (33%) of neutral yellow material was obtained. This product evidently resulted from acylation of the anhydride; that the acetyl group was located in the side chain rather than on the aromatic ring was proved by ozonolysis of the product. The isolation of veratraldehyde located the olefinic bond and indicated that the aromatic ring was unchanged. The compound X did not undergo cyclization when treated with polyphosphoric acid, possibly because of a different stereochemical arrangement from that indicated in Fig. 2; this is not certain because attempts at cyclization after hydrogenation also gave negative results. When the anhydride system was opened with dilute sodium hydroxide solution, one of the carboxylic acid groups was lost, and when the acidified solution was allowed to stand for several days the product was a naphthoic acid to which structure XI has been assigned.

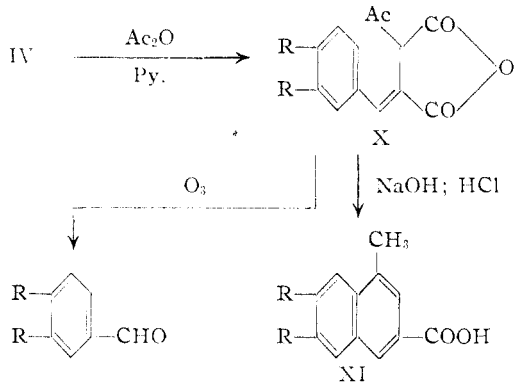

Fig. 2.

This product results from a rather remarkable cyclization which apparently occurred in aqueous acid solution at room temperature, and which indicates that favorable stereochemical factors were involved. The evidence for structure XI includes analytical data, an infrared spectrum which was compatible with the proposed structure, and a comparison of the ultraviolet spectrum with that for compound III (Fig. 3).

The acetylation reaction leading to X could not be extended to aromatic systems through the use of benzoic anhydride, and it did not occur with simpler compounds like phenylitaconic anhydride.

Acknowledgment.—We are indebted to Dr. William Alford and his staff for the microanalytical data.

Experimental

General Procedure in Modified Stobbe Condensation.—Sodium (0.97 g. atom) was dissolved in absolute ethanol (500 ml.) and a solution of 0.41 mole of the aldehyde and 0.45 mole of succinate ester was added over a period of 15 minutes with good stirring at room temperature. The mixture was refluxed and stirred for two hours; approximately

half the ethanol was then removed by distillation; water (200 ml.) was added and solvent, corresponding in volume to the remainder of the alcohol originally employed, was distilled from the solution. The solution was refluxed for three hours, cooled, and diluted with 500 ml. of water. Concentrated hydrochloric acid (50 ml.) was added, and oily material was removed. The aqueous solution was acidified strongly with hydrochloric acid and was chilled. The product was collected, washed with small portions of water, dried and triturated with several small portions of ether. Material sufficiently pure for further work was thus obtained; the products and their respective yields are listed in Table I. Pure samples were obtained by recrystallization from ethanol or ethyl acetate.

o-Methoxyphenylitaconic acid was precipitated directly from the diluted alkaline solution after hydrolysis. α'-Methyl-α-benzylidenesuccinic acid was precipitated from a more dilute solution (1400 ml.) than that indicated above.

Diethyl α-methyl succinate was prepared by hydrogenation of 100 g. of redistilled ethyl itaconate (b.p. 222–229°) in the presence of 3.0 g. of 5% palladium–charcoal catalyst at room temperature and an initial pressure of 40 lb.; the material obtained by filtration of the catalyst was employed directly. In other cases, diethyl succinate was used as the ester component.

Reduction of Arylitaconic Acids to Benzylsuccinic Acids.—A mixture of 12 g. of the acid, 3 g. of 5% palladium–charcoal catalyst and 100 ml. of glacial acetic acid was shaken at 75° under hydrogen (initially at 40 lb.) for one hour. Absorption of the theoretical amount of hydrogen occurred within 20 minutes. The catalyst was removed by filtration, and the acetic acid was evaporated. Products were obtained in each case in essentially quantitative yield.

