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

The Formation of Five and Six-membered Rings by the Acyloin Condensation. I. The Cyclization of Glutaric and Adipic Esters

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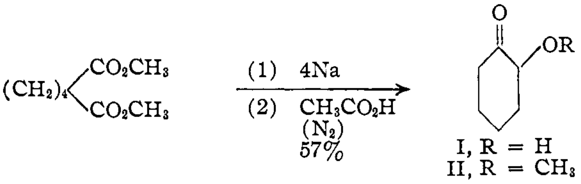
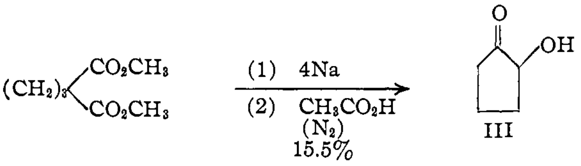
The preparation of open-chain α-ketols by the action of excess sodium on aliphatic esters was first investigated in 1906.[1] Hansley[2] extended the scope of the acyloin condensation by preparing cyclic acyloins of eight or more carbon atoms from the esters of saturated and unsaturated dicarboxylic acids. Later workers[3,4] obtained very good yields (67–96%) of the larger cyclic acyloins containing from nine to twenty carbon atoms in the ring. More recently, Cope and Herrick[5] reported the preparation of a four-membered cyclic acyloin.

It is surprising that the preparation of five and six-membered cyclic α-ketols by the acyloin condensation has not been reported in view of the success of other cyclization procedures for five and six-membered carbocycles. In the present work it was found that the cyclization of dimethyl adipate gave a 55–57% yield of adipoin (I).



I, R = H
II, R = CH₃



III

Efficient high-speed stirring (2500 r. p. m.), an oxygen-free inert atmosphere, and a ratio of four gram-atoms of sodium per mole of diester were the essential conditions employed. Use of the high dilution technique (see Experimental Section) did not increase the yield appreciably, nor did doubling the amount of sodium used. This new preparation of adipoin is of particular interest when contrasted with the high yield obtained by the Dieckmann condensation of adipic esters to carbalkoxycyclopentanones using sodium as the condensing agent.[6] In the latter case only one gram-atom of sodium is used for every mole of diester. No Dieckmann product was isolated in our experiments.

Even under high dilution reaction conditions dimethyl glutarate gave only a 15.5% yield of crude glutaroin (III). The crude glutaroin distillate was tinted yellow with a small amount of the corresponding α-diketone. The major portion of the product appeared to be polymeric acyloin material.[2] No distillable product was isolated when the diester was added to a toluene slurry of sodium sand through a conventional dropping funnel.

It is interesting to observe that, although macrocyclic acyloins are formed in uniformly high yields with ordinary addition methods, a relatively low yield of the five-membered carbocycle was obtained even with the aid of a high dilution reflux cycle. This contrasts with conventional cyclization procedures, which give optimum yields for the five and six-membered rings, but require special high dilution techniques for satisfactory yields of the macrocyclic compounds.

Although adipoin (I) is a colorless, mobile liquid when freshly distilled, it gradually crystallizes on standing. The solid product displays anomalous physical and chemical properties. Unlike the homologous cyclic acyloins, solid adipoin is insoluble in the common organic solvents. It was found, in agreement with previous workers,[7–12] that the melting points of purified adipoin samples varied from 93 to 130°. These values are substantially higher than those of the largest cyclic acyloin homologs. Carbonyl derivatives of solid adipoin were difficult to prepare, and catalytic hydrogenation attempts failed. Rast molecular weight determinations (camphor) indicate that the solid acyloin is dimeric, but a cryoscopic measurement in acetic acid corresponded to a monomer.

Bergmann and Gierth[11] showed that samples of adipion of widely different melting points all analyzed correctly. Bergmann also found that, depending on the degree of heating, adipoin yielded two different methyl ethers when suspended in methanolic hydrogen chloride. They assumed structure II for the normal ketonic ether and structure V for the non-ketonic dimer. Therefore, Bergmann and Gierth suggested that in the solid state adipoin existed as a variable mixture of the normal

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[1] For a general review of the acyloin condensation, see S. M. McElvain, "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 256.

[2] Hansley, U. S. Patent 2,228,268, Jan. 14, 1941; *C. A.*, **35**, 2534 (1941).

[3] Prelog, Frenkiel, Kobelt and Barman, *Helv. chim. acta*, **30**, 1741 (1947).

[4] Stoll, *et al.*, *ibid.*, **30**, 1815, 1822, 1837 (1947).

