[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

The Synthesis of 1,2-Benzo-6-methylcyclohepta-1,5-diene-3-one[1]

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The synthesis of 1,2-benzo-6-methylcyclohepta-1,5-diene-3-one was effected by cyclization of the appropriately substituted phenylpentenoic acids. The acids were prepared by the modified Stobbe condensation of phenylacetone and diethyl or di-*t*-butyl succinate.

We have investigated the possibility of using the Stobbe condensation as the first reaction in a general method for the synthesis of analogs of benzocycloheptanone. In these model compound experiments phenylacetone was used as the carbonyl reagent.[3]

Under optimum conditions the condensation of diethyl or di-*t*-butyl succinate with phenylacetone using potassium *t*-butoxide as the catalyst[4] gave almost quantitative yields of 3-carbethoxy-4-methyl-5-phenyl-3-pentenoic acid (Ia) and 3-(carbo-*t*-butoxy)-4-methyl-5-phenyl-3-pentenoic acid (Ib), respectively. The proportion of the γ-lactone by-products (IIa, IIb) was increased if an excess of catalyst was used or if the reaction was quenched after a short time. Some ethyl 3-carbethoxy-4-methyl-5-phenyl-3-pentenoate (Ic) was isolated from one experiment that was allowed to run only a short time. This is of interest since it is apparently the first recorded case of the isolation of the unsaturated diester from the Stobbe condensation.[5] The significance of this finding with regard to the postulated mechanism[5] of the Stobbe condensation is not clear. The use of sodium hydride[6] as the catalyst was unsuccessful.

Saponification of either the ethyl or *t*-butyl half ester (Ia, Ib) gave 3-carboxy-4-methyl-5-phenyl-3-pentenoic acid (III). That this acid was a derivative of itaconic acid was indicated by the facile transformation into the cyclic anhydride (IV) on being treated with acetyl chloride[7] and by the melting point (178–179°) which falls in the range characteristic of itaconic acid derivatives prepared by this reaction.[8] Oxidative degradation using potassium permanganate or ozone gave a good yield of phenylacetone (isolated as the semicarbazone).

In one experiment, which could not be repeated, the attempted vacuum distillation of, what was apparently wet, 3-(carbo-*t*-butoxy)-4-methyl-5-phenyl-3-pentenoic acid (Ib) gave 3-carboxy-4-methyl-5-phenyl-4-pentenoic acid (V) (m.p. 138–140°). The melting point indicated tentatively that the compound was an alkylidenepyrotartaric acid derivative and this was confirmed by ozonolysis which gave a good yield of benzaldehyde (as the semicarbazone). The ultraviolet absorption spectra of the acids (III and V) are given in Fig. 1. Treatment of 3-carboxy-4-methyl-5-phenyl-4-pentenoic acid (V) with refluxing acetic acid–hydrochloric acid gave 3-carboxy-4-methyl-5-phenyl-3-pentenoic acid (III). The two acids form mixed crystals.

