

hexanone, 140.2. The procedure was repeated with hydroxymethylencyclohexanone, ethanol and ethyl orthoformate. A 70% yield of ethoxymethylencyclohexanone, b.p. 95-96° at 2.0-2.5 mm., n_D^{25} 1.4940, was obtained. Equivalent weights found were 161.3 and 160.8; calcd. for ethoxymethylencyclohexanone, 154.2.

Attempted fractional distillation of ethoxymethylencyclohexanone gave much resinification and no well-defined fractions.^{12a} It was observed that both methoxymethylencyclohexanone and ethoxymethylencyclohexanone slowly

became very viscous on standing, the latter much faster than the former.

Procedure for Equivalent Weight Determinations.—A weighed sample of the β -ketodimethylacetal or the alkoxy-methylene ketone was refluxed for 0.5-2 hours with excess standard 0.1 *N* sodium hydroxide and back-titrated to phenolphthalein with 0.1 *N* hydrochloric acid. The equivalent weight is then equal to the sample weight in g. \times 1000 meq. of base used.

EMORY UNIVERSITY, GEORGIA

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

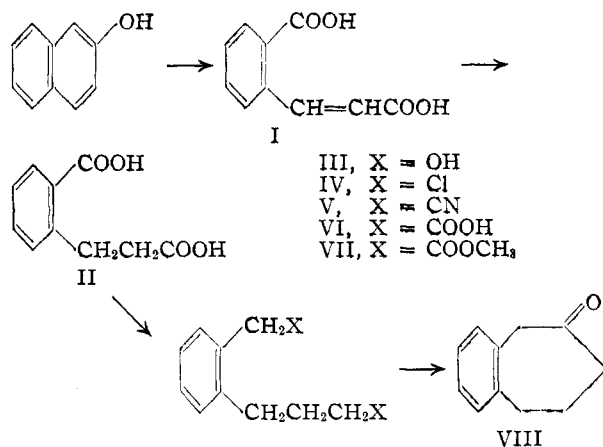
The Synthesis of Benzcyclohepten-6-one¹

BY G. A. PAGE AND D. S. TARBELL

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The preparation of benzcyclohepten-6-one, a compound of use for syntheses in the general field of colchicine chemistry, is described.

A benzcyclohepten-6-one was required as an intermediate compound for use in studies aimed at the synthesis of the three carbon ring system of colchicine. Although the preparation of 2,3,4-trimethoxybenzcyclohepten-6-one has been described,² the synthetic route to the parent ketone (VIII), outlined below, appeared worthy of investigation.



o-Carboxycinnamic acid (I), prepared by the oxidation of β -naphthol using peracetic acid,³ was reduced by means of the Schwenk procedure⁴ to give β -(*o*-carboxyphenyl)-propionic acid (II) in excellent yield. Reduction of II using ethereal lithium aluminum hydride gave the expected diol (III),⁵ which was obtained pure in relatively low yield. Conversion of the diol to the corresponding dichloride (IV) went smoothly and a satisfactory yield of this compound was obtained from II when the crude diol was treated directly with thionyl chloride in dimethylaniline.⁶ Cyanation of IV,

using procedures in the literature,^{2,7} and modifications thereof, failed to give a pure compound upon fractional distillation. No attempt was made to cyclize this crude dinitrile (V), although our original intention was to effect ring closure at this stage using an established procedure.⁸

Hydrolysis of crude V gave a fair yield of γ -(*o*-carboxymethylphenyl)-butyric acid (VI). Using the Arndt-Eistert procedure as adapted to bis-homologation,⁹ an attempt to convert the acid chloride of II to the required acid (VI) resulted in a very low yield of product. Although this method was not considered suitable here for the large-scale preparation of VI, it is felt that considerable improvement of the Arndt-Eistert procedure is possible and would provide a short-path route to the ketone (VIII).

The dimethyl ester (VII) of γ -(*o*-carboxymethylphenyl)-butyric acid was cyclized by means of a Dieckmann-type ring closure¹⁰ and the resultant crude β -ketoester(s) saponified and decarboxylated to give benzcyclohepten-6-one (VIII) in moderately good yield.