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

[6] *Cf.* the preparation of 2-carbethoxycyclopentanone by P. S. Pinkney, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 116.

[7] Kötz and Grethe, *J. prakt. Chem.*, [2] **80**, 488 (1919).

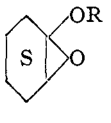
[8] Kötz, Blendermann, Rosenbusch and Sirringhaus, *Ann.*, **400**, 62 (1913).

[9] Bouveault and Chereau, *Compt. rend.*, **142**, 1086 (1906).

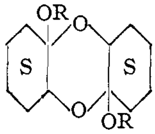
[10] Willstätter and Sonnenfeld, *Ber.*, **46**, 2957 (1913).

[11] Bergmann and Gierth, *Ann.*, **448**, 48 (1926).

[12] A. E. Venus-Danilova, *J. Gen. Chem.* (*U. S. S. R.*), **6**, 1784–1795 (1936); *C. A.*, **31**, 4279 (1937).



IV, R = H
V, R = CH_3



VI, R = H
VII, R = CH_3

α-hydroxy ketone form I and the internal hemiketal or lactolide isomer IV. Later Criegee and Schnorrenberg[13] advanced VII as the structure of the dimeric methyl ether of adipoin.

In order to detect any alterations in the functional groups of adipoin during crystallization, the infrared absorption spectra (Fig. 1) of a freshly distilled sample of liquid adipoin and of a solid sample of I were determined. The liquid sample (Curve A) shows a fairly strong OH band at 2.87 μ (3484 cm.$^{-1}$), and a very intense C=O band at 5.83 μ (1715 cm.$^{-1}$). The spectrum of the solid dimeric adipoin (Curve B) exhibits an intense, broad hydrogen-bonded OH band at 2.98 μ (3355 cm.$^{-1}$), but the C=O band 5.83 μ is scarcely detectable. On the basis of the infrared spectra, the molecular weight determinations, and the ready reversibility of the dimerization we suggest the bimolecular lactolide structure VI for the solid adipoin itself.

The infrared spectrum of glutaroin (III) (Curve C) showed a strong OH band at 2.90 μ (3450 cm.$^{-1}$), indicative of considerable hydrogen bonding, and an intense C=O band at 5.72 μ (1749 cm.$^{-1}$).

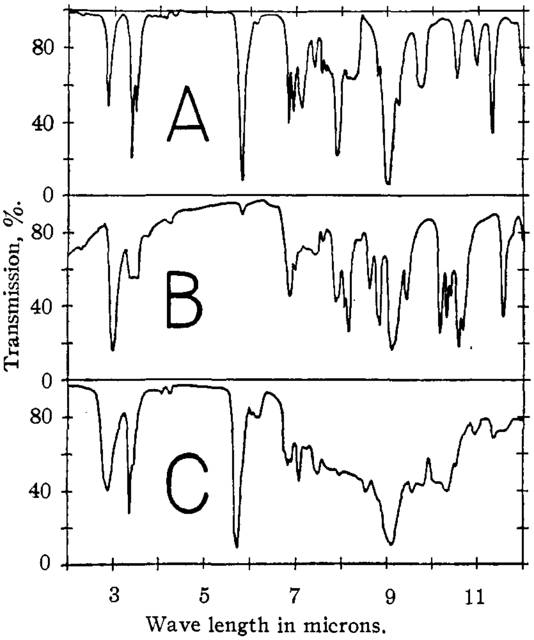


Fig. 1.—Infrared absorption spectra: curve A, freshly distilled adipoin (I); curve B, Nujol mull of solid adipoin; curve C, glutaroin (III).

Experimental[14]

2-Hydroxycyclohexanone (Adipoin, I). The Acyloin Condensation of Dimethyl Adipate.—A 3-liter, three-necked, creased flask was equipped with a thermometer, a high speed stainless steel stirrer,[15] and a dropping funnel. An almost static atmosphere of dry, prepurified nitrogen, containing not more than 0.0002% oxygen by volume maintained a slight positive pressure throughout the reaction. In the flask were placed 23.0 g. (1.0 g.-atom) of freshly cut sodium, and 1200 ml. of dry toluene. After the system had been thoroughly swept with nitrogen, the solvent was heated to vigorous reflux with an electric heating mantle. The molten sodium was easily dispersed as very finely divided "sand" by one or two minutes stirring at 4500–5000 r. p. m.; the stirring speed was then reduced to 2500 r. p. m. A solution of 40.0 g. (0.23 mole) of dimethyl adipate (n^{25}D 1.4261) and 400 ml. of dry toluene was added to the refluxing toluene slurry in one hour. The reaction mixture was stirred at reflux for an additional hour.