3,4-Dimethoxybenzylsuccinic acid did not crystallize; it was dissolved in hot water, the solution was clarified, and the acid was recovered as an oil by acidification with hydrochloric acid. **Benzylsuccinic anhydride** was obtained as the product (crude m.p. 92–102°; reported[5] m.p. 102°) when acetic acid–acetic anhydride was used as the solvent in the reduction. **α'-Methyl-α-benzylsuccinic acid** had crude m.p. 113–118°. **o-Methoxybenzylsuccinic acid** had crude m.p. 123–134°; recrystallization from aqueous ethanol gave a colorless analytical sample, m.p. 142–145.5°.

Anal. Calcd. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.51; H, 5.99.

3-Carboxytetralone-1 (A).—Crude benzylsuccinic anhydride (3.0 g.) and polyphosphoric acid (60 g.) were stirred and heated to 100° for two hours. Treatment of the dark brown solution with cold water gave a brown solid; the yield of crude product after collecting, washing with water, triturating with ether, and drying was 1.9 g. (69%), m.p. 143–146°. Recrystallization from aqueous ethanol raised the m.p. to 146–149°.

(B).—A solution of 6.0 g. of benzylsuccinic anhydride in 45 ml. of concentrated sulfuric acid was allowed to stand at room temperature overnight. The carmine-red solution was poured over ice; the product was collected, washed with water, and air-dried. The yield of crude material was 3.5 g. (64%). Trituration with ether and recrystallization from dilute alcohol gave material of m.p. 144–147°; a mixed m.p. with material obtained in (A) was 146–149°. This compound is reported[5] to melt at 144°.

The 2,4-dinitrophenylhydrazone was triturated with ethanol and chloroform and recrystallized from acetone; fine, red crystals, m.p. 272.5–274° (dec.).

Anal. Calcd. for $C_{17}H_{14}O_6N_4$: C, 55.14; H, 3.81. Found: C, 55.20; H, 3.85.

2-Methyl-3-carboxytetralone-1.—A solution of 10.4 g. of α'-methyl-α-benzylsuccinic acid in 50 ml. of concentrated sulfuric acid was allowed to stand for 12 hours and was then poured over ice. The crude product, after washing with cold water and drying, amounted to 7.2 g. (76%). Recrystallization from aqueous alcohol gave colorless crystals, m.p. 183–185°.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.93. Found: C, 70.57; H, 6.11.

The 2,4-dinitrophenylhydrazone was triturated with hot ethanol and recrystallized from acetone; red-orange crystals, m.p. 240–245° (dec.).

Anal. Calcd. for $C_{18}H_{16}O_6N_4$: C, 56.25; H, 4.20. Found: C, 56.38; H, 4.45.

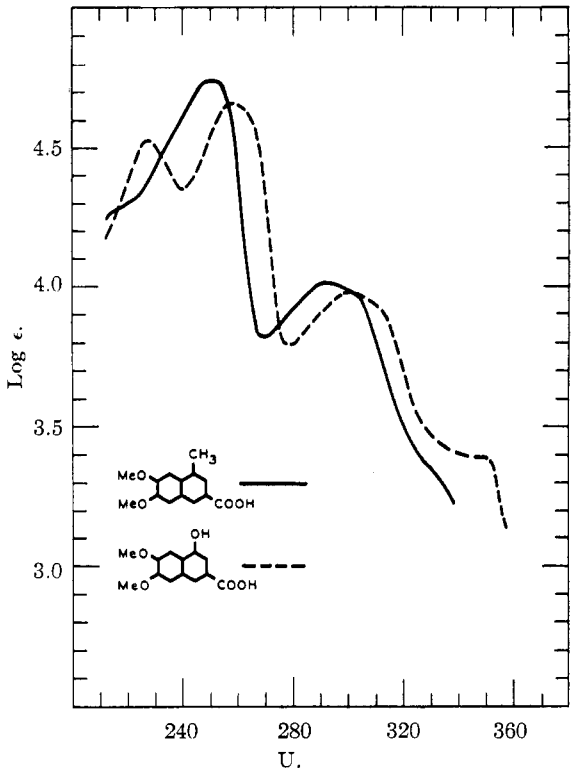

Fig. 3.