Experimental¹¹

Oxidation of β -Naphthol; Formation of I.—The procedure used was essentially that reported in the literature.³ However, the use of a 10% excess of the peracetic acid¹² resulted in slightly higher and more consistent yields of *o*-carboxycinnamic acid, over a period of 4 to 5 days, than when the theoretical 3.0 molecular proportion of oxidant was employed. Starting from 10 g. or 20 g. of β -naphthol, the yield of crude I was 73-75%. After purification by solution in 5% bicarbonate solution and subsequent acidification with mineral acid, the yield of *o*-carboxycinnamic acid, m.p. 205°, n_D^{25} 1.33 was 67-70%.

A small portion of the acid was crystallized from aqueous alcohol to give small, white, felted prisms, m.p. 205°, having the correct neutralization equivalent.

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(8) E. M. Fry and L. F. Fieser, *THIS JOURNAL*, **62**, 3489 (1940).

(9) W. E. Bachmann and W. S. Struve, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 45, 51.

(10) R. E. Beyler and L. H. Sarett, *THIS JOURNAL*, **74**, 1397 (1952).

(11) All melting points are corrected; microanalyses by Miss Claire King and Miss Viola Williams.

(12) Commercial 40% peracetic acid is available from the Becco Sales Corporation, Buffalo 7, N. Y.

(13) After melting, the acid solidifies and remelts at 150-151° due to formation of phthalideacetic acid, m.p. 153°.

(1) This work was supported by a grant from the National Institutes of Health.

(2) H. Rapoport and J. E. Campion, *THIS JOURNAL*, **73**, 2289 (1951).

(3) J. Boeseken and Lochmann von Königsfeldt, *Rec. trav. chim.*, **54**, 318 (1935); F. P. Greenspan, *Ind. Eng. Chem.*, **39**, 847 (1947).

(4) E. Schwenk, *et al.*, *J. Biol. Chem.*, **118**, 792 (1937); *J. Org. Chem.*, **7**, 587 (1942); **9**, 1, 175 (1944).

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(6) A. Cohen, *J. Chem. Soc.*, 429 (1935).

β -(*o*-Carboxyphenyl)-propionic Acid (II).—Using the general procedure reported,⁴ 20-g. batches of the cinnamic acid dissolved in 60 ml. of 10% sodium hydroxide solution were reduced by the gradual addition of 60 g. of nickel-aluminum alloy powder, at 90°. The product obtained upon acidifying the alkaline filtrate amounted to 18.6–19.2 g. Extraction of the mother liquor with ether and working up in the usual manner gave an additional 0.3–0.4 g. of the same product, m.p. 165.5–167°. The total yield of II was 19.0–19.5 g. (94–96.5%); this was recrystallized from 380–400 ml. of hot water to give the pure acid, m.p. 166.5–167.5°,¹⁴ possessing the required value for the neutralization equivalent.

γ -(*o*-Hydroxymethylphenyl)-propyl Alcohol (III).—An ethereal solution of lithium aluminum hydride (430 ml., 0.7 molar) and 200 ml. of anhydrous ether were placed in a 1-l. round-bottomed flask fitted with a soxhlet extractor. Then 19.4 g. (0.10 mole) of the acid (II) was placed in the extraction thimble and the apparatus fitted with a guard-tube (drierite). After refluxing for 15 hours, all of the acid had been transferred to the reaction mixture. After cooling, the excess reducing agent was destroyed by the addition of ethyl acetate and a small amount of water. The white suspension was then dissolved by the addition of ice-cold 10% sulfuric acid, with agitation. After separation, the aqueous layer was extracted twice with ether and the combined ethereal solutions washed in turn with 5% bicarbonate solution and water, followed by drying and removal of solvent. No acidic material was recovered from the bicarbonate washings upon acidification.

The residual oil was fractionally distilled, giving the alcohol (III), b.p. 155–160° at 2.0 mm., as a turbid, faintly yellow oil (12.6 g.). The turbidity was attributed to the presence of water.⁵ Redistillation of the main fraction (12.6 g.) gave finally the pure compound, b.p. 146–147.5° at 0.9 mm. (8.28 g., 49.8%). A considerable amount of higher-boiling material remained in the still-pot.

A small portion of the alcohol was purified further by redistillation in a short-path still. A sample thus obtained was a colorless, viscous oil, n_D^{20} 1.5500, n_D^{25} 1.5485, n_D^{30} 1.5469. The analytical data obtained were poor and possibly indicated that the material was still contaminated with water.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.75; H, 8.25.

