Ethyl γ-(1-Carbethoxy-2-hydroxy-1-cyclopentyl)-butyrate. The preparation of ethyl γ-(1-carbethoxy-2-keto-1-cyclopentyl)-butyrate was accomplished by a modification of the procedure of Bachmann and Struve,[15] and is recorded here. A mixture of 64 g. of clean sodium and 2170 ml. of pure toluene was heated to reflux temperature, and the sodium was dispersed through violent stirring. The resulting mixture was cooled in an ice-bath and 433 g. of 2-carbethoxycyclopentanone[16] was added dropwise but rapidly. The ice-bath was replaced with a steam-bath, and the reaction mixture was heated *cautiously* with good stirring. After 16 minutes a spontaneous reaction set in, and the flask was *immediately* cooled in an ice-bath. When the reaction had subsided, the thick pasty reaction mixture was heated for one hour on the steam-bath, cooled in an ice-bath, and 541 g. of ethyl γ-bromobutyrate was added. The mixture was then held at reflux temperature for 17 hours.

The suspension of sodium bromide in a yellow solution was then cooled in an ice-bath and cautiously acidified with 1 l. of 1 *N* hydrochloric acid. The layers were separated, the toluene layer was washed thoroughly with water, dried and evaporated at 100° under reduced pressure. The tan oil remaining was distilled to give 562 g. of oil, b.p. 130–163° (0.8 to 1.0 mm.), which was redistilled to give 525 g. (70% yield) of colorless oil, b.p. 136–142° (0.20 mm.), $n^{25}\text{D}$ 1.4573. This material was used directly in the next step.

A mixture of 60 g. of the above ethyl γ-(1-carbethoxy-2-keto-1-cyclopentyl)-butyrate, 100 ml. of 95% ethanol and 1.0 g. of platinum oxide was shaken in an atmosphere of hydrogen for 24 hours. The up-take of hydrogen leveled at a calculated value of 82–89% of theory. The catalyst was removed by filtration of the mixture through a cake of Celite, the ethanol was evaporated from the filtrate under vacuum, and the residual oil was distilled to give 51 g. (91% yield) of product, b.p. 128–130° (0.4 mm.), $n^{25}\text{D}$ 1.4619.

Anal. Calcd. for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 61.70; H, 9.03.

A *p*-nitrobenzoate derivative of this alcohol was prepared by the usual method to give only one readily isolable diastereomer in 39% yield, m.p. 84–86° (fine needles from methanol).

Anal. Calcd. for $C_{21}H_{27}O_8N$: C, 59.85; H, 6.46. Found: C, 59.79; H, 6.39.

1-Keto-6-hydroxyspiro[4.4]nonane (XI).—To a mixture of 7.7 g. of sodium hydride and 60 ml. of pure benzene was added 0.2 ml. of pure methanol, and the mixture was heated to reflux temperature. To the stirred mixture was added dropwise (two hours) a solution of 20 g. of ethyl γ-(1-carbethoxy-2-hydroxy-1-cyclopentyl)-butyrate. The resulting brown, pasty reaction mixture was held at reflux with stirring for 12 hours. Butyl ether (4 ml.) and 13 ml. of toluene were then added, the condenser was replaced with a thermometer, and the mixture was cooled to −5° in an ice–salt-bath as 13.5 ml. of methanol was added dropwise, followed by the dropwise addition of 140 ml. of ice-water. The mixture was then heated to reflux and stirred for 30 minutes, again cooled to 0° and acidified by the dropwise addition of 16 ml. of 30% sulfuric acid solution. The mixture was heated to reflux for one hour, cooled, and the layers were separated. The water layer was extracted with three 100-ml. portions of ether, the organic layers were combined and washed with two 50-ml. portions of 3% sodium carbonate solution and three 50-ml. portions of water. The organic layer was dried, evaporated and the residual oil was distilled to give two fractions, b.p. 135–146° (18 mm.), wt. 3.77 g., and b.p. 146–160° (18 mm.), wt. 1.0 g. Fraction 1 was redistilled for analysis, 3.0 g., b.p. 70–76° (0.07 mm.), $n^{25}\text{D}$ 1.4909.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.81; H, 9.26.