The heating mantle was replaced with an ice–salt-bath, and the stirring speed was considerably reduced. Acidification of the sodio enolate was accomplished by dropwise addition of 62 ml. of glacial acetic acid to the cold (0–8°) slurry in thirty minutes. Using a filter aid, the sodium acetate formed was removed by suction filtration, and washed thoroughly with toluene. The combined yellow filtrates were concentrated under reduced pressure in a nitrogen atmosphere. The crude concentrate, consisting of colorless crystalline material mixed with an orange oil, was chilled for several hours. The semisolid residue was triturated with 30–40 ml. of ether, filtered, and the precipitate was washed liberally with cold, dry ether. The first crop of colorless adipoin (I), m. p. 93–98°, amounted to 12.4 g. (47.4%). After standing for several days in the cold, 2.0 g. more of I, m. p. 99.8–105.0°, was obtained; the combined yield was thus increased to 14.4 g. (55%). Evaporative distillation of the residual viscous brown oil at 93–118° (40 μ) gave only a small amount of an orange sirup which reduced Fehling solution immediately in the cold. This sirup apparently consisted of higher molecular weight acyloin material.

An analytical sample, obtained by concentrating an acetone solution of adipoin, melted at 113.6–117.8°; a mixed melting point with a sample of I prepared from cyclohexanone by chlorination[16] and subsequent hydrolysis[8] was undepressed.

Anal. Calcd. for $C_6H_{10}O_2$: C, 63.13; H, 8.83; mol. wt., 114. Found: C, 62.97; H, 8.60; mol. wt., 234, 230 (Rast, using camphor); mol. wt. 129 (freezing point, acetic acid).

Bergmann and Gierth[11] reported molecular weights of 113, 117, 119 for I (freezing point, acetic acid; no Rast determinations were recorded).

A sample of I, m. p. 103.5–104°, was distilled through a semimicro fractionating still with a 30 × 0.8 cm. column packed with a wire spiral.[17] Three fractions were collected: b. p. 71° (7 mm.); n^{25}D 1.4709, 1.4702, 1.4700. The infrared absorption spectrum of the middle fraction (Fig. 1) was determined before solidification began. After standing for two days, the three fractions had completely solidified, and possessed the following melting points: 103.4–109.8°; 94.5–98.6°; 94–98.0°. The pure solid adipoin is insoluble in all common organic solvents, including carbon tetrachloride, ethylene dichloride and tetrachloroethane. It reduces both Fehling and Tollens solutions immediately at room temperature.

A slightly higher yield (57%) was obtained by adding the diester solution through a high dilution reflux cycle

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[13] Criegee and Schnorrenberg, *Ann.*, **560**, 144 (1948).

[14] All melting points are corrected and all boiling points are uncorrected. We are indebted to Mr. S. M. Nagy and associates for the elemental analyses and the infrared measurements.

[15] Morton and Redman, *Ind. Eng. Chem.*, **40**, 1190 (1948).

[16] Newman, Farbman and Hipsher, "Organic Syntheses," Vol. 25, John Wiley and Sons, Inc., New York, N. Y., 1945, p. 22.

[17] Gould, Holzmann and Niemann, *Ind. Eng. Chem.*, *Anal. Ed.*, **20**, 361 (1948).

(see below). The use of twice the calculated amount of sodium did not increase the yield. Dimethyl adipate did not appear to react with lithium sand in refluxing toluene in a helium atmosphere; 86% of the starting material was recovered.

A 2,4-dinitrophenylosazone of I was prepared from 0.3 g. of solid adipoin and 0.4 g. of 2,4-dinitrophenylhydrazine in strongly acid aqueous ethanol.[18] An analytical sample recrystallized from ethanol–ethyl acetate was obtained as bright orange prisms; m. p. 221° with decomposition. Adkins and Rossow[19] reported m. p. 218–219° uncor.

Anal. Calcd. for $C_{18}H_{16}O_8N_8$: C, 45.77; H, 3.41; N, 23.72. Found: C, 46.06; H, 3.72; N, 23.38.