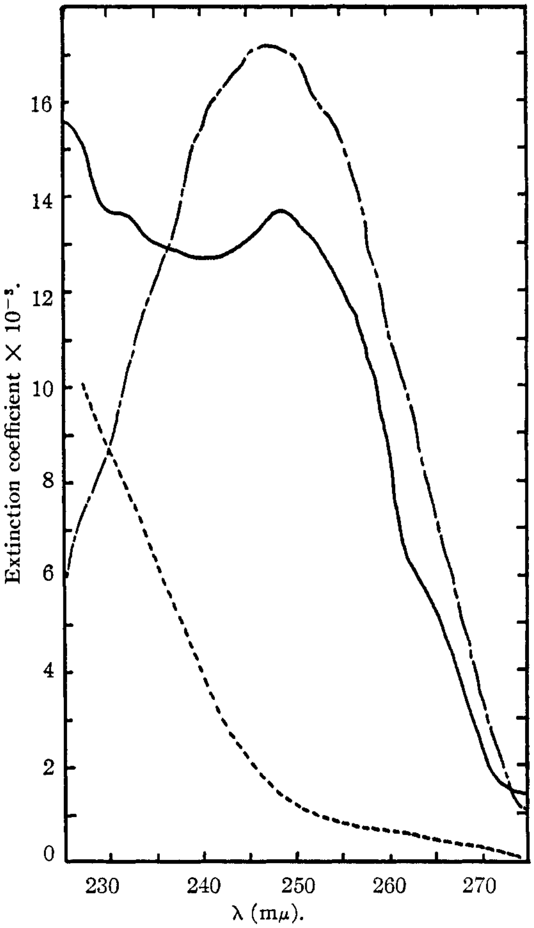

Fig. 1.——, 1,2-benzo-6-methylcyclohepta-1,5-diene-3-one (VII); - - - - - -, 3-carboxy-4-methyl-5-phenyl-3-pentenoic acid (III); -·—·-, 3-carboxy-4-methyl-5-phenyl-4-pentenoic acid (V).

Cyclization of 3-carbethoxy-4-methyl-5-phenyl-3-pentenoic acid (Ia) and 3-(carbo-*t*-butoxy)-4-methyl-5-phenyl-3-pentenoic acid (Ib) and the corresponding γ-lactones (IIa and b) to yield 1,2-benzo-5-carbethoxy-6-methylcyclohepta-1,5-diene-3-one (VIa) and 1,2-benzo-5-(carbo-*t*-butoxy)-6-methylcyclohepta-1,5-diene-3-one (VIb) was accomplished using zinc chloride, aluminum chloride and stannic chloride as catalysts. The yields obtained were not consistent but in general stannic chloride was the most satisfactory with the ethyl esters and zinc chloride was best with the *t*-butyl esters. Acid-

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(1) From the M. A. thesis of G. R. Allen, Jr., The University of Texas, 1951.

(2) Parke, Davis and Co., Detroit 32, Michigan.

(3) In a private communication, Dr. C. D. Gutsche has informed us that he has carried out a similar series of reactions starting with phenylcyclohexanone.

(4) W. S. Johnson, A. Goldman and W. P. Schneider, THIS JOURNAL, **67**, 1357 (1945).

(5) W. S. Johnson and M. W. Miller, *ibid.*, **72**, 511 (1950); W. S. Johnson, D. A. Dunnigan and A. L. McCloskey, *ibid.*, **72**, 514 (1950).

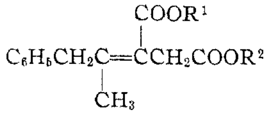
(6) G. H. Daub and W. S. Johnson, *ibid.*, **72**, 502 (1950).

(7) W. S. Johnson, G. E. Davis, R. H. Hunt and G. Stork, *ibid.*, **70**, 3021 (1948).

(8) H. Stobbe, *Ann.*, **308**, 67 (1899).

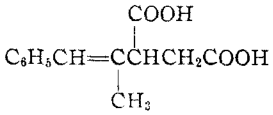
catalyzed hydrolysis and decarboxylation of the carbethoxy ketone (VIa) gave 1,2-benzo-6-methylcyclohepta-1,5-diene-3-one (VII).

Acid-catalyzed hydrolysis and decarboxylation of 3-carbethoxy-4-methyl-5-phenyl-3-pentenoic acid (Ia) yielded 4-methyl-5-phenyl-3-pentenoic acid (VIII) which on cyclization gave 1,2-benzo-6-methylcyclohepta-1,5-diene-3-one (VII) identical with that prepared by the previously described method. (See Fig. 1 for spectrum.)