The 2,4-dinitrophenylhydrazone of this material was prepared by the usual method, a 93% yield of what appears to be a mixture of diastereomers resulting, m.p. 114–118°. Three recrystallizations of this material from ethanol gave rust colored granules, m.p. 138–144°.

Anal. Calcd. for $C_{15}H_{18}O_5N_4$: C, 53.88; H, 5.43. Found: C, 53.80; H, 5.43.

The *p*-nitrobenzoate of the ketol was prepared by the usual method, a brown pasty product resulting. The material was triturated with methanol, filtered, and the filtrate was concentrated and cooled. The solid that separated was recrystallized five times from methanol to give a 15% yield of one diastereomer, m.p. 90.5–92° (yellow plates).

Anal. Calcd. for $C_{16}H_{17}NO_5$: C, 63.35; H, 5.65. Found: C, 63.48; H, 5.50.

Conversion of 1-Keto-5-hydroxyspiro[4.4]nonane (XI) to 1,5-Dihydroxyspiro[4.4]nonane (VIII).—Reduction of XI with lithium aluminum hydride by the same method used with diketone III as starting material (see above) gave an 86% yield of glycol, b.p. 159–161° (21 mm.), $n^{25}\text{D}$ 1.5026. This material (2.60 g.) was converted to a mixture of diastereomeric bis-*p*-nitrobenzoates of VIII by the method reported above. Fractional crystallization of this material from acetone gave 1.6 g. of racemate A, m.p. 192–194° undepressed by admixture with an authentic sample.

LOS ANGELES, CALIFORNIA

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(15) W. E. Bachmann and R. S. Struve, THIS JOURNAL, **63**, 2589 (1941).

(16) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 119.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Cyclic Polyolefins. XXXII. *cis*- and *trans*-1,3-Diphenylcycloöctane[1]

BY ARTHUR C. COPE, MARK R. KINTER[2] AND RICHARD T. KELLER

RECEIVED JANUARY 16, 1954

Authentic samples of the two geometric isomers of 1,3-diphenylcycloöctane have been prepared and proved to be identica with the two isomers previously obtained from carbonyl-bridged intermediates. The synthetic route involved Friedel-Crafts addition of benzene to 2-cycloöcten-1-one (III), followed by reaction of the resulting 3-phenylcycloöctanone (IV) with phenyllithium, dehydration of the tertiary alcohol, and reduction of the mixture of olefins that was formed. 2-Cycloocten-1-one was prepared by Oppenauer or chromic acid oxidation of 2-cycloöcten-1-ol (II), obtained from the acetate I, which in turn was prepared from 3-bromocycloöctene and silver acetate or *cis*-cycloöctene and mercuric acetate.

Convenient routes for the synthesis of eight-membered ring compounds from carbonyl-bridged intermediates have been described for the preparation of 2,4-diphenylcycloöcta-1,4-diene, 2,4-diphenylcycloöctene and 3,5-diphenylcycloöctene.[3] Evidence for the structure of these compounds was based on ultraviolet absorption spectra, oxidative degradation, analogy with a similar synthesis of 1-phenylcycloöcta-1,3-diene,[4] and reduction to one or both of two solid hydrocarbons, believed to be the two geometric isomers of 1,3-diphenylcycloöctane.[3] The presence of an eight-membered ring in the

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[1] Supported in part by the Office of Naval Research under Contract N5ori-07822, Project Designation NR-356-096.

[2] du Pont Fellow, 1950–1951.

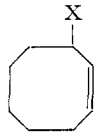
[3] A. C. Cope, F. S. Fawcett and G. Munn, THIS JOURNAL, **72**, 3399 (1950).

