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Four-Membered Rings by the Acyloin Condensation. A Peculiar Result in Liquid Ammonia[1,2]

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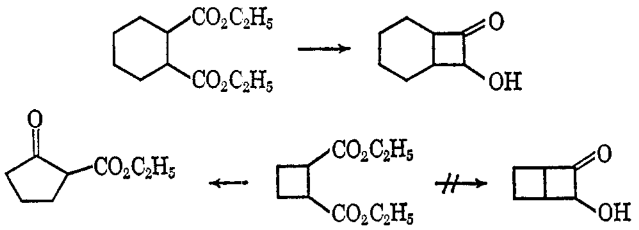
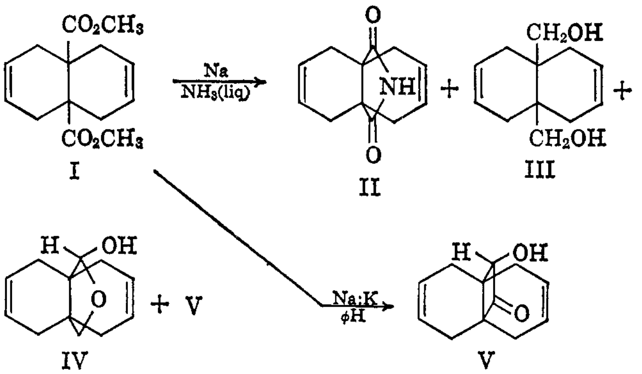
There is only one published account of the successful application of the acyloin condensation to the synthesis of a four-membered ring.[3] In that example, the cyclization of *cis*-1,2-dicarbethoxycyclohexane, the yield was 12%. In a similar attempt to cyclize *cis*-1,2-dicarbethoxycyclobutane the only identifiable product was 2-carbethoxycyclopentanone.[4]



In the course of developing a method for the introduction of a 9,10-ethano bridge into the decalin ring system we have investigated the acyloin condensation of dimethyl $\Delta^{2,6}$-hexalin-9,10-dicarboxylate, I (Chart I). When the condensation was conducted in liquid ammonia a mixture of products consisting of the cyclic imide, II (35.6%), the diol, III (21.1%), the hemiacetal, IV (6.4%), and the desired acyloin, V (10.1%) was obtained.

Although there are examples of the failure of the acyloin condensation or of competition with the Dieckmann condensation under the conditions described above[5] there are no clear examples of the formation of any products such as II, III, or IV in such a reaction. In one case,[6] an unsuccessful attempt to cyclize to a seven-membered ring in a steroid derivative, there is a suggestion that a very small amount of diol may have been formed as a side product. The imide apparently arises through an ammonolysis reaction. The hemiacetal is a logical intermediate in the formation of the diol, in what appears to be a kind of Bouveault–Blanc reduction with ammonia serving as the proton source.

Chart I



We have been able to successfully cyclize the diester in good yield when a 1:1 sodium–potassium alloy is used in refluxing benzene or xylene.[7] Sodium in refluxing toluene failed to effect cyclization.

Table I

Effect of Metal–Diester Mole Ratio on Yield of Acyloin

Mole ratio				
Diester[a]	Na	K	Solvent	Yield, %[b]
1 (0.05)	4.0	. . .	Toluene	c
1 (0.05)	6.1	3.6	Xylene	26[d]
1 (0.10)	7.65	4.46	Xylene	32[d]
1 (0.5)	3.07	1.84	Benzene	39[e]
1 (0.4)	3.84	2.32	Benzene	. .[f]
1 (0.3)	3.95	2.30	Benzene	61[e]
1 (0.24)	4.42	2.54	Benzene	57[e]
1 (0.10)	5.05	2.97	Benzene	70[g]
1 (0.4)	5.60	3.15	Benzene	76[g]
1 (0.3)	5.97	3.32	Benzene	70[g]
1 (0.10)	6.69	4.11	Benzene	71[g]

[a] The parenthetical number is the actual number of moles of ester used. [b] Recrystallized product free of diester by thin layer chromatography. [c] 61% of starting material recovered. No acyloin observed. [d] The crude yields were 77 and 87% for the smaller and larger runs, respectively, but the product was contaminated by unreacted diester. [e] The product contained diester. The yield is based on starting diester although considerable quantities of diester and additional acyloin were recovered by combining the residues of several runs. [f] A crude yield of 89% was obtained. The entire amount was used, however, in a subsequent reaction and a substantial amount of diester was recovered. [g] Crude yields of 91.2–93.7% were obtained. The tabular figure represents the yield after one recrystallization without attempt to work up mother liquors. The combined mother liquors from several runs were mined for additional product. That no ester was present in the *crude* product was indicated by thin layer chromatography.