The bis-*p*-nitrobenzoate was pale yellow, m.p. 138.5°, after four crystallizations from amyl alcohol.

Anal. Calcd. for $C_{22}H_{20}N_2O_6$: C, 62.06; H, 4.34; N, 6.03. Found: C, 61.93; H, 4.50; N, 5.92.

The bis- α -naphthylurethane was obtained as white, felted prisms, m.p. 150.5–151°, after several crystallizations from ethyl acetate.

Anal. Calcd. for $C_{32}H_{28}N_2O_4$: C, 76.17; H, 5.59; N, 5.55. Found: C, 76.18; H, 5.74; N, 5.88.

γ -(*o*-Chloromethylphenyl)-propyl Chloride (IV).—The crude diol obtained by reducing 110 g. (0.566 mole) of II with 60 g. of lithium aluminum hydride in 3 l. of ether, was dissolved in 300 ml. of dry chloroform and mixed with 253 g. of dimethylaniline. With rapid stirring under anhydrous conditions at 0–5° (ice-water-bath), pure thionyl chloride (250 g.) in 300 ml. of chloroform was added dropwise during 90 minutes. The mixture was stirred for an additional hour at low temperature, followed by heating on a steam-bath for 3 hours. After cooling, the dark-colored solution was poured, with stirring, into 1500 ml. of cold 2.0 *N* hydrochloric acid. The organic phase was separated, washed until neutral, and dried. After removal of chloroform, the residue was fractionally distilled to give pure IV, b.p. 95–96° at 0.5 mm. (87.3 g., 75% over-all from II). Other yields noted were 72–76%.

After redistillation, the dichloride was analytically pure, n_D^{20} 1.5497, n_D^{25} 1.5484, n_D^{30} 1.5472.

Anal. Calcd. for $C_{10}H_{12}Cl_2$: C, 59.13; H, 5.96. Found: C, 58.92; H, 5.96.

(b).—The crude diol obtained by reducing 110 g. (0.566 mole) of II with 60 g. of lithium aluminum hydride in 3 l. of ether (3 days) was dissolved in 300 ml. of chloroform and mixed with 253 g. of dimethylaniline. After cooling to

0–5°, 250 g. of thionyl chloride in 300 ml. of chloroform was added dropwise, with stirring, during 90 minutes. After refluxing for 3 hours, the mixture was worked up as described previously. The main fraction from the distillation, b.p. 95–96° at 0.5 mm. (101–102° at 1.0 mm., 114–115° at 1.8 mm.) amounted to 87.3 g. (75% over-all yield from II), n_D^{20} 1.5487. Over-all yields of the chloride obtained in subsequent runs varied between 72–76%.

γ -(*o*-Cyanomethylphenyl)-butyronitrile (V).—A solution of 85.9 g. (0.423 mole) of IV in 200 ml. of benzene was added to 130 g. (2.0 mole) of potassium cyanide dissolved in 400 ml. of water. With rapid stirring at the interface, the two phases were refluxed vigorously for five hours. The cooled benzene layer was separated, washed with water, and the benzene distilled, leaving an oily residue which was taken up in 750 ml. of ethanol and mixed with 65 g. (1.0 mole) of potassium cyanide and 3.32 g. (0.02 mole) of potassium iodide dissolved in 250 ml. of water. This mixture was refluxed for 45 hours, with addition of 200 ml. of water after 15 hours to dissolve separated inorganic salts. Finally, after adding 500 ml. of water, most of the alcohol was removed under reduced pressure. The cooled residue was made slightly acid (to litmus) and extracted thoroughly with benzene. After washing with bicarbonate solution and water, the benzene was distilled to give the crude nitrile, 69 g. (88%). Yields encountered in other runs were 83–94% (crude).

The pure compound (V) was not obtained after repeated fractional distillation; some decomposition occurred during the first distillation.