6,7-Dimethoxy-3-carboxytetralone-1 (IV).—A mixture of 9.1 g. of 3,4-dimethoxybenzylsuccinic acid and 37 g. of polyphosphoric acid was stirred and heated to 90° for 15 minutes. After treatment of the carmine solution with water, the crude product was collected, washed with cold water, dried, and triturated with hot ethanol. The crude yield was 5.2 g. (61%), m.p. 219.5–221.5°. Recrystallization from methanol gave colorless crystals, m.p. 226–227. 5°.

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.68; H, 5.80.

The 2,4-dinitrophenylhydrazone was triturated with hot ethanol and chloroform, and recrystallized from dry benzene; bright red crystals, m.p. 260–263° (dec.).

Anal. Calcd. for $C_{19}H_{18}O_8N_4$: C, 53.02; H, 4.22. Found: C, 53.54; H, 4.44.

Benzylidenesuccinic Anhydrides (Arylitaconic Anhydrides) (A).—A mixture of 10.3 g. of the arylitaconic acid and 101 g. of polyphosphoric acid was stirred and heated to 100° for one-half hour. The dark brown mixture was treated with water; the product was collected, washed with water and dried. Trituration with ethanol gave the yields of products indicated in Table II. Recrystallization from ethanol or ethyl acetate afforded pure samples. *o*-Methoxyphenylitaconic acid, when treated in this way, led to dark, glassy material and partial recovery of the starting compound.

TABLE II

ARYLITACONIC ANHYDRIDES

Compound anhydride	Yield, % from (A)	M.p., °C.	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Phenylitaconic	95	166–168.5 (from EtOH)				
3,4-Dimethoxyphenylitaconic	36	168–170 (from EtOAc)	62.90	4.88	62.82	5.18
o-Methoxyphenylitaconic	..	130.5–132.5 (from EtOH)	66.05	4.62	66.07	4.63

(B).—A solution of the arylitaconic acid (2.0 g.) in acetic anhydride (25 ml.) was refluxed for one hour. Excess acetic anhydride was removed by evaporation, and the residue was triturated with ethanol. Further purification was

effected as indicated above. Products from (A) and (B) were identical.

6,7-Dimethoxy-3-carbethoxytetralone-1 (VIII).—A solution of 2.0 g. of 6,7-dimethoxy-3-carboxytetralone-1 in 75 ml. of absolute ethanol containing 5 ml. of concentrated sulfuric acid was refluxed for three hours. Excess ethanol was removed by distillation, and the residual oil was extracted with ether. The ether solution was washed with 5% sodium hydroxide solution and with successive portions of dilute acetic acid, dilute sodium bicarbonate solution, and water. After drying the solution (magnesium sulfate), the ether was removed by evaporation, and the residual crystals (1.6 g., 72%) were triturated with ether and recrystallized from ether–benzene; fine, colorless needles, m.p. 118.5–119°.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.77; H, 6.52. Found: C, 64.61; H, 6.59.

Monoethyl Ester of 3,4-Dimethoxyphenylitaconic Acid (IX).—A solution of 33.4 g. (0.20 mole) of redistilled veratraldehyde and 35.7 g. (0.20 mole) of ethyl succinate was added rapidly to a stirred solution of 5.8 g. (0.25 g. atom) of sodium in 130 ml. of absolute ethanol. The suspension was refluxed and stirred for three hours, and most of the ethanol was removed by distillation. The residue was cooled and dissolved in 900 ml. of water; the solution was washed with ether and was acidified with hydrochloric acid. The oil which separated was extracted with ether. The ether solution was washed with two portions of water and was dried over magnesium sulfate. Removal of the ether by evaporation afforded 58.5 g. (99%) of dark red oil which did not crystallize. The product was not purified further at this stage.

