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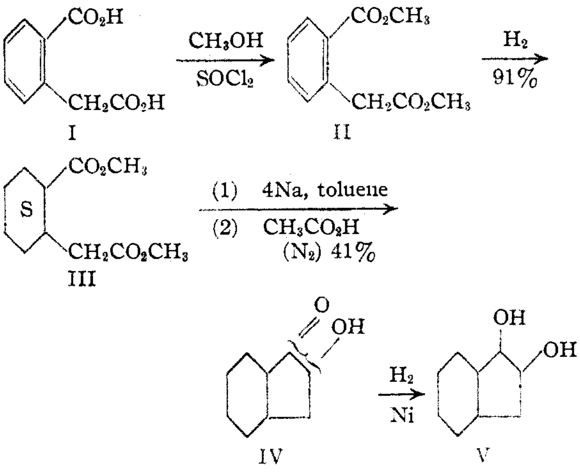
The Formation of Five and Six-membered Rings by the Acyloin Condensation. II. The Cyclization of Dimethyl Hexahydrohomophthalate

BY JOHN C. SHEEHAN AND R. C. O'NEILL

As a model for a projected total synthesis of estriol and related sex hormones and analogs, the fused cyclopentanediol structure characteristic of the steroidal D ring has been synthesized by a new route involving an acyloin condensation. Cyclization of dimethyl hexahydrohomophthalate (III) by treatment with excess metallic sodium led to an intermediate acyloin IV, which afforded bicyclo[4.3.0]nonan-7,8-diol (V) on hydrogenation.



The only previous recorded example of the synthesis of a fused cyclic acyloin is the recent preparation of bicyclo[4.2.0]octan-7-ol-8-one (containing a four-membered acyloin ring) by Cope and Herrick.[1] The sole reported cyclization of a dibasic ester to a five-membered acyloin (2-hydroxycyclopentanone) was described in the first communication of this series.[2]

Dimethyl hexahydrohomophthalate (III) was prepared by high pressure hydrogenation of dimethyl homophthalate (II) over W-4 Raney nickel catalyst.[3] The most convenient and efficient large-scale esterification of homophthalic acid was found to be treatment of the methanolic solution of the acid with thionyl chloride followed by refluxing. Apparently the methyl sulfite generated carries the acid-catalyzed esterification more nearly to completion by consuming the water formed.

Cyclization was carried out both on the pure *cis* diester and on the mixture obtained directly by hydrogenation. The acyloin condensation of the *cis–trans* mixture of diesters gave rise to a complex mixture of isomeric saturated hydroxyindanones in 38–41% yield as determined by a gravimetric Fehling procedure.[4] On the basis of the experimental evidence at hand no assignment of the relative positions of the two functional groups of the isomeric α-ketols can be made. It is indeed possible that both types of position isomers are formed in the cyclization. Redistillation of the isomeric mixture permitted the separation of a crystalline acyloin, m. p. 65.2–67.3°, in 15% yield.

That this crystalline material possessed the *cis* configuration with respect to the two hydrogen atoms attached to the fusion carbons is indicated by synthesis from the pure *cis* diester. It is possible, however, that isomerization may have taken place prior to or during the cyclization. By mild saponification of the *cis–trans* mixture of III, and repeated recrystallization of the resulting acid mixture, pure *cis*-hexahydrohomophthalic acid, m. p. 146°, was isolated. Re-esterification with diazomethane gave the pure *cis* diester for the acyloin cyclizations. The crystalline acyloin isolated from this reaction, m. p. 67.2–68°, was shown to be identical to that obtained from the cyclization of the *cis–trans* mixture of III by comparison of the semicarbazones.

In every run, a small amount (2–3%) of a high melting bimolecular acyloin was obtained. The use of the high dilution reflux cycle decreased the yield of this sparingly soluble, tricyclic acyloin product which was presumably formed by the condensation of two molecules of the starting diester.

Evaporative distillation of the reaction residues remaining after separation of the acyloin material led to the isolation of a 1–2% yield of a colorless, crystalline compound, m. p. 118–119.2°. The analysis of this product corresponds to the α-diketone, bicyclo[4.3.0]nonan-7,8-dione.

Catalytic reduction of crystalline IV with alkaline Raney nickel (W-7)[5] gave a crystalline 1,2-glycol, bicyclo[4.3.0]nonan-7,8-diol (V), in 34% yield as well as a non-crystalline mixture of isomeric α-glycols.