[4] A. C. Cope and E. C. Hermann, *ibid.*, **72**, 3405 (1950); D. F. Rugen, Ph.D. Thesis, Massachusetts Institute of Technology, 1952.

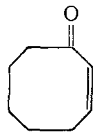
series of compounds was not definitely proved, but is established by the synthesis of *cis*- and *trans*-1,3-diphenylcycloöctane reported in this paper.

3-Bromocycloöctene, prepared from *cis*-cycloöctene and N-bromosuccinimide,[5] was treated with silver acetate in glacial acetic acid at room temperature, and yielded 79% of 2-cycloöctene-1-yl acetate (I) and 4% of 1,3-cycloöctadiene. The allylic acetate I also was prepared in 32% yield from cycloöctene and mercuric acetate,[6] with 34% recovery of the olefin Saponification of the acetate I with potassium hydroxide in aqueous ethanol yielded 2-cycloöcten-1-ol (II) (91%), which was characterized as the phenylurethan and by quantitative reduction to cycloöctanol.

Oxidation of the alcohol II to the pure α,β-unsaturated ketone, 2-cycloöcten-1-one (III) was accomplished by two oxidations with chromic acid in aqueous acetic acid; a third oxidation did not change the intensity of the absorption maximum of III at 230 mμ. This oxidation procedure resulted in a poor yield of the pure ketone III, however, and Oppenauer oxidation with *p*-benzoquinone and aluminum isopropoxide in benzene was preferable. The latter procedure yielded 66% of the ketone III which was 92% pure according to the extinction coefficient at 230 mμ, and accordingly contained 8% of the alcohol I. The ketone III obtained by this procedure was sufficiently pure for use in the synthesis described below.



I, X = $OCOCH_3$
II, X = OH

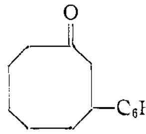


III

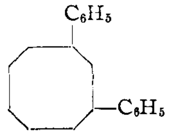
Since 2-cyclohexen-1-one can be prepared directly by the oxidation of cyclohexene with chromic acid in acetic acid,[7] an effort was made to prepare the ketone III by oxidation of *cis*-cycloöctene under similar conditions. The product obtained from cycloöctene, however, was *cis*-cycloöctene oxide[8] (28%) rather than the ketone III.[9]

Friedel–Crafts addition of benzene to the carbon–carbon double bond of the ketone III in the presence of aluminum chloride yielded 3-phenylcyclooctanone (IV) (51%). The ketone IV was isolated as a solid, m.p. 61–62.5°, and characterized further as the semicarbazone. The presence of an eight-membered ring in the ketone was established by reduction by a modified Wolff–Kishner method[10] to phenylcycloöctane, which was identified by comparison with an authentic sample.

The reaction of phenyllithium with 3-phenylcycloöctanone yielded 1,3-diphenylcycloöctan-1-ol, a viscous, high-boiling liquid that was not isolated, but was dehydrated by heating with iodine in benzene solution. The product, which was isolated in 82% yield, presumably was a mixture of 1,3- and 2,4-diphenylcycloöctene; its ultraviolet spectrum (λ_{max} 248 mμ, log ϵ 4.13 in cyclohexane) was very similar to the spectra of 2,4-diphenylcycloöctene[3] (λ_{max} 248.5 mμ, log ϵ 4.00) and 1-phenylcycloöctene[11] (λ_{max} 248 mμ, log ϵ 4.07). Catalytic hydrogenation of the mixture of 1,3- and 2,4-diphenylcycloöctenes with a palladium catalyst resulted in the absorption of 102% of one molar equivalent of hydrogen and formation of a mixture of the *cis* and *trans* forms of 1,3-diphenylcycloöctane (V). Fractional crystallization from methanol yielded the less soluble isomer, m.p. 83.5–85.8°, which was identical (by mixed melting point and comparison of infrared spectra) with the 1,3-diphenylcycloöctane isomer with the same melting point previously prepared from a carbonyl-bridged intermediate.[3] The more soluble isomer was isolated from the methanol mother liquors as a slightly impure solid, m.p. 56–60°, which however did not give a melting point depression with the purer sample from the earlier synthesis (m.p. 60.6–61°). The two samples of the low-melting isomer also had infrared spectra that were identical within experimental error.