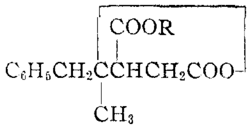
$C_6H_5CH_2\underset{CH_3}{C}{=}\overset{COOR^1}{C}CH_2COOR^2$

Ia, $R^1 = C_2H_5$, $R^2 = H$
Ib, $R^1 = C(CH_3)_3$, $R^2 = H$
Ic, $R^1 = R^2 = C_2H_5$
III, $R^1 = R^2 = H$



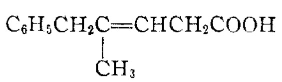
$C_6H_5CH{=}\underset{CH_3}{C}\overset{COOH}{C}HCH_2COOH$

V



$C_6H_5CH_2\underset{CH_3}{C}\overset{COOR}{C}HCH_2COO$

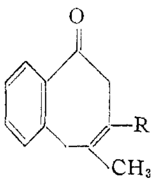
IIa, $R = C_2H_5$
IIb, $R = C(CH_3)_3$



$C_6H_5CH_2\underset{CH_3}{C}{=}CHCH_2COOH$

VIII

VI, $R = COOC_2H_5$
VIb, $R = COOC(CH_3)_3$ →
VII, $R = H$



Experimental

3-Carbethoxy-4-methyl-5-phenyl-3-pentenoic Acid (Ia).—Under an atmosphere of dry nitrogen, a cooled, rigorously anhydrous, stirred solution of 2.3 g. of potassium in 50 ml. of *t*-butyl alcohol was treated with a mixture of 15.3 g. of diethyl succinate[9] (b.p. 216–217° at 745 mm.) and 7.6 g. of phenylacetone (b.p. 213.5–214° at 750 mm.). The orange solution was allowed to reflux for six hours. The cooled solution was hydrolyzed with 10 ml. of hydrochloric acid and 50 ml. of water and the layers were separated. The aqueous layer was extracted with ether and the combined organic portion was extracted several times with saturated sodium bicarbonate solution. Acidification of the basic wash gave 14.8 g. (the yields ranged from 85–99%) of the half ester (Ia) as a light orange oil which decolorized aqueous potassium permanganate. Distillation at 140–144° (7–8 mm.) yielded the half ester as a light yellow oil; $n^{20}D$ 1.5189.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.7; H, 6.9; neut. equiv., 262. Found: C, 68.9; H, 6.7; neut. equiv., 259.

In experiments which gave a low yield of half ester, the neutral organic layer was concentrated and washed with 10% aqueous sodium hydroxide. The basic extract was neutralized and extracted with ether. Evaporation of the solvent left a brown solid which was triturated several times with benzene. By recrystallization of the benzene soluble material from 90–100° petroleum ether, there was obtained a 7–10% yield of the **lactone of 3-carbethoxy-4-hydroxy-4-methyl-5-phenyl-pentanoic acid (IIa)** as white plates; m.p. 88–90°.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.7; H, 6.92; neut. equiv., 262. Found: C, 68.6; H, 6.75; neut. equiv., 256.

In one run which was hydrolyzed after refluxing for 45 minutes, the yield of half ester (Ia) was 23% and the neutral extract was distilled to recover the unreacted starting materials. The residue from the distillation was triturated with several small portions of benzene and gave a 2% yield of **ethyl 3-carbethoxy-4-methyl-5-phenyl-3-pentenoate (Ic)** as white crystals; m.p. 148–150°.

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.4; H, 7.6; sapn. no., 347. Found: C, 70.8; H, 7.6; sapn. no., 350.

3-(Carbo-*t*-butoxy)-4-methyl-5-phenyl-3-pentenoic Acid (Ib).—In a manner similar to the above experiments an 85–98% yield of the half ester (Ib) was obtained as white crystals; m.p. 88–90° after washing with 90–100° petroleum ether. A typical preparation used 2.15 g. of potassium, 40 ml. of *t*-butyl alcohol, 3.35 g. of phenylacetone and 18.30 g. of di-*t*-butyl succinate[6] and was refluxed for six hours.

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.4; H, 7.59; neut. equiv., 290. Found: C, 70.4; H, 7.84; neut. equiv., 291.