Reduction.—A solution of 53.1 g. of the crude monoester in 300 ml. of glacial acetic acid, containing 3.2 g. of 5% palladium–charcoal catalyst, was hydrogenated at 70° and an initial pressure of 40 lb.; reduction was complete in about one hour. The catalyst was removed and the solution was evaporated. The product, obtained quantitatively, was a colorless, viscous oil, soluble in aqueous sodium bicarbonate solution.

Cyclization.—A mixture of 2.8 g. of the crude reduction product and 19 g. of polyphosphoric acid was stirred and heated (steam-cone) for seven minutes. The solution was treated with water. The red, crystalline material which separated was extracted with ether. The ether solution was washed with successive portions of 5% sodium hydroxide solution, dilute acetic acid, dilute sodium bicarbonate solution, and water, and was dried over magnesium sulfate. The ether was evaporated. The crystalline material (1.8 g., 68%) was recrystallized from methanol–ether; colorless crystals, m.p. 116–118°. The mixed m.p. with 6,7-dimethoxy-3-carbethoxytetralone-1, prepared as in the preceding experiment, was 117.5–119° (undepressed).

Monoethyl Ester of 6,7-Dimethoxyphenylitaconic Acid (V).—Crude anhydride, prepared from 32.0 g. (0.120 mole) of this acid and 110 g. of polyphosphoric acid, was dissolved in 200 ml. of hot absolute ethanol. The solution was allowed to stand for two weeks. Evaporation of the excess ethanol and trituration of the resulting gummy material with methanol afforded crystals; one recrystallization from methanol gave 9.0 g. (26% from the acid) of crystals in two crops, m.p. 130–136°. Further recrystallization from methanol led to yellow crystals, m.p. 142–144°.

Anal. Calcd. for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 61.23; H, 6.24.

Hydrolysis of this acid ester was accomplished by allowing a solution of it in excess 5% sodium hydroxide to stand for 15 minutes. Acidification with hydrochloric acid gave a quantitative yield of the corresponding acid.

Reduction and cyclization of this acid ester was carried out according to the procedure described in the preceding experiment; the yield in the cyclization of 0.9 g. of the crude reduction product was 0.5 g. (60%). Recrystallization from methanol–ether gave colorless crystals, m.p. 118.5–119°; a mixed m.p. was undepressed with a sample of 6,7-dimethoxy-3-carbethoxytetralone-1.

6,7-Dimethoxy-2-carbethoxytetralin (X).—A solution of 7.6 g. (0.021 mole) of 6,7-dimethoxy-3-carbethoxytetralone-1 in 150 ml. of glacial acetic acid, containing 4.0 g. of 5% palladium–charcoal catalyst, was hydrogenated at 75° and 40 lb. for one hour. Filtration of the catalyst and evaporation of the acetic acid gave 6.4 g. (89%) of crystalline product. Recrystallization from methanol afforded colorless crystals, m.p. 67–69°.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.06; H, 7.76.

6,7-Dimethoxy-2-carboxytetralin (XI).—A solution of 4.6 g. (0.017 mole) of 6,7-dimethoxy-2-carbethoxytetralin and 13 g. of potassium hydroxide in 36 ml. of ethanol and 31 ml. of water was refluxed for three hours. The ethanol was removed by evaporation. The solution was diluted to 200 ml., filtered, and acidified with hydrochloric acid. The product was collected, washed with water, and dried; the crude yield was 3.5 g. (85%). Recrystallization from aqueous methanol with Norite afforded colorless, powdery crystals, m.p. 137–139°.

Anal. Calcd. for $C_{13}H_{15}O_4$: C, 66.08; H, 6.83. Found: C, 66.35; H, 6.73.

6,7-Dimethoxy-2-naphthoic Acid (XII).—To a solution of 2.8 g. of 6,7-dimethoxy-2-carboxytetralin in 60 ml. of redistilled *p*-cymene was added 1.7 g. of 5% palladium–charcoal catalyst. The suspension was refluxed vigorously for three hours, and was filtered while hot. When the solution was cooled, crystallization occurred. The product was collected (quantitative crude yield) and recrystallized from methanol; colorless crystals, m.p. 247–248.5°, soluble in sodium bicarbonate solution.