IV



Va, m.p. 83.5–85.8°
Vb, m.p. 60.6–61.0°

Experimental[12]

2-Cycloöcten-1-yl Acetate (I).—A suspension of 28.2 g. of silver acetate in 50 ml. of glacial acetic acid was added in portions with stirring and cooling to a solution of 26.7 g. of 3-bromocycloöctene[5] in 50 ml. of glacial acetic acid. The mixture was allowed to stand overnight and then was filtered to separate the silver bromide, which was washed with 75 ml. of acetic acid. The combined filtrates were concentrated by distillation through a 20 × 1.5-cm. column packed with glass helices to remove acetic acid. The distillate contained 1,3-cycloöctadiene, which was isolated by dissolving it in ether, washing with water and then with 5% aqueous sodium carbonate to remove acetic acid, drying over magnesium sulfate, and distilling through a semimicro column. The yield was 0.62 g. (4%), b.p. 74–76° (86 mm.), n^{25}D after passing through a small column of silica gel to remove traces of ether 1.4901, λ_{max} 228–230 mμ (ϵ 5740 in cyclohexane) (compare properties in ref. 5). The residue remaining after distillation of the acetic acid was filtered to remove a small amount of solid and distilled through a semimicro column. The yield of 2-cycloöcten-1-yl acetate was 18.7 g. (79%), b.p. 55–59° (1 mm.), n^{25}D 1.4672. A redistilled analytical sample had the following physical properties: b.p. 57° (1 mm.), n^{25}D 1.4680, d^{25}_4 0.9898.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.11; H, 9.49.

2-Cycloöcten-1-yl acetate also was prepared by heating a mixture of 10.0 g. of cycloöctene, 29.0 g. of mercuric acetate and 10 ml. of glacial acetic acid under reflux in an oil-bath at 140° for 3 hours. The mixture was cooled, distilled rapidly at 1 mm., and the distillate was fractionated, yielding 4.83 g. (32%) of 2-cycloöcten-1-yl acetate, b.p. 116–118° (30 mm.), n^{25}D 1.4680. By the procedure described above for isolation of 1,3-cycloöctadiene, 3.4 g. (34%) of the cycloöctene was recovered from the acetic acid fraction.

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(5) A. C. Cope and L. L. Estes, Jr., This Journal, **72**, 1129 (1950).

(6) Preparation of allylic acetates from cyclic olefins and mercuric acetate is described by W. Treibs and H. Bast, *Ann.*, **561**, 165 (1949).

(7) F. C. Whitmore and G. W. Pedlow, Jr., This Journal, **63**, 758 (1941).

(8) K. Ziegler and H. Wilms, *Ann.*, **567**, 1 (1950); A. C. Cope, S. W. Fenton and C. S. Spencer, This Journal, **74**, 5884 (1952).

(9) The oxidation of other (usually hindered) olefins to epoxides with chromic acid has been reported. See W. J. Hickinbottom and D. G. M. Wood, *Nature*, **168**, 33 (1951).

(10) Huang Minlon, This Journal, **68**, 2487 (1946).

(11) A. C. Cope and A. A. D'Addieco, *ibid.*, **73**, 3419 (1951).

(12) Melting points are corrected and boiling points are uncorrected. We are indebted to Dr. S. M. Nagy and his associates for analyses.

2-Cycloöcten-1-ol (II).—2-Cycloöcten-1-yl acetate (7.7 g.) was added to a solution of 5.2 g. of potassium hydroxide in 7 ml. of water and 15 ml. of ethanol, and the solution was allowed to stand for 4 hours with occasional shaking. The solution was diluted with 25 ml. of water and extracted with 50- and 25-ml. portions of ether. The extracts were washed with water, dried over magnesium sulfate, concentrated, and the residue was distilled through a semimicro column. The yield of 2-cycloöcten-1-ol was 5.28 g. (91%), b.p. 74° (2 mm.), $n^{25}\text{D}$ 1.4959, d^{25}_4 0.9756.