The infrared absorption spectrum of the slightly soluble bimolecular acyloin (Fig. 1, curve B) shows a strong, unperturbed C=O band at 5.82μ (1718 cm.$^{-1}$), a fairly intense OH band at 3.03μ (3300 cm.$^{-1}$), and a second weaker OH band at 2.88μ (3472 cm.$^{-1}$). The intensity of the C=O band in this spectrum is evidence against a hemiketal (lactolide) structure analogous to that suggested for adipoin.[2] In addition, the

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[1] Cope and Herrick, THIS JOURNAL, **72**, 983 (1950).

[2] Sheehan, O'Neill and White, *ibid.*, **72**, 3376 (1950).

[3] Pavlic and Adkins, *ibid.*, **68**, 1471 (1946).

[4] Browne and Zerban, "Sugar Analysis," John Wiley and Sons, Inc., New York, N. Y., 1941, pp. 765–772.

[5] Adkins and Billica, THIS JOURNAL, **70**, 695 (1948).

normal position of the carbonyl band suggests that this function may be part of a strain-free ring system. It contrasts with the shifted C=O band of crystalline IV at 5.74μ (1743 cm.$^{-1}$) shown in curve A.

Experimental[6]

Homophthalic Acid (I).—This compound was prepared by oxidation of indene according to the method described[7] except that considerably larger runs were made. In two preparations, an average of 188.6 g. (74.5%) of I was obtained from 583 g. (1.98 moles) of technical potassium dichromate, 3195 g. (31.1 moles) of concentrated sulfuric acid (s. g. 1.84), and 173 g. (1.415 moles) of 95% indene.[8] The product melted at 177–179°.

Dimethyl Homophthalate (II).—In a 2-liter, three-necked flask fitted with a glass stirrer, a reflux condenser, and a dropping funnel was placed a mixture of 600 ml. of commercial absolute methanol (99.5%) and 120 g. (0.667 mole) of homophthalic acid. While the temperature of the oil-bath was maintained at 35–40°, 178.5 g. (1.5 moles) of thionyl chloride was added portionwise over a one and one-half hour period. After overnight reflux, the solvent was removed under reduced pressure. The crude product was dissolved in 400 ml. of ether, washed with two 100 ml. portions of water, and with four 50-ml. portions of 10% sodium bicarbonate. These combined washings yielded 4.4 g. of incompletely esterified material upon acidification. After the ethereal solution had been dried over anhydrous potassium carbonate, the solvent was removed and the crude brown diester (108.3 g.) was distilled through a short Vigreux column. The yield of colorless diester amounted to 102.5 g. (76.8 or 74% conversion); b. p. 110–113° (0.6 mm.); m. p. 54.5–56.2°. Three recrystallizations from ligroin gave II as massive, hard, colorless needles, m. p. 54.8–56.2°.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.29; H, 5.89.

The literature[9] reports m. p. 39–42° for dimethyl homophthalate after recrystallization from methanol.

Other methods of direct esterification gave much lower yields.

***cis*- and *trans*-Dimethyl Hexahydrohomophthalate (III).**—Prior to reduction, the dimethyl homophthalate was refluxed in methanol with Raney nickel catalyst (W-4)[3] for three hours. A solution of 96.1 g. (0.46 mole) of dimethyl homophthalate and 150 ml. of absolute methanol (99.5%) containing two teaspoonfuls of Raney nickel catalyst[3] was shaken for three hours at 150–210° under a hydrogen pressure of 2450–2550 p.s.i. The catalyst was removed by cautious suction filtration through Filter-Cel. After removal of the solvent, the reduced diester was distilled through a 6-inch, vacuum-jacketed Vigreux column. The yield of colorless III amounted to 90.3 g. (91.3%); b. p. 86.5–87.5° (0.4 mm.); $n^{25}D$ 1.4575. A sample purified for analysis by redistillation through a semimicro fractionating still containing an 8 × 300 mm. column packed with a wire spiral had the following physical properties: b. p. 88° (0.7 mm.); $n^{25}D$ 1.4570.

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.67; H, 8.47. Found: C, 61.42; H, 8.48.

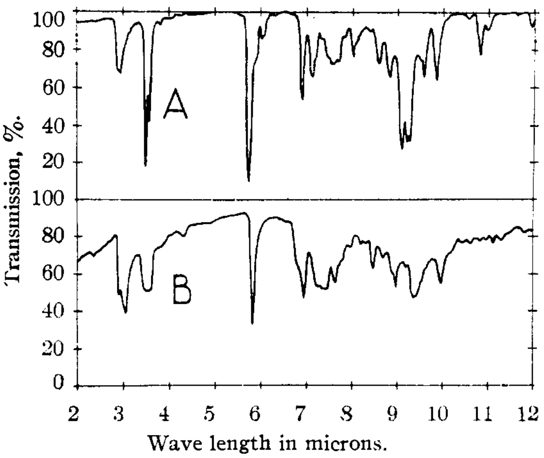

Fig. 1.—Infrared absorption spectra: curve A, crystalline bicyclic acyloin (IV); curve B, bimolecular, tricyclic acyloin (Nujol mull).