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.27; H, 5.08.

6,7-Dimethoxy-3-carboxynaphthol-1 (V).—A mixture of 1.3 g. of 6,7-dimethoxy-3-carboxytetralone-1, 20 g. of biphenyl and 1.5 g. of 5% palladium–charcoal catalyst was refluxed vigorously for four hours. The suspension was filtered while hot, and the catalyst was washed thoroughly with acetone. The solution was steam distilled until biphenyl could no longer be detected in the distillate; the remaining aqueous solution was filtered and chilled. The crystals were collected and air-dried; the crude yield of discolored material, m.p. 243–245°, was 0.6 g. Recrystallization from aqueous ethanol with Darco gave colorless crystals, m.p. 252–254° (shrinking). Analysis indicated that the product crystallized as a monoethanolate.

Anal. Calcd. for $C_{15}H_{18}O_6$: C, 61.21; H, 6.16. Found: C, 61.39; H, 5.77.

The infrared absorption spectrum of this compound confirmed the presence of an hydroxyl group. It was soluble in sodium bicarbonate solution, and gave a slight orange coloration with ferric chloride. With diazotized sulfanilic acid there was produced, after acidification, a dark red solid.

α-Acetyl-α′-(3,4-dimethoxybenzylidene)-succinic Anhydride (VI).—To a solution of 6.8 g. (0.027 mole) of 3,4-dimethoxyphenylitaconic anhydride in 75 ml. of acetic anhydride was added eighteen drops of pyridine. The solution was refluxed for 40 minutes; a dark red color developed rapidly. Excess acetic anhydride was removed by evaporation (steam-cone). The residual mixture of crystals and black gum was triturated, first with ether, then with ethyl acetate; there was obtained 2.6 g. (33%) of yellow crystals. Recrystallization from ethyl acetate gave bright yellow needles, m.p. 189–191°.

Anal. Calcd. for $C_{15}H_{14}O_6$: C, 62.07; H, 4.86. Found: C, 62.18; H, 5.02.

A mixture of 9.9 g. (0.037 mole) of 3,4-dimethoxyphenylitaconic acid and 100 ml. of acetic anhydride was refluxed for ten minutes. Pyridine (ten drops) was added, and the refluxing was continued for one hour. The product was isolated in the manner described above; 3.1 g. (29%) of material was obtained.

Variations in experimental conditions did not increase the yield. The product was insoluble in sodium bicarbonate and sodium carbonate solutions, but dissolved slowly in 5% sodium hydroxide solution. Ultraviolet and infrared spectra were in agreement with the proposed formula, but no close analogs were available for comparison. Reaction with 2,4-dinitrophenylhydrazine in the usual way led to a high-melting orange solid which could not be purified.

In one experiment, using a larger amount of pyridine, a second yellow high-melting material was isolated. This product, m.p. 263–268°, was insoluble in hot ethyl acetate and was separated through treatment of the crude material with heated ethyl acetate. Recrystallization from methyl

ethyl ketone gave a yellow product, m.p. 264–266°; analysis (calcd. for $C_{15}H_{14}O_6$: C, 62.06; H, 4.86. Found: C, 62.10; H, 5.00) indicated that this material of unknown structure had the same composition as the usual product.

Ozonolysis of VI.—A solution of 0.30 g. of VI in 150 ml. of chloroform was treated with a stream of ozone for 30 minutes. The solution was stirred vigorously with 75 ml. of 5% sodium hydroxide solution containing 24 ml. of perhydrol (30%) for 15 minutes, and after separation of the chloroform the organic solution was washed with 5% sodium hydroxide solution, with dilute acetic acid, with 5% sodium bicarbonate solution, and with water. After drying and evaporation of the chloroform there was obtained 0.1 g. of veratraldehyde, identified through the 2,4-dinitrophenylhydrazone (m.p. 260–262°, undepressed on mixture with an authentic sample).