The results of several runs with varying mole ratios of ester to metals are tabulated below. It appears that the amount of sodium is the critical factor and that an excess of sodium over the theoretical 4 g-atoms/mole of ester is necessary.

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(1) The work described in this paper was supported by National Science Foundation Grants GP-260 and GP-4439.

(2) Presented at the 54th Annual Meeting of the Oklahoma Academy of Science, Stillwater, Okla., Dec 3, 1965, and before the Division of Organic Chemistry at the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, Abstracts, p K23.

(3) A. C. Cope and E. C. Herrick, *J. Am. Chem. Soc.*, **72**, 983 (1950).

(4) J. J. Bloomfield, R. G. Todd, and L. T. Takahashi, *J. Org. Chem.*, **28**, 1474 (1963).

(5) See the review by K. T. Finley, *Chem. Rev.*, **64**, 573 (1964).

(6) N. A. Nelson and R. N. Schut, *J. Am. Chem. Soc.*, **80**, 6630 (1958).

(7) The use of the alloy was suggested by the work of Ya. L. Goldfarb, S. Z. Taits, and L. I. Belen'kii, *Tetrahedron*, **19**, 1851 (1963).

Experimental Section[8]

Dimethyl $\Delta^{2,6}$-Hexalin-9,10-dicarboxylate (I).—The crude $\Delta^{2,6}$-hexalin-9,10-dicarboxylic acid anhydride obtained in the Diels–Alder condensation of butadiene with acetylene dicarboxylic acid[9] was refluxed for 2–3 days with methanol (3–5 ml/g of anhydride mixture) containing 1% of toluenesulfonic acid. The methanol was evaporated under reduced pressure, the residue was dissolved in 10% sodium carbonate solution, and the aqueous solution was extracted with ether. The aqueous solution was then heated with charcoal and filtered hot. The cooled solution was poured into excess 6 *N* hydrochloric acid and after the precipitated half-ester was washed with water on a sintered funnel, it was allowed to dry *in vacuo*. The crude half-ester was obtained in 55–67% yield, mp 138–147°. Recrystallization from 1:1 benzene–hexane gave the analytical sample: mp 146.6–147.4° (lit.[10] mp 143–144°). *Anal.* Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.25; H, 6.87.

Thoroughly dried half-ester, 132.1 g, was mixed with phosphorus pentachloride, 116 g, in 1 l. of dry benzene and the mixture was refluxed gently on a steam bath for 2 hr. The solvent and phosphorus oxychloride were removed under reduced pressure (aspirator); then an additional 100 ml of benzene was added and removed as before. The residue was held at 50° under 0.5 mm of pressure for 1 hr; then 500 ml of dry methanol was added and the mixture was warmed briefly. The solvent was evaporated under reduced pressure and the residue was crystallized from methanol to give 122 g (87.2%), mp 98–100° (lit. mp 98°,[10] 100°[9]) of the diester.

Tricyclo[4.4.2.0^{1,6}]-11-one-12-ol-dodeca-3,8-diene (V).—All glass equipment was dried overnight in an oven at 100° and was flushed with dry, oxygen-free nitrogen during assembly and cooling. A slight positive nitrogen pressure was maintained until the addition of water (or hydrochloric acid in the case of ammonia) at the end of the reaction.

A. **Reaction in Benzene.**[11]—Benzene, 600 ml, dried by overnight reflux over calcium hydride was distilled directly into a 1-l. three-necked flask fitted with a Hershberg dropping funnel, a "Stir-O-Vac"[12] high-speed stirrer, and a reflux condenser. The benzene was brought to reflux (heating mantle) and then potassium, 11.6 g (0.297 g-atom), and sodium, 11.6 g (0.504 g-atom), were added in small pieces. (The metal was freshly cut, trimmed, and weighed under dry benzene.) The stirrer was operated at high speed for 5 min to disperse the metal, and then at a slower speed while a solution of 25.0 g (0.10 mole) of dimethyl $\Delta^{2,6}$-hexalin-9,10-dicarboxylate in 160 ml of dry benzene was added through the Hershberg funnel over a period of 100 min. Stirring, under reflux, was continued for an additional 60 min. Then the reaction mixture was cooled in a water bath while 18.4 g (0.40 mole) of absolute ethanol and then 50 g (0.834 mole) of glacial acetic acid was added dropwise. Water, 200 ml, was then added to the thick white slurry. The benzene solution was washed with bicarbonate and then with saturated sodium chloride solution. Each aqueous solution was washed once with benzene and the combined organic solutions were dried over anhydrous magnesium sulfate. The benzene was removed under vacuum leaving 17.8 g (93.7%) of a light pink solid, mp 77.6–80.4°. One recrystallization from cyclohexane gave 13.3 g of fluffy white needles, mp 79.6–80.3°. The analytical sample was recrystallized once from ethanol–water and five times from cyclohexane, mp 81.5–82.5°. *Anal.* Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.65, 75.64; H, 7.26, 7.43. The infrared spectrum showed a strong band at 1780 cm^{-1} for the cyclobutanone. The nmr spectrum in chloroform showed four major bands downfield from tetramethylsilane, a multiplet at 1.7–2.8 ppm (8 H), a broad singlet at 3.59 ppm (1 H), a broad singlet at 4.53 ppm (1 H), and a multiplet at 5.55–6.10 ppm (4 H).