Increasing the amount of potassium to 2.40 g. and decreasing the amount of di-*t*-butyl succinate to 13.3 g. gave a 70% yield of half ester (Ib) and a 23% yield of the γ-**lactone of 3-(carbo-*t*-butoxy)-4-hydroxy-4-methyl-5-phenylpentanoic acid (IIb)**. The lactone was filtered from the hydrolysis mixture as fine, white needles; m.p. 159–161°.

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.4; H, 7.59; neut. equiv., 290. Found: C, 70.3; H, 7.48; neut. equiv., 286.

In one experiment, which could not be duplicated, an attempt was made to distil (bath temperature 175°, and 10 mm.) 6.5 g. of, apparently wet, crude half ester (Ib). White fumes were evolved and the distillation was discontinued. After washing a 1.0-g. sample of the residue (total residue 6.0 g.) with several portions of cold benzene, there was obtained 0.78 g. of an acidic compound which was later, *vide infra*, shown to be **3-carboxy-4-methyl-5-phenyl-4-pentenoic acid** (V); m.p. 138–140° after crystallization from benzene.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.7; H, 5.98; neut. equiv., 117. Found: C, 66.5; H, 5.80; neut. equiv., 117.

Attempted acid-catalyzed decarboxylation of 1.0 g. of this acid following the method described later yielded 0.8 g. of 3-carboxy-4-methyl-5-phenyl-3-pentenoic acid (III); m.p. 178–180° alone and when mixed with an authentic sample.

3-Carboxy-4-methyl-5-phenyl-3-pentenoic Acid (III).—A mixture of 2.0 g. of 3-carbethoxy-4-methyl-5-phenyl-3-pentenoic acid (Ia) and 20 ml. of 50% potassium hydroxide solution was refluxed for four hours. The mixture was neutralized and extracted with ether. The ether solution was extracted with 10% sodium bicarbonate solution from which there was obtained, after crystallization from benzene, 1.4 g. (78% yield) of 3-carboxy-4-methyl-5-phenyl-3-pentenoic acid (III) as white crystals; m.p. 178–180°.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.7; H, 5.98; neut. equiv., 117. Found: C, 66.8; H, 6.00; neut. equiv., 117.

Various mixtures of this acid with 3-carboxy-4-methyl-5-phenyl-4-pentenoic acid (V) gave melting ranges such as 151–160° and 148–155°.

Hydrolysis of 3-(carbo-*t*-butoxy)-4-methyl-5-phenyl-3-pentenoic acid gave acid III, identical with that obtained above, in about 60% yield.

Ozonolysis of 3-Carboxy-4-methyl-5-phenyl-3-pentenoic Acid.—A cold solution of 0.34 g. of (III) in 40 ml. of 75% ethyl bromide–25% methyl alcohol was treated with an ozone–oxygen mixture for 45 minutes and then zinc dust was added. After being filtered, the solution was concentrated and yielded 0.21 g. (76%) of the semicarbazone of phenylacetone; m.p. 187–190° after crystallization from dilute methyl alcohol. Admixture with a known sample gave no depression of the melting point. The same product (60% yield) was obtained by adding 30 ml. of 1% potassium permanganate to a 1% sodium carbonate solution of 0.2 g. of the acid.

Ozonolysis of 3-Carboxy-4-methyl-5-phenyl-4-pentenoic Acid.—Using the procedure described previously, there was obtained a 48% yield of the semicarbazone of benzaldehyde; m.p. 220–222°, from 0.30 g. of unsaturated acid (V). There was no depression of the melting point when mixed with known material.

3-Carboxy-4-methyl-5-phenyl-3-pentenoic Anhydride (IV).—A mixture of 0.40 g. of 3-carboxy-4-methyl-5-phenyl-3-pentenoic acid (III) and 16 ml. of acetyl chloride was refluxed for three hours and then concentrated *in vacuo*. The oily residue crystallized slowly and yielded 0.25 g. (68%) of (IV); m.p. 100–105° after crystallization from carbon bisulfide. An additional crystallization from carbon bisulfide using Darco G-60 gave white crystals; m.p. 101–102°.