Reduction of VI.—When VI was subjected to catalytic reduction in acetic acid at 70° with a 5% palladium–carbon catalyst, sufficient hydrogen to reduce the olefinic linkage was absorbed. It was not possible to isolate crystalline material after the reduction; cyclization studies on the reduced material were inconclusive, and, while a reaction apparently occurred with 2,4-dinitrophenylhydrazine, the product could not be purified.

Hydrolysis and Cyclization of VI.—A suspension of 2.0 g. of VI in 30 ml. of 5% sodium hydroxide solution was heated (95–100°) for 20 minutes; the resulting clear solution was diluted and acidified strongly with concd. hydrochloric acid. After standing at room temperature for one hour, a small amount of gum was removed, and after further dilution to a total volume of 100 ml. the solution was allowed to stand for five days. The crystalline product was separated and recrystallized from aqueous ethanol to yield nearly colorless plates, m.p. 248–247° (with shrinking and discoloration), of material whose analysis and ultraviolet spectrum (Fig. 3) indicated that cyclization had occurred; the product was evidently **1-methyl-6,7-dimethoxy-3-naphthoic acid.**

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73; neut. equiv., 246.3. Found: C, 68.71; H, 5.87; neut. equiv., 246.

Acylation Experiments.—In attempts to define the scope of the acylation reaction leading to VI, reactions were carried out with the corresponding diester (obtained by complete esterification of I) rather than the diacid or anhydride, with benzylsuccinic anhydride, and with benzoic anhydride in place of acetic anhydride in the usual acylation. No products corresponding to VI could be found.

BETHESDA, MARYLAND

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Beckmann Rearrangements. Aldoximes

BY E. C. HORNING AND V. L. STROMBERG

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The Beckmann rearrangement has been extended to aldoximes through use of polyphosphoric acid as a reagent for the rearrangement. For the first time this permits a direct study of the configuration of an aldoxime through examination of the products of rearrangement. The present assignment of *syn* and *anti* structures to the two known benzaldoximes has been confirmed.

A few limited observations may be found in the older literature[1–3] on reactions involving the conversion of an aldoxime to an amide *via* a Beckmann rearrangement. In general, however, the usual conditions of Beckmann rearrangements result in partial or complete dehydration of aldoximes to give the corresponding nitriles, and as a result special or indirect methods have been employed where rearrangement is desired. N-Alkyl ethers[4,5] and acetyl derivatives[6] have been used in such studies.

We have recently found that polyphosphoric acid is an excellent agent for effecting Beckmann rearrangements of ketoximes,[7] and the study has now been extended to aldoximes. As an example of an aliphatic aldoxime, we investigated the rearrangement of *n*-heptaldoxime. Under the conditions described in the experimental section, a 92% yield of *n*-heptamide was obtained. This result is comparable to the yields obtained with ketoximes,[7] and it indicates that the Beckmann rearrangement is indeed a general reaction of both ketoximes and aldoximes.

Since the Beckmann rearrangement is stereospecific, the structure of the starting oxime may be determined from the structure of the product, provided that the configuration of the oxime is not affected during the reaction, or that both oximes can be isolated and are found to give different products. In the case of ketoximes, it is sometimes possible to isolate two stereochemically different oximes whose structure can be determined in this way. Some oximes, such as acetophenone oxime, are known to exist in only one form, and in these cases only one rearrangement product has been observed. Other ketoximes, including methyl *n*-propyl ketoxime, are apparently homogeneous, but give two amides on rearrangement, indicating that both forms of the oxime are present during rearrangement.

The assignment of configuration to aldoximes has of necessity been based upon indirect evidence. Hantzsch[8] first recognized the possibility of isomerism of aldoximes, and it has since become standard practice to treat the acetyl[6] or benzoyl[9] derivatives of aldoximes with alkali in order to determine the structure. The acylated *anti*-oxime yields a nitrile, while the *syn* compound does not react or regenerates the original oxime. The rearrangement of an aldoxime with polyphosphoric acid provides a means of studying aldoxime structures in a direct way, and we have therefore examined the best-known case of aldoxime isomerism, that of benzaldoxime,[10] with this method. When the *syn*-oxime (liquid) was treated with poly-

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