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.33; H, 11.18.

2-Cycloöcten-1-ol also was prepared by treating 3-bromocycloöctene with silver acetate in acetic acid and adding the solution of the crude acetate to an excess of alcoholic potassium hydroxide. The yield of the alcohol by this procedure was 73%.

2-Cycloöcten-1-yl phenylurethan was prepared by warming 0.28 g. of 2-cycloöcten-1-ol with 0.27 g. of phenyl isocyanate briefly and allowing the mixture to stand overnight in a stoppered tube. The solid product was extracted with hot ligroin and crystallized on cooling as colorless needles (0.39 g., 72%), m.p. 92.5–93°. Recrystallization did not change the melting point.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.43; H, 7.81; N, 5.71. Found: C, 73.55; H, 7.94; N, 5.70.

Hydrogenation of a solution of 0.415 g. of 2-cycloöcten-1-ol in 4 ml. of acetic acid in the presence of 0.4 g. of prereduced platinum oxide was complete in 2 hours and 104% of one molar equivalent of hydrogen was absorbed. Cyclooctanol was isolated as the reduction product in a yield of 0.32 g. (76%) and identified as the phenylurethan by m.p. and mixed m.p.

2-Cycloöcten-1-one (III). (a).—A solution of 4.2 g. of chromium trioxide in 2 ml. of water and 9 ml. of acetic acid was added dropwise in a period of 50 minutes with rapid stirring and cooling in an ice-bath to a solution of 5.7 g. of 2-cycloöcten-1-ol in 10 ml. of glacial acetic acid. The mixture was stirred at room temperature for 2 hours, partially neutralized by addition of a solution of 10.1 g. of potassium hydroxide in 50 ml. of water with cooling, and extracted continuously with ether for 12 hours. The extract was neutralized to phenolphthalein by addition of aqueous potassium hydroxide, and the aqueous layer was extracted with three portions of ether. The combined ethereal solutions were dried over magnesium sulfate, concentrated by distillation through a helix-packed column, and the residue was fractionated through a semimicro column, yielding 3.87 g. (69%) of a mixture of 2-cycloöcten-1-one and 2-cycloöcten-1-ol, b.p. 94–97° (15 mm.), $n^{25}\text{D}$ 1.4940. A redistilled sample was found to contain 58% of the ketone by comparison of its ultraviolet absorption spectrum with the spectrum of pure 2-cycloöcten-1-one. A second oxidation of the mixture by a similar procedure gave the pure ketone, with physical constants that were not changed by a third oxidation. The 2-cycloöcten-1-one isolated after the third oxidation had b.p. 89° (14 mm.), $n^{25}\text{D}$ 1.4953, $\lambda_{\max_1}$ 230 mμ (ε 7700), $\lambda_{\max_2}$ 310 mμ (ε 80) (in 95% ethanol).

Anal. Calcd. for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.38; H, 10.08.

(b).—2-Cycloöcten-1-one containing a small amount of 2-cycloöcten-1-ol as an impurity was obtained conveniently by Oppenauer oxidation of the alcohol. A mixture of 10.1 g. of 2-cycloöcten-1-ol, 43.2 g. of pure, dry *p*-benzoquinone, 16.3 g. of aluminum isopropoxide and 600 ml. of dry benzene was heated under reflux protected from atmospheric moisture for 30 minutes. The mixture was allowed to cool to room temperature and stand for 23 hours, after which it was again heated under reflux for 1 hour. After cooling the mixture with ice, 1 l. of 5% hydrochloric acid was added with shaking, and the benzene layer was combined with an ether extract of the aqueous layer. The solution was washed with three 700-ml. portions of 5% sodium hydroxide, then with water, and dried over magnesium sulfate. Distillation through a semimicro column after removal of the solvent through a helix-packed column yielded 6.48 g. (66%) of 2-cycloöcten-1-one, b.p. 88–90° (12 mm.), $n^{25}\text{D}$ 1.4961, that was 92% pure according to the intensity of the principal absorption maximum at 230 mμ (ε 7060 in 95% ethanol, compared to 7700 for the pure ketone).