The acyloin formed a semicarbazone, mp 187.5–189.5°, from ethanol–water and then chloroform–cyclohexane. *Anal.* Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.28; H, 6.80; N, 16.95.

An acetate was prepared from the acyloin and acetyl chloride in pyridine–ether. The product, obtained in 89% yield, was recrystallized from chloroform–cyclohexane and then from ethanol–water, mp 73.0–73.7°. *Anal.* Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.19; H, 6.88. The infrared spectrum showed bands at 1790 cm^{-1}, cyclobutanone, and 1740 cm^{-1}, acetate. The nmr spectrum in chloroform showed three bands downfield from TMS at 1.68–2.85 ppm (multiplet, 11 H), 5.48 ppm (singlet, 1 H), and 5.75–6.10 ppm (multiplet, 4 H). The CH_3 group shows up as a sharp singlet at 2.1 ppm superimposed over part of the CH_2 spectrum.

A tosylate was prepared from the acyloin and toluenesulfonyl chloride in pyridine. Recrystallization from benzene-hexane six times gave the analytical sample, mp 123.8–124.6°. *Anal.* Calcd for $C_{19}H_{20}O_4S$: C, 66.26; H, 5.85; S, 9.31. Found: C, 66.46; H, 5.85; S, 9.44.

B. **Reaction in Liquid Ammonia.**—Gaseous anhydrous ammonia, filtered through a large plug of glass wool, was condensed into a 2-l. three-neck flask equipped with a Trubore[13] stirrer, dropping funnel, and Dry Ice condenser. To the condensed ammonia, 800 ml, was added 400 ml of anhydrous ether and 4.6 g (0.20 g-atom) of sodium. Then 12.5 g (0.05 mole) of diester in 250 ml of anhydrous ether was added over 2 hr. The ammonia was evaporated with continuous stirring over a period of 2 days, after which time ammonia vapors were no longer noticeable in a stream of nitrogen swept through the flask. Ether (a total of 1-l.) was added from time to time during this period and the reaction mixture was warmed with the aid of a heating mantle maintained at low voltage (15–25 v). The mixture was cooled in an ice bath and 18 ml of concentrated hydrochloric acid in 200 ml of water was added rapidly with vigorous stirring. The ether solution was washed with saturated sodium bicarbonate and then with 5% sodium hydroxide and finally twice with water. The combined aqueous solution was acidified to produce 3.86 g (35.6%) of the imide, II, which, after recrystallization from chloroform–cyclohexane, had mp 205–218° (lit.[10] 215°). The infrared spectrum in chloroform showed a strong band at 1705 cm^{-1} and a weaker band at 1775 cm^{-1} for the carbonyl groups of the cyclic imide.[14] *Anal.* Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.83; H, 6.58; N, 7.01. The ether solution was evaporated to leave 4.5 g of a mixture which was crystallized from ethyl acetate to produce 1.48 g of the diol, III. The diol was reported in an earlier paper[15] to melt at 130–134° while ref 10 gives 125–127°. In this work we have found that samples treated in different ways give just about any melting point desired between 130 and 172°. All samples had the same infrared spectra, showing a broad intense band for –OH at 3300 cm^{-1}, KBr disk. In chloroform the –OH bands were at 3625 and 3360 cm^{-1}. The nmr spectrum was particularly revealing. In chloroform or deuteriochloroform the vinyl protons appear as a triplet at 5.55 ppm downfield from TMS. The –OH protons are, of course, variable in position according to the solvent and the temperature of the probe, but they appear from δ 3.59 to 4.2 ppm. The lower shift corresponds with the position of the singlet due to the protons of the hydroxymethyl groups. The allylic protons appeared as a singlet at δ 2.02 ppm. In dimethyl sulfoxide the methylene protons appeared as a doublet, J = 5.5 cps, δ = 3.42 ppm, while the –OH protons appeared as a triplet, J = 5.5 cps, δ = 4.51 ppm. The best analytical sample was obtained from an attempt to form a cyclic acetonide. It was recrystallized from benzene and from 50% methanol–water, mp 165–168°. *Anal.* Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.02, 73.95; H, 9.27, 9.22. The tosylate and mesylate were prepared from the diol and corresponding acid chloride in pyridine. The tosylate, crystallized from methanol, benzene and then di-*n*-butyl ether had mp 128–130° (lit.[10] mp 120–121°). *Anal.* Calcd for $C_{26}H_{30}S_2O_6$: C, 62.12; H, 6.02. Found: C, 62.11; H, 6.02. The mesylate was recrystallized from ethanol–benzene and then ethanol, mp 119–121° (lit.[10] mp 115°). *Anal.* Calcd for $C_{14}H_{22}S_2O_6$: C, 47.98; H, 6.33. Found: C, 48.04; H, 6.34. The diacetate was prepared by