γ -(*o*-Carboxymethylphenyl)-butyric Acid (VI) (a).—The crude nitrile (69 g.) was dissolved in 800 ml. of ethanol and mixed with a solution of 140 g. of potassium hydroxide in 200 ml. of water. After refluxing for 72 hours (evolution of ammonia), 150 ml. of water was added and ethanol removed by distillation. After shaking with ether, the cooled alkaline solution was acidified using a moderate excess of hydrochloric acid with vigorous stirring. The flocculent precipitate which separated was filtered by suction and washed on the filter with a small amount of cold benzene to remove brown oil. The filtrate was extracted with benzene and finally gave more solid material after working up in the usual manner. The combined solid (75.1 g.) was stirred mechanically for 2 hours with an excess of 5% sodium bicarbonate solution. Insoluble material (essentially silica) was removed by filtration and the hot filtrate treated with charcoal (Norit) prior to acidification with hydrochloric acid. The crystalline product was obtained by filtration and combined with an additional amount recovered from the filtrate by extraction with ether. After two recrystallizations from benzene, the pure acid (VI), m.p. 110.5–111.5°, weighed 64.1 g. (68% based on IV). Other yields observed were 65 and 70%. After crystallizing twice from benzene and once from water, the acid melted at 111–111.5°.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 64.85; H, 6.35; neut. equiv., 111.1. Found: C, 65.14; H, 6.58; neut. equiv., 112.8, 113.0.

(b).—A solution of the acid chloride of II in benzene, prepared from 3.88 g. (0.02 mole) of II and 15 g. of thionyl chloride in benzene containing two drops of pyridine, and after removal of excess reagents, was added dropwise to ethereal diazomethane (from 20 g. of nitrosomethylurea) with stirring and temperature control at 0–5°. After standing at room temperature for a day, the yellow solution was concentrated under reduced pressure. The residual oil failed to crystallize and was taken up in 60 ml. of warm dioxane, to which an aqueous mixture of ammonia (50 ml., sp. gr. 0.89) and silver nitrate (10 ml. of 10% solution) was added with caution. When the initial effervescence subsided, the mixture was held at 60–70° overnight, followed by filtration and concentration of the filtrate under reduced pressure. After dilution with water, the dark mixture was extracted with benzene and the organic solution passed through a short column of alumina to remove colloidal silver. Removal of the solvent gave an oil which failed to crystallize. After hydrolysis by heating with excess aqueous alcoholic potassium hydroxide for 20 hours, acidic material was recovered in the usual manner. It was separated (from benzene solution) on silica gel into two identifiable components: (a) m.p. 109–111° (from water), 0.46 g. (10%) of VI (no depression of m.p. on admixture with authentic

(14) Reported m.p. 168–168.5°; W. S. Johnson and W. E. Shelberg, *THIS JOURNAL*, **67**, 1754 (1945).

VI), and (b) m.p. 137–138° (from water), neut. equiv., 105.4 (0.06 g.). Fraction (b) was almost certainly γ -(*o*-carboxyphenyl)-butyric acid,¹⁵ (reported m.p. 138–139°).

Dimethyl Ester (VII) (a).—A solution of 30 g. (0.135 mole) of VI in 500 ml. of anhydrous methanol containing 20 ml. of concentrated sulfuric acid was refluxed for 30 hours. Working up in the customary manner gave, finally, the pure dimethyl ester, b.p. 112.5–113° at 0.08 mm., n_D^{25} 1.5046 (30.11 g., 89%). Acidic oil (recovered from bicarbonate washings) crystallized only after saponification with aqueous alkali and yielded 0.54 g. of pure VI after crystallizing from benzene, m.p. and mixed m.p. 110–111°.

Yields observed in other experiments were 89 and 90% (slightly higher if allowing for recovered VI).

Redistillation of the ester gave a pure sample with n_D^{20} 1.5065, n_D^{25} 1.5044, n_D^{30} 1.5025.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25; sapn. equiv., 125.1. Found: C, 67.25; H, 7.41; sapn. equiv., 127.2, 127.9.

(b).—A suspension of 6.66 g. (0.03 mole) of VI in 50 ml. of cold methanol was treated with an excess of ethereal diazomethane (from 12 g. of nitrosomethylurea). The reaction mixture was handled in the usual manner to give 6.92 g. (92%) of the ester, b.p. 115–116° at 0.09 mm., n_D^{25} 1.5044, after fractional distillation. No acidic material was found in the reaction product.