This liquid mixture of *cis* and *trans* isomers was used directly in several acyloin cyclizations. In order to isolate the pure *cis* diacid and dimethyl ester for a comparison run, the following mild procedure was employed. To a solution of 68.2 g. (0.319 mole) of the liquid diester mixture and 1200 ml. of methanol was added 250 ml. of 20% sodium hydroxide at room temperature. After five days of standing at room temperature, the precipitated disodium salts (62.3 g., 85%) were collected by filtration, and washed thoroughly with methanol. The mixture of *cis* and *trans* acids (42.1 g., 84%) which resulted from acidification of the disodium salts melted over a wide range. After one recrystallization from water, the acid melted at 144.0–145.8°. After several more recrystallizations from water, 26.0 g. of substantially pure *cis* hexahydrohomophthalic acid, m. p. 145.6–146.6°, was obtained.[10]

The acid was converted to the *cis* diester by esterification with diazomethane. From 26.0 g. (0.140 mole) of the *cis* diacid was obtained 25.2 g. (84.4%) of *cis*-dimethyl hexahydrohomophthalate, b. p. 88° (0.7 mm.); $n^{25}D$ 1.4578.

The Acyloin Condensation of Dimethyl Hexahydrohomophthalate (*cis–trans* Mixture).—The technique employed in the condensation itself was similar to that previously described for the preparation of glutaroin.[2] In a 2-liter, three-necked, creased flask equipped with a high speed stirrer, a thermometer, and the high dilution reflux cycle, were placed 750 ml. of dry, sulfur-free toluene and 6.44 g. (0.28 gram-atom) of freshly cut sodium. The system was thoroughly swept with dry, oxygen-free nitrogen. With the solvent at vigorous reflux, the stirrer was started, and a solution of 15.0 g. (0.07 mole) of III and 250 ml. of dry toluene was added in a four and one-half hour period. The development of a characteristic pale yellow color signified onset of the reaction. The bright yellow mixture was heated at reflux for an additional two hours after the diester addition was complete. Glacial acetic acid (16.90 g., 0.28 mole) in 70 ml. of toluene was then cautiously added to the chilled sodio enolate slurry. The precipitate of sodium acetate formed during acidification was removed by suction filtration with the aid of Filter-Cel, and the filter cake was washed well with toluene.

The combined yellow filtrate was concentrated under reduced pressure in a nitrogen atmosphere. As the concentration progressed, colorless, matted needles deposited. This crystalline material, m. p. 203–205°, which was removed from the chilled toluene concentrate (25 ml.) by filtration, amounted to 0.35 g. (3.2% calculated as acyloin). The melting point of this by-product fluctuated on successive recrystallizations. On the basis of the

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(6) All melting points are corrected. We are indebted to Mr. S. M. Nagy, Mrs. Louise Spencer and their associates for the analytical data.

(7) Buck, Grummitt and Egan, "Organic Syntheses," Vol. 29, John Wiley and Sons, New York, N. Y., 1949, p. 49.

(8) The 95% indene was generously furnished by Eastern Gas and Fuel Associates, Boston, Mass.

(9) Wegscheider and Glogau, *Monatsh.*, **24**, 939 (1903).

(10) Windaus, Hückel and Reverey, *Ber.*, **56**, 93 (1923), report m. p. 146° for this compound and 158° for the *trans* isomer. They based the assignment of geometrical configuration of the acids chiefly on the relative ease of anhydride formation.

molecular weight, elemental analysis, and the infrared absorption spectrum (Fig. 1, curve B) this high melting fraction is presumably an isomeric mixture of tricyclic acyloins formed by the condensation of two molecules of III. After two recrystallizations from methanol–acetone, an analytical sample melted at 205.6–207°.

Anal. Calcd. for $C_{18}H_{28}O_4$: C, 70.10; H, 9.16; mol. wt., 308. Found: C, 69.93; H, 9.23; mol. wt., 257 (Rast, using camphor).