Oxidation of Cycloöctene with Chromic Acid.—A solution of 15.4 g. of chromium trioxide in 9 ml. of water and 35 ml. of acetic acid was added dropwise with stirring over a period of several hours to a solution of 11.2 g. of *cis*-cyclooctene in 22 ml. of glacial acetic acid with cooling in ice. The mixture was allowed to stand at room temperature for 2 days, after which 57 g. of potassium hydroxide in 200 ml. of water was added and the mixture was steam distilled. Ether extraction of the distillate followed by concentration and fractionation separated 0.9 g. of recovered cycloöctene and 3.56 g. (28%) of cycloöctene oxide, which after treatment with Girard reagent to remove a very small amount of a ketonic impurity had m.p. and mixed m.p. with an authentic sample[8] of 57–59°.

3-Phenylcycloöctanone (IV).—2-Cycloöcten-1-one (6.2 g., from procedure b above) was added in one portion to a stirred mixture of 33.3 g. of powdered anhydrous aluminum chloride and 500 ml. of dry benzene. The mixture was stirred and heated under reflux for 3.5 hours, after which it was cooled in ice and shaken with a mixture of 500 ml. of ice-water and 100 ml. of concentrated hydrochloric acid. The organic layer was separated, combined with a 250-ml. ether extract of the aqueous layer, washed three times with water, and dried over magnesium sulfate. After removal of the solvent, distillation yielded 7.7 g. of crude 3-phenylcycloöctanone, b.p. 75–134° (0.3 mm.). A mixture of the crude product and 7.63 g. of Girard reagent "T" in 10 ml. of glacial acetic acid and 100 ml. of absolute ethanol was heated under reflux for 1 hour. The solution was cooled, poured into 400 ml. of ice-water containing 8 g. of sodium carbonate, and non-ketonic material was removed by extraction with two 200-ml. portions of ether. Concentrated hydrochloric acid (25 ml.) was added to the aqueous solution, and after 1 hour the product was extracted with two 200-ml. portions of ether. The extracts were washed with water, dried over magnesium sulfate, and concentrated. Distillation through a semimicro column yielded 5.11 g. (51%) of 3-phenylcycloöctanone, b.p. 118–121° (0.5 mm.). The ketone solidified rapidly, and was recrystallized to a constant melting point of 61–62.5° from 5:1 methanol–water.

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.21; H, 9.04.

3-Phenylcycloöctanone semicarbazone was prepared by heating 50 mg. of the ketone, 31 mg. of semicarbazide hydrochloride and 23 mg. of sodium acetate in 2 ml. of 50% ethanol. The semicarbazone (52 mg., m.p. 170–171°) was recrystallized from 2:1 ethanol–water as white leaflets, m.p. 173–174°.

Anal. Calcd. for $C_{15}H_{21}N_3O$: C, 69.46; H, 8.16. Found: C, 69.67; H, 8.29.

3-Phenylcycloöctanone (0.15 g.) was reduced to phenylcycloöctane by heating with 0.5 g. of potassium hydroxide and 1.0 ml. of 85% hydrazine hydrate in 10 ml. of diethylene glycol in a bath at 180° for 1.5 hours, and then at 210° for 3 hours while about 2 ml. of liquid distilled. The solution was cooled, combined with the distillate, and poured into 50 ml. of water, which was extracted with two 25-ml. portions of ether. The extracts were washed with water, dried over magnesium sulfate and concentrated. The residue was distilled through a semimicro column, yielding 90 mg. (64%) of phenylcycloöctane, b.p. approximately 95° (0.3 mm.), $n^{25}\text{D}$ 1.5304, m.p. 5.8–7.5° and mixed m.p. with an authentic sample[11] 6.2–8.0°.