Benzcyclohepten-6-one (VIII).—A mixture of 9.83 g. (0.039 mole) of the ester (VII), 1.92 g. (0.08 mole) of sodium hydride¹⁰ (small pellets) and 200 ml. of dry ether was stirred and refluxed under nitrogen for 2 days. After about 30 hours, a dense white precipitate was thrown out of the previously opalescent mixture. (In repeated experiments, precipitate appeared after periods of up to 45 hours; refluxing was continued for at least 12 hours after the precipitation.)

After cooling, the suspension was dissolved by the dropwise addition of aqueous acetic acid (15 ml. of acid and 20 ml. of water) with vigorous stirring. The organic phase was separated and the aqueous portion extracted thoroughly with fresh ether. The combined ether solutions were washed in turn with several portions (50 ml. each) of ice-cold 5% potassium hydroxide solution, and the individual alkaline extracts acidified immediately by running into separate portions of ice-cold 2.0 *N* hydrochloric acid. The alkaline extraction procedure was continued until no turbidity was observed upon acidification of the individual extracts (about six extractions required). The combined acidified extracts were shaken with several portions of ether and the combined solutions washed with 5% bicarbonate solution to remove acidic material (recovered finally as 0.27 g. of saponified ester, *viz.*, VI, m.p. and mixed m.p. 110–111°).

After washing with water, the main ether solution was dried and distilled, giving 7.21 g. (84%) of crude β -ketoester(s) as a pale yellow viscous oil.

In one such run, a portion of the product was fraction-

ally distilled twice to give the pure β -ketoester(s), b.p. 91–91.5° at 0.09 mm., n_D^{25} 1.5686. On standing, the pure material solidified and was crystallized twice from pentane, m.p. 55.5–56.5°. It gave an immediate violet coloration with alcoholic ferric chloride.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.35; H, 6.27.

The crude β -ketoester(s) (7.21 g.) was dissolved in a mixture of acetic acid (300 ml.), concentrated hydrochloric acid (150 ml.) and water (75 ml.) and the solution heated under reflux for five hours. Evolution of carbon dioxide was observed during the first 50 minutes. Most of the solvent was removed under reduced pressure and the residue made alkaline by adding a slight excess of saturated bicarbonate solution.

After making the mixture slightly acid to litmus, it was extracted with three portions of ether and the combined ether solutions washed in turn with 5% bicarbonate solution and water. After drying, distillation in a short-path still gave 3.46 g. (55%) of colorless mobile oil, n_D^{25} 1.5550, and 0.51 g. (8%) of pale yellow oil, n_D^{25} 1.5553. This latter fraction was converted to the oxime, m.p. 108–109°, which was mixed with an excess of oxalic acid and the mixture subjected to steam distillation. Volatile oil was recovered from the distillate by ether extraction and was distilled in a short-path still (block temperature 55° at 0.06 mm.) to give the pure ketone (VIII), with n_D^{20} 1.5570, n_D^{25} 1.5551, n_D^{30} 1.5530.

Anal. Calcd. for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.49; H, 7.78.

The oxime was obtained as white prisms, m.p. 108.5–109.5°, from aqueous methanol.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.39; H, 7.76; N, 7.90.

The semicarbazone crystallized from benzene as white, felted prisms, m.p. 177.5–178°.

Anal. Calcd. for $C_{12}H_{15}N_3O$: C, 66.33; H, 6.96; N, 19.34. Found: C, 66.08; H, 7.20; N, 19.52.

The 2,4-dinitrophenylhydrazone (orange needles) crystallized from methanol, m.p. 169–170°.

Anal. Calcd. for $C_{17}H_{16}N_4O_4$: C, 59.99; H, 4.74; N, 16.46. Found: C, 59.98; H, 4.93; N, 16.27.

The ketone turned yellow upon keeping in a sealed tube (air present). A solution of VIII in cold concentrated sulfuric acid was greenish-yellow and a solution in alcoholic potassium hydroxide, in presence of air, turned green-yellow immediately, with a slow change (overnight) to a deep red color.

The ketone was removed from an ethereal solution by extraction with saturated sodium bisulfite solution. Steam distillation of the bisulfite layer in presence of sodium carbonate regenerated VIII, identified as the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 168–169°.

ROCHESTER, N. Y.

(15) J. W. Cook, *et al.*, *J. Chem. Soc.*, 603 (1952).