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 72.2; H, 5.59. Found: C, 72.0; H, 5.29.

4-Methyl-5-phenyl-3-pentenoic Acid (VIII).—A solution of 10.0 g. of 3-carbethoxy-4-methyl-5-phenyl-3-pentenoic

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[9] E. Fischer and A. Speier, *Ber.*, **28**, 3255 (1895).

acid in 24 ml. of 48% hydrobromic acid, 12 ml. of glacial acetic acid and 6 ml. of water was refluxed for 22 hours. The cool solution was extracted with ether and the ether layer was washed several times with water. The ether extract was then washed with several portions of aqueous sodium bicarbonate. The mixture of acids obtained by extracting the neutralized bicarbonate layer was crystallized from benzene; the first crop consisted of 1.00 g. of 3-carboxy-4-methyl-5-phenyl-3-pentenoic acid (III) and the combined residues afforded 3.45 g. of 4-methyl-5-phenyl-3-pentenoic acid (VIII) as a viscous oil. Evaporative distillation at 137–138° and 0.15 mm. gave a colorless viscous oil; n^{20}_{D} 1.5430.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.9; H, 7.42; neut. equiv., 190. Found: C, 75.7; H, 7.49; neut. equiv., 189.

1,2-Benzo-5-(carbo-*t*-butoxy)-6-methylcyclohepta-1,5-diene-3-one (VIb).—Under anhydrous conditions a mixture of 0.50 g. of crude 3-(carbo-*t*-butoxy)-4-methyl-5-phenyl-3-pentenoic acid (Ib), 10 ml. of acetic anhydride and 5 ml. of a stock solution containing 5 mg. of freshly fused zinc chloride per ml. of glacial acetic acid was refluxed for six hours. The cooled solution was extracted with ether and the ether solution was washed with 10% sodium bicarbonate solution and then 10% sodium hydroxide solution. The neutral residue from the ether extract was treated with 1.0 g. of semicarbazide hydrochloride, 10 ml. of absolute alcohol and 1 ml. of dry pyridine to yield 0.43 g. (75%)[10] of the **semicarbazone** of (VIb). After crystallization from dilute ethyl alcohol the melting point was 130–132°.

Anal. Calcd. for $C_{18}H_{23}O_3N_3$: C, 65.6; H, 6.99; N, 12.75. Found: C, 65.5; H, 7.01; N, 12.84.

Using a similar procedure 0.40 g. of the lactone 3-(carbo-*t*-butoxy)-4-hydroxy-4-methyl-5-phenyl-3-pentenoic acid (IIb) yielded 0.40 g. (89%) yield[10] of the semicarbazone of VIb; m.p. 130–132°. A mixture melting point determination showed no depression.

1,2-Benzo-5-carbethoxy-6-methylcyclohepta-1,5-diene-3-one (VIa).—To 13.13 g. of 3-carbethoxy-4-methyl-5-phenyl-3-pentenoic acid (Ia) was added 50 ml. of dry ether, 0.5 ml. of dry pyridine and 5.5 ml. of thionyl chloride and the solution was allowed to reflux for four hours. The ether and excess thionyl chloride were removed under reduced pressure; benzene was added and similarly removed. The crude acid chloride was dissolved in 50 ml. of carbon bisulfide and treated with 10 ml. of anhydrous stannic chloride. A red complex formed immediately. After standing one hour at 25° the mixture was hydrolyzed in 50 ml. of hydrochloric acid. The aqueous layer was washed with carbon bisulfide and the combined extract was washed with sodium bicarbonate solution and 10% sodium hydroxide solution. The residue from the carbon bisulfide layer was distilled in a two-bulb flask at 200–210° (oil-bath temperature) and 5–9 mm. to yield the ketone (VIa) as fine yellow needles which weighed 2.00 g. after crystallization from methyl alcohol; m.p. 159–160.5°.