1,3- and 2,4-Diphenylcycloöctenes.—A solution of 2.02 g. of 3-phenylcycloöctanone in 20 ml. of dry ether was added with stirring during a period of 5 minutes in a nitrogen atmosphere to the phenyllithium prepared from 4.72 g. of bromobenzene and 0.46 g. of lithium in 40 ml. of ether. The mixture was heated under reflux for 0.5 hour, after which 30 ml. of water was added with cooling and stirring. The ether layer was combined with an ethereal extract of the aqueous layer, washed with water, and dried over magnesium sulfate. One-fifth of the solution was reserved for (unsuccessful) attempts to purify the tertiary alcohol, and the remaining four-fifths was concentrated. A solution of the residue in 50 ml. of benzene was heated under reflux with 50 mg. of iodine for 6 hours, with separation of the small amount of water formed in a Dean and Stark separator. The solution was cooled, washed with sodium thiosulfate solution and water, and concentrated. The residue was heated in a short-path still for 2.5 hours at 150° and 0.5 mm. to remove biphenyl, and then was distilled with a heating block temperature of 200–250° (0.5 mm.). A solution of the distillate in 50 ml. of pentane was again washed with sodium thiosulfate solution, water, and concentrated. Slow distillation of the residue in a short-path still at 0.5 mm. with a heating block temperature of 170° yielded 1.71 g. (82%) of a mixture of 1,3- and 2,4-diphenylcycloöctenes as a viscous liquid, $n^{25}\text{D}$ 1.5954.

Anal. Calcd. for $C_{20}H_{22}$: C, 91.55; H, 8.45. Found: C, 91.23; H, 8.51.

1,3-Diphenylcycloöctane (V).—A solution in 10 ml. of acetic acid of 0.466 g. of the mixture of 1,3- and 2,4-diphenylcycloöctenes described above was hydrogenated at room temperature and atmospheric pressure in the presence of 0.45 g. of 10% palladium on Norit. Reduction was complete in 45 minutes and resulted in absorption of 102% of one molar equivalent of hydrogen. The catalyst was separated, washed with acetic acid and pentane, and the filtrates were washed with water and sodium carbonate solution to remove acetic acid. Concentration of the pentane solution yielded 0.456 g. of a mixture of *cis*- and *trans*-1,3-diphenylcycloöctanes as an oil which solidified; m.p. 54–66°. The mixture was fractionally crystallized from methanol, and after nine crystallizations the least soluble isomer had m.p. 83.5–85.8° and mixed m.p. with a sample prepared by hydrogenation of 2,4-diphenylcycloöcta-1,4-diene[3] (m.p. 83.6–85.1°) of 83.2–85.8°. Recrystallization of the more soluble isomer obtained from the mother liquors yielded a slightly impure sample, m.p. 56–60° and mixed m.p. with a sample obtained by hydrogenation of 2,4-diphenylcycloöctene[3] (m.p. 60.6–61.0°) of 56.5–60°.

CAMBRIDGE, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BOSTON COLLEGE]

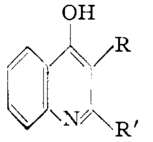
A Study of the Camps Synthesis of 4-Hydroxy-3-quinolinecarboxylic Acid

BY JOSEPH BORNSTEIN, WILLIAM J. REID[1] AND DONALD J. TORRES[1]

RECEIVED DECEMBER 28, 1953

The Camps synthesis of 4-hydroxy-3-quinolinecarboxylic acid from ethyl *o*-formamidophenylpropiolate has been duplicated. The crude reaction product contained, in addition, appreciable amounts of 4-hydroxycarbostyril. The identity of each compound was established by comparison with the corresponding authentic sample. Improved procedures for the preparation of intermediates in the synthesis have been devised. Homer's proposal of intramolecular loss of water from 4-hydroxy-3-quinolinecarboxylic acid on heating to yield a β-lactone has not been substantiated.