2-Hydroxycyclopentanone (Glutaroin, I). The Acyloin Condensation of Dimethyl Glutarate.—A 3-liter, three-necked creased flask was equipped with a thermometer, a high speed, stainless steel stirrer,[15] and a simplified Ziegler reflux cycle[20,21] to which was attached an efficient reflux condenser, and a 500 ml. Hershberg dropping funnel. After placing 23.2 g. (1.01 g.-atom) of freshly cut sodium and 900 ml. of dry toluene in the flask, the system was swept with dry, prepurified nitrogen. The solvent was heated to vigorous reflux with an electric heating mantle, and the sodium was dispersed by one minute of stirring at 4500–5000 r. p. m. With the stirring speed reduced to 2500 r. p. m., a solution of 40.0 g. (0.25 mole) of dimethyl glutarate (E. I. du Pont de Nemours and Co., Inc., b. p. 75–76° (3 mm.), n^{25}D 1.4236) and 400 ml. of dry toluene was added through the dilution cycle in eight hours. The initial slate grey color of the sodium dispersion gradually changed through several shades of tan to a brilliant orange at the end of the addition. Rapid stirring of the refluxing toluene slurry was continued for an additional forty-five minutes.

The reaction mixture was then chilled, acidified with acetic acid (60.9 g., 1.01 mole), and the sodium acetate was separated as in the adipoin preparation. An orange, viscous oil (24.6 g.) remained after concentration of the combined filtrates and washings under reduced pressure in a dry nitrogen atmosphere. This crude concentrate was transferred to a 125-ml. short-path still[22] for a rapid preliminary distillation. The distillate amounted to 3.9 g. (15.5% calculated as glutaroin) of a faintly yellow oil, b. p. 70–85° (8 mm.). The nearly solid, non-distillable distillation residue was presumably chiefly polymeric acyloin judging by its ready solubility in water and alcohol and rapid reduction of Fehling solution. An analytical sample of III (b. g. 73.5–74.5° (10 mm.), n^{25}D 1.4701) was prepared by redistillation of the original distillate through a semimicro fractionating column.[17]

Anal. Calcd. for $C_5H_8O_2$: C, 60.05; H, 8.06; mol. wt., 100. Found: C, 59.53; H, 8.59; mol. wt., 199 (Rast, camphor).

For III Staudinger and Ruzicka[23] reported b. p. 77–78° (10 mm.) and Godchot and Taboury[24] reported b. p. 80° (12 mm.).

Purified colorless III reduced Fehling and Tollens reagents immediately at room temperature but gave no color with ethanolic ferric chloride. This acyloin is very soluble in all common organic solvents and in water (in which it is unstable). No distillable product was isolated from several runs made without the high dilution reflux cycle.

An analytical sample of the 3,5-dinitrobenzoate of III crystallized from 95% ethanol as straw yellow prisms, m. p. 120.6–121.2°.

Anal. Calcd. for $C_{12}H_{19}O_7N_2$: C, 48.98; H, 3.43; N, 9.52. Found: C, 49.01; H, 3.48; N, 9.50.

After recrystallization from 95% ethanol a sample of the semicarbazone of III was obtained as a white powder; m. p. 186° with decomposition (reported,[24] 170° dec.).

Anal. Calcd. for $C_6H_{11}O_2N_3$: C, 45.85; H, 7.06. Found: C, 46.02; H, 7.20.

Infrared Absorption Spectra.—The three infrared spectra shown in Fig. 1 were determined with a Baird Infrared Recording Spectrophotometer, Model B. Ten per cent. solutions of liquid acyloins I and III in dried, redistilled tetrachloroethane were used for curves A and C. For curve B finely powdered solid adipoin (50 mg.) was suspended in 0.4 ml. of anhydrous Nujol.

Summary

The acyloin condensation has been extended to the preparation of five and six-membered carbocyclic rings, using as examples 2-hydroxycyclohexanone (adipoin) and 2-hydroxycyclopentanone (glutaroin). Molecular weight values and infrared data consistent with a dimeric lactolide structure for solid adipoin have been obtained.

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[18] Shriner and Fuson, "The Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 58.

[19] Adkins and Rossow, THIS JOURNAL, **71**, 3836 (1949).

[20] Ziegler, Eberle and Ohlinger, *Ann.*, **504**, 123 (1933).

[21] Cope and Herrick (ref. 5) described the basic operation of the modified "U" type dilution cycle employed in this work.

[22] Similar to the boiling still described by Hickman and Weyerts, THIS JOURNAL, **52**, 4714 (1930).

[23] Staudinger and Ruzicka, *Helv. Chim. Acta*, **7**, 380 (1924).

[24] Godchot and Taboury, *Bull. soc. chim.*, [4] **13**, 546-547 (1913).