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(8) All microanalyses were performed by A. Bernhardt, Mikroanalytisches Laboratorium. Melting points and boiling points are uncorrected. Infrared spectra were taken on a Beckman IR-8. Nmr spectra were taken on a Varian A-60 which was purchased with the aid of funds from the National Science Foundation, Grant GP-830.

(9) K. Alder and K. H. Backendorf, *Ber.*, **71**, 2199 (1938).

(10) G. Snatzke and G. Zanati, *Ann.*, **684**, 62 (1965).

(11) This is a typical experiment. Conditions for reactions in toluene and xylene were similar.

(12) Lab-Line Instruments, Inc., Melrose Park, Ill., Cat. No. 1280.

(13) Ace Glass Co.

(14) K. Nakanishi, "Infrared Absorption Spectroscopy-Practical," Holden-Day Inc., San Francisco, Calif., 1962, p 47, lists 1700 and 1770 cm^{-1} for five-membered imides.

(15) J. J. Bloomfield and W. T. Quinlin, *J. Am. Chem. Soc.*, **86**, 2738 (1964).

heating a solution of the diol in a 50% aqueous acetic acid solution (containing 5% sulfuric acid) for 20 min on a steam bath, mp 71–72°. Two recrystallizations from methanol–water followed by two recrystallizations from hexane did not change the melting point. The nmr spectrum in chloroform or carbon tetrachloride showed only three peaks. The vinyl protons appeared as a triplet at $\delta = 5.53$ ppm; the $-CH_2O$ group protons appeared as a singlet at $\delta = 4.14$ ppm while the allylic and $-CH_3$ protons appeared together as a sharp singlet at $\delta = 2.04$ ppm; infrared spectrum, 1735 cm^{-1}. *Anal.* Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.95; H, 7.93. The acetate was also prepared from acetic anhydride and pyridine but the product was harder to purify.

The residue from the ethyl acetate crystallization of the diol was chromatographed on 140 g of silicic acid in a 3.7 × 27 cm column; 100-ml fractions were collected. Fractions 14–22, eluted with 5% ethyl acetate in benzene, contained the pure acyloin V, 0.96 g (10.1%). Fractions 23–24, 0.13 g, contained a mixture of the acyloin and the hemiacetal IV. Fractions 25–38 were pure hemiacetal, 0.61 g (6.4%). The solvent mixture was changed slowly from 5 to 20% ethyl acetate and fractions 76–87 gave an additional 0.55 g of diol for a total of 2.03 g (21.1%). Nothing else could be eluted.

The hemiacetal showed infrared bands in chloroform at 3600 and 3380 cm^{-1} for –OH. The region between 2800 and 1670 cm^{-1} was virtually transparent. A very weak band, 6% below the base line, appeared at 1720 cm^{-1} for the aldehyde which is likely to be present in equilibrium with the hemiacetal. The nmr spectrum gave no evidence, however, for any significant quantity of aldehyde. In chloroform the vinyl protons appeared as a poorly resolved multiplet at $\delta = 5.56$ ppm; the single methinyl hydrogen adjacent to –O– and –OH appeared as a partially resolved doublet at $\delta = 5.30$ ppm; the –OH proton is also a poorly resolved doublet at $\delta = 4.6$–4.95 ppm; the protons of the $-CH_2O-$ appear as an AB quartet at $\delta = 3.90$ and 3.55 ppm, $J = 7.6$ cps; the allylic protons appear as a group of multiplets from $\delta = 2.67$ to 1.40 ppm with the principal peak at $\delta = 2.08$ ppm. In deuteriochloroform the spectrum is very similar except that the –OH peak overlaps the downfield doublet of the AB group at 35° and the upfield doublet at 60°. The peak positions are shifted *ca.* 1 or 2 cps. The lone methinyl hydrogen appears as a doublet at $\delta = 5.3$ ppm, $J = 6$ cps. In dimethyl sulfoxide the –OH proton moves downfield to $\delta = 6.23$ ppm and the methinyl hydrogen slightly upfield to $\delta = 5.17$ ppm. Both are well resolved doublets, $J = 5.5$ cps.[16] Five recrystallizations from 5:1 hexane–benzene gave the analytical sample, mp 97.0–98.0°. *Anal.* Calcd for $C_{16}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.09; H, 8.29.