The brown, viscous oil remaining after removal of all the solvent was distilled through a short Vigreux column. The nearly colorless "acyloin fraction" thus obtained, 4.85 g., b. p. 66–70° (0.1 mm.), deposited 1.6 g. (14.8%) of colorless rosettes, m. p. 55.5–69°, on standing. Both crystalline IV and the liquid isomeric mixture reduced Fehling and Tollens reagents immediately at room temperature. An analytical sample of crystalline IV obtained by repeated recrystallization from petroleum ether and cyclohexane melted at 65.2–67.3°.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.16. Found: C, 69.91; H, 9.09.

On long standing, purified, crystalline IV gradually turned to a pale yellow oil even when stored under nitrogen.

A 3,5-dinitrobenzoate of the crystalline acyloin, prepared by the pyridine method,[11] recrystallized as straw yellow crystals from aqueous ethanol; m. p. 156.6–158°.

Anal. Calcd. for $C_{16}H_{16}O_7N_2$: C, 55.17; H, 4.63; N, 8.04. Found: C, 55.46; H, 4.81; N, 7.89.

The semicarbazone of crystalline IV proved difficult to obtain analytically pure. A sample twice recrystallized from 95% ethanol melted sharply at 212.4–212.6° with decomposition.

Anal. Calcd. for $C_{10}H_{17}O_2N_3$: C, 56.85; H, 8.11; N, 19.89. Found: C, 57.24; H, 8.26; N, 20.20.

Sublimation at 85–140° (0.1 mm.) of the reaction residues remaining after distillation of the acyloin fraction gave 0.2 g. (1.9% calculated as the α-diketone corresponding to IV) of a colorless, crystalline sublimate, m. p. 114.5–118.5°, admixed with a small amount of a yellow, viscous oil. After several recrystallizations from cyclohexane, an analytical sample of this compound was obtained as stout, colorless prisms; m. p. 119.8–120.8°.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.00; H, 7.89.

This material dissolved in ethanolic ferric chloride to give a transient deep purple coloration which slowly faded to a permanent olive green. It did not reduce Fehling solution even on prolonged heating.

Evaluation of Total Yield of Isomer Bicyclic Acyloins (IV).—Advantage was taken of the fact that both crystalline IV and the liquid mixture of isomers reduce Fehling solution within ten seconds at room temperature. The gravimetric Fehling procedure used was based on a determination recommended for sugar analyses.[4] In a typical run employing 14.6 g. (0.068 mole) of diester, the concentrate remaining after removal of the solvent was subjected to a short path distillation without fractionation. The faintly yellow distillate, b. p. 60–80° (0.1–0.2 mm.), amounted to 5.9 g. The acyloin distillate yielded 73.2% of the theoretical amount of ignited cupric oxide; this corresponds to a 41% yield of IV.

A catalytic hydrogenation of 1.00 g. (6.5 millimoles) of the same acyloin distillate using alkaline Raney nickel (W-7)[5] at room temperature and atmospheric pressure resulted in the absorption of 145.4 ml. of hydrogen (85% of theoretical based on IV) in four and one-half hours.

Bicyclo[4.3.0]nonan-7,8-diol (V).—To a solution of 0.30 g. (1.95 millimoles) of crystalline IV and 15 ml. of absolute ethanol in a micro-hydrogenator was added one-third teaspoonful of Raney nickel catalyst (W-7).[5] The theoretical volume of hydrogen (48.4 ml.) was absorbed within one hour. After removal of the catalyst and concentration of the filtrate, colorless crystals suspended in an oil remained. On trituration with ethanol and filtration, 104 mg. (34%) of a crystalline α-glycol, m. p. 102.8–103.8°, was obtained. After two recrystallizations from cyclohexane, an analytical sample of V melted at 105.8–106.6°.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.33. Found: C, 69.44; H, 10.37.

The use of either palladium or platinum catalyst for this reduction resulted in no appreciable hydrogen uptake in a twenty-four hour period.

Infrared Absorption Spectra.—The two infrared spectra shown in Fig. 1 were determined with a Baird Infrared Recording Spectrophotometer, Model B. A five per cent. carbon tetrachloride solution of crystalline IV, contained in a cell 0.1 mm. thick, was used for curve A. For curve B, finely powdered, purified tricyclic acyloin (50 mg.) was suspended in 0.5 ml. of anhydrous Nujol. The Nujol mull was contained in a cell 0.025 mm. thick.

Summary

A bicyclic model compound, bicyclo[4.3.0]-nonan-7,8-diol, possessing the fused cyclopentanediol structure characteristic of estriol has been synthesized by means of the acyloin condensation and subsequent reduction of the intermediate α-ketol.

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[11] Shriner and Fuson, "The Identification of Organic Compounds," 3rd edition, John Wiley and Sons, Inc., New York, N. Y., p. 164.