During his investigation on the structure of kynurenic acid, Camps[2] claimed to have synthesized 4-hydroxy-3-quinolinecarboxylic acid (I) and an isomer, 4-hydroxy-2-quinolinecarboxylic acid (II). Heating of ethyl *o*-formamidophenylpropiolate (V) under reflux with sodium hydroxide in aqueous ethanol was reported to give I, while similar alkaline treatment of *o*-ethoxalylaminoacetophenone yielded II. Structure I was assigned to kynurenic acid.



I, R = COOH, R′ = H
II, R = H, R′ = COOH

Subsequently, Homer[3] prepared highly purified samples of natural kynurenic acid and showed that this substance was represented correctly by structure II and not by structure I. She successfully duplicated Camps' synthesis of II, but her attempts to prepare I by his method led to the isolation of a material whose structure was not conclusively established. Following the Camps procedure, Homer found that formylation of ethyl *o*-aminophenylpropiolate (IV) with anhydrous formic acid in ether gave little or no yield of V. Attempted conversion of V to I afforded a material whose melting point and quantitative elemental analysis differed from the expected values.

Recently, Schofield and Simpson[4] abandoned their efforts to prepare I by the Camps route because of the difficulty encountered in preparing the starting materials. In their hands, esterification of *o*-aminophenylpropiolic acid (III) by the procedure of Baeyer and Bloem[5] yielded primarily a substance believed to be 4-chlorocarbostyril. Moreover, formylation of IV by the Camps method failed. In the light of these facts, a reinvestigation of the Camps synthesis of 4-hydroxy-3-quinolinecarboxylic acid (I) seemed appropriate.[6]

The esterification of III by the procedure of Baeyer and Bloem[5] was modified by us so as to give 60% yields of purified IV consistently. In this modification III was added to a cold, freshly prepared, saturated ethanolic hydrogen chloride solution, the suspension gently warmed until solution occurred, and the reaction mixture kept at 0° overnight. The unmodified procedure[5] gave poor yields (3%) as observed by Schofield and Simpson[4] and by us. The ester IV was also obtained by us by reaction of III with ethereal diazoethane, but the yields were erratic (20–60%).

We were unable to convert IV to ethyl *o*-formamidophenylpropiolate (V) with anhydrous formic acid in dry ether at 0°. Camps[2] reported a 70% yield of purified V under these conditions. Attempted formylation of IV by heating either under reflux or in a sealed tube with ethanolic ethyl formate[7] led only to the recovery of the starting material. The desired formyl derivative V was finally obtained in reproducible high yield (70–87%) by treatment of an anhydrous ethereal solution of IV with mixed formic–acetic anhydride.

Heating V under reflux with sodium hydroxide in aqueous ethanol according to the Camps pro-

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[1] Abstracted in part from the M.S. theses of William J. Reid and Donald J. Torres.

[2] R. Camps, *Ber.*, **34**, 2703 (1901); *Z. physiol. Chem.*, **33**, 390 (1901).

[3] A. Homer, *J. Biol. Chem.*, **17**, 509 (1914); *cf.* also E. Späth, *Monatsh.*, **42**, 91 (1921).

[4] K. Schofield and J. C. E. Simpson, *J. Chem. Soc.*, 1033 (1946).

[5] A. Baeyer and F. Bloem [*Ber.*, **15**, 2147 (1882)] prepared IV by bubbling hydrogen chloride into an ethanolic suspension of III at low temperature; few details were given, however.

[6] *Cf.* A. W. Johnson, "The Chemistry of the Acetylenic Compounds," Vol. II, Edward Arnold and Co., London, 1950, p. 106, for a more detailed summary of the historical background of this investigation.

[7] J. P. E. Human and J. A. Mills, *J. Chem. Soc.*, 1457 (1948).