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(16) *Cf.* O. L. Chapman and R. W. King, *J. Am. Chem. Soc.*, **86**, 1256 (1964).

The Chromic Acid Oxidation of Diastereoisomeric 1,2-Diols[1]

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In chromic acid oxidations of *cis*- and *trans*-1,2-dimethyl-1,2-cyclopentanediol, Rocek and Westheimer reported a *cis/trans* rate ratio of 800 in 90% acetic acid[2] compared to a *cis/trans* ratio of 320 reported by Criegee for lead tetraacetate cleavages in the same system.[3] Since stereochemical principles[4] and hydrogen-bonding studies[5] point to the fact that the diastereoisomeric symmetrical dialkyldiarylethanediols would be excellent acyclic models for the more rigid *cis–trans* systems and, since Criegee has already reported a *dl/meso* rate ratio of 2.9/1 for lead tetraacetate oxidation of 2,3-diphenyl-2,3-butanediol,[3] we proposed to investigate the chromic acid cleavages in this system.

Considerable evidence is available in the literature supporting a five-membered cyclic chromate ester intermediate in the oxidative scission of 1,2-diols.[2,6,7] Repeated comparisons have been made with the well-known lead tetraacetate cleavage of pinacols and glycols in which a cyclic plumbate ester has been postulated to justify the considerably faster rates obtained with *cis*-diols.[3]

Pure diastereoisomeric forms of 2,3-diphenyl-2,3-butanediol (I) and 4,5-diphenyl-4,5-octanediol (II) were synthesized according to published procedures[5] and were oxidized as 5.0×10^{-3} and 10.0×10^{-3} M solutions in 55% dioxane–45% water containing 0.10 M perchloric acid, 0.30 M sodium perchlorate, and 5×10^{-4} to 10.0×10^{-4} M chromic acid (as CrO_3).

Because of the exceedingly fast reaction velocities observed with I in acetic acid–water reaction medium it was necessary to modify conditions to obtain a measurable rate. With a solvent of lower dielectric, dioxane–water, and a spectral method to follow chromium(VI) loss at 3500 A, it was possible to obtain convenient and reproducible rate data in the 15–25° range. No temperature conditions were available at which the isomers of I could be directly compared in relative rate to the isomers of II. Since the latter compounds oxidized with great reluctance at ambient temperatures, they were studied at 40°. The 2,3-diphenyl-2,3-butanediols demonstrated immeasurably rapid rates at 40° and these were studied at 20°. See Table I for kinetic data.

Table I[a]

Compound	Temp, °C	Diol, M	k,[b] min^{-1}
I mixed			
isomers[c]	25	0.005	0.83
isomers[c]	25	0.01	2.06
isomers[c]	25	0.01	2.00[d]
meso	20	0.01	1.28
meso	20	0.01	1.35[d]
dl	20	0.01	1.46
dl	20	0.01	1.48[d]
II *meso*	40	0.005	0.045
dl	40	0.005	0.088

[a] All runs performed at 0.10 M perchloric acid, 0.30 M sodium perchlorate, and 5×10^{-4} M chromic acid. [b] The k's are pseudo-first-order rate constants. [c] Because of the difficulty in obtaining pure forms of the diastereoisomers, initial oxidations were performed on mixtures to establish reaction conditions. [d] Occasional runs were calculated by the classical graphic method to verify conformity with the Swinbourne computer technique.

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(1) (a) Supported in part by Petroleum Research Fund Grant 222-G to N. D. H. and by Marshall University Research Board Benedum Faculty Fellowships to N. D. H. and E. S. H. (b) Taken in part from the M.S. Thesis of R. J. S., Marshall University, 1965. (c) Presented at the Southeast–Southwest Regional Meeting of the American Chemical Society, Memphis, Tenn., Dec 3, 1965.

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(5) W. A. Mosher and N. D. Heindel, *J. Org. Chem.*, **28**, 2154 (1963).

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(7) Y. W. Chang and F. H. Westheimer, *ibid.*, **82**, 1401 (1960).