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.8; H, 6.56. Found: C, 73.7; H, 6.62.

The residue from the distillation was treated with semicarbazide hydrochloride in pyridine–ethyl alcohol and gave 3.50 g. (total yield as ketone and semicarbazone, 31%) of the **semicarbazone** of 1,2-benzo-5-carbethoxy-6-methylcyclohepta-1,5-diene-3-one; m.p. 250–251.5° dec. (introduced in bath at 248°).

Anal. Calcd. for $C_{16}H_{19}O_3N_3$: C, 63.7; H, 6.32; N, 13.95. Found: C, 64.1; H, 6.54; N, 14.04.

1,2-Benzo-6-methylcyclohepta-1,5-diene-3-one (VII). **Method A, Decarboxylation of VIa.**—A mixture of 2.16 g. of 1,2-benzo-5-carbethoxy-6-methylcyclohepta-1,5-diene-3-one (VIa), 12 ml. of 48% hydrobromic acid, 8 ml. of glacial acetic acid and 4 ml. of water was refluxed for eight hours. The reaction mixture was washed with water and 10% sodium hydroxide solution. The residue from the ether layer was evaporatively distilled at 104–105° (0.03 mm.) as the slightly yellow ketone VII; m.p. 41–42.5°, 1.20 g. (79% yield). An analytical sample was prepared by a second evaporative distillation; m.p. 40.5–41.5°.

Anal. Calcd. for $C_{12}H_{12}O$: C, 83.7; H, 7.05. Found: C, 83.8; H, 7.02.

The semicarbazone as prepared by the previously described method was obtained as fine, white needles; m.p. 193.5–195°.

Anal. Calcd. for $C_{13}H_{15}ON_3$: C, 68.2; H, 6.60; N, 18.35. Found: C, 68.5; H, 6.81; N, 18.40.

Method B. Cyclization of 4-Methyl-5-phenyl-3-pentenoic Acid.—To 0.87 g. of 4-methyl-5-phenyl-3-pentenoic acid (VIII) was added 20 ml. of anhydrous ether, 3 drops of pyridine and 1 ml. of thionyl chloride and the mixture was refluxed for 2.5 hours. After the solvent and excess reagents had been removed under reduced pressure, the crude acid chloride was dissolved in 20 ml. of carbon bisulfide and cooled in an ice-bath. The addition of 1.0 ml. of anhydrous stannic chloride and 2 ml. of carbon bisulfide caused the immediate precipitation of an orange complex. After standing at 0° for 15 minutes the mixture was allowed to stand at 25° for 1.5 hours. Hydrolysis was accomplished with 30 ml. of hydrochloric acid in 20 ml. of water. The ketone VII was isolated as in the previous synthesis and after evaporative distillation at 0.05 mm. and 110° was obtained as yellow crystals; yield 0.51 g. (64%). A second evaporative distillation yielded 1,2-benzo-6-methylcyclohepta-1,5-diene-3-one (VII) as colorless crystals; 40.5–42.0°. A mixture melting point with a sample from Method A gave m.p. 40–41°. The semicarbazone melted at 191–193°. Admixture with a sample from Method A gave no depression of the melting point.

Ultraviolet Absorption Spectra.—The ultraviolet adsorption spectra (see Fig. 1) were measured with a Beckman, Model DU spectrophotometer using quartz cells and a hydrogen discharge lamp. Absolute ether was used as the solvent.

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(10) The yields obtained in these cyclizations varied irregularly from practically nothing to those given above. The results could not be correlated with the purity of the starting materials. Attempts to obtain more consistent yields *via* the acid chloride and cyclization by means of aluminum chloride gave no ketone. The only apparent reaction was a small amount of lactonization.