The Reductive Cyclization of Ethyl 3-(2-Ketocyclohexyl)propionate[1]

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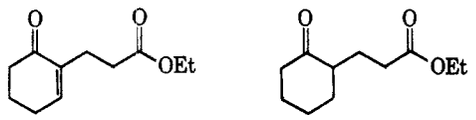
Reduction of ethyl 3-(2-ketocyclohexyl)propionate with lithium in liquid ammonia followed by mild chromic acid oxidation affords *trans*-4H-4a,5,6,7,8,8a-hexahydro-1-benzopyran as the major product along with lesser amounts of 5,6,7,8-tetrahydrochroman, *trans*-octahydrocoumarin, 6-hydroxybicyclo[4.3.0]nonan-7-one, and 6-ketononanolide. These results are in marked contrast to the reduction of similar systems with sodium in liquid ammonia.

During the course of some studies on the dissolving metal reductions of some unsaturated ketones, we examined the reduction of **1** with lithium and liquid ammonia and found that the products isolated under certain reaction conditions appeared to be derived from the corresponding saturated keto ester **2**. Because of



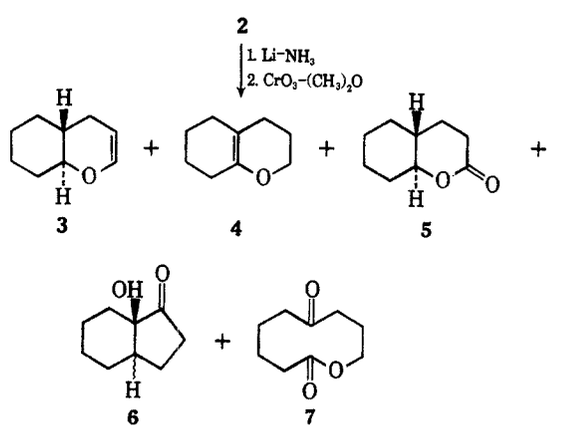
1 **2**

the capricious nature of the reduction of **1** in our hands, we examined in more detail the reduction of the more readily available saturated keto ester **2**.

Gutsche[2a] had previously reported the reductive ring closure of methyl 3-(2-ketocyclopheptyl)propionate and shown that fair yields of products containing the bicyclo[5.3.0]decane ring system could be obtained under appropriate reaction conditions. Under our reaction conditions, however, we have obtained only minor amounts of the corresponding bicyclo[4.3.0]nonane-type products, the major products arising from carbon–oxygen bond formation.[3]

Reduction of **2** with an excess of lithium in liquid ammonia followed by oxidation of the crude alcohol mixture with Jones' reagent[4] gave a mixture of at least six products (Scheme I) of which five were characterized. The products were separated by an involved

SCHEME I



3 **4** **5** **6** **7**

series of fractional distillation and preparative vapor phase chromatography (vpc) and identified as *trans*-4H-4a,5,6,7,8,8a-hexahydro-1-benzopyran (**3**), 5,6,7,8-tetrahydrochroman (**4**), *trans*-octahydrocoumarin (**5**), 6-hydroxybicyclo[4.3.0]nonan-7-one (**6**), and 6-ketononanolide (**7**) on the basis of the evidence outlined below.

Compound **3**, the major product of the reaction (~60% of the vpc volatile material), exhibited a molecular ion in the mass spectrum at *m/e* 138 and elemental analysis indicated the formula $C_9H_{14}O$. The infrared spectrum indicated the presence of an enol ether[5a] and a *cis*-1,2-disubstituted double bond.[5b] The nmr spectrum showed two vinyl hydrogens and the angular hydrogen adjacent to the oxygen appeared as a broad singlet (half-band width 17 cps) attributable to an axial hydrogen and indicating that the ring fusion is *trans*.[6]

Molecular weight determination by mass spectrometry indicated that compound **4** was isomeric with **3**. The infrared spectrum again showed the presence of an enol ether[5a] and the nmr spectrum indicated the absence of vinyl hydrogens. Finally, comparison with an authentic sample[7] established the structure.

Compound **5** exhibited infrared absorption at 1730 cm^{-1} indicative of a δ-lactone[5c] and showed a one proton absorption in the nmr spectrum at δ 3.85 (broad singlet, half-band width 20 cps) consistent with a *trans* ring fusion. Comparison with an authentic sample[6c] confirmed the structural assignment. None of the isomeric *cis*-lactone was detected by vpc.

Compound **6** was present in only trace amounts and its structure was tentatively assigned on the basis of infrared absorption characteristic of the hydroxyl group and a cyclopentanone.[8] No traces of further reduction products of **6** (*e.g.*, hexahydroindanone) could be detected by vpc in the crude products.

Compound **7** was a crystalline solid which exhibited a molecular ion in the mass spectrum at *m/e* 170 and had an elemental analysis corresponding to $C_9H_{14}O_3$. The infrared spectrum indicated the presence of two carbonyl groups (1730 and 1708 cm^{-1}) and the nmr spectrum indicated the presence of the group

(1) This work was supported in part by the National Science Foundation under Grant No. GP-5157.

(2) (a) C. D. Gutsche and I. Y. C. Tao, *J. Org. Chem.*, **28**, 883 (1963); (b) C. D. Gutsche, I. Y. C. Tao, and J. Kozma, *ibid.*, **32**, (1967). We are indebted to Professor Gutsche for informing us of his results prior to publication.

(3) Gutsche[2b] has examined the cyclization of the methyl ester analog of **2** using sodium in liquid ammonia and obtained a considerably different product distribution.

(4) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958: (a) p 36; (b) p 34; (c) p 185.

(6) (a) J. I. Musher, *J. Am. Chem. Soc.*, **83**, 1146 (1961); (b) N. O. Brace, *ibid.*, **84**, 3022 (1962); (c) H. O. House, R. G. Carlson, and H. Babad, *J. Org. Chem.*, **28**, 3359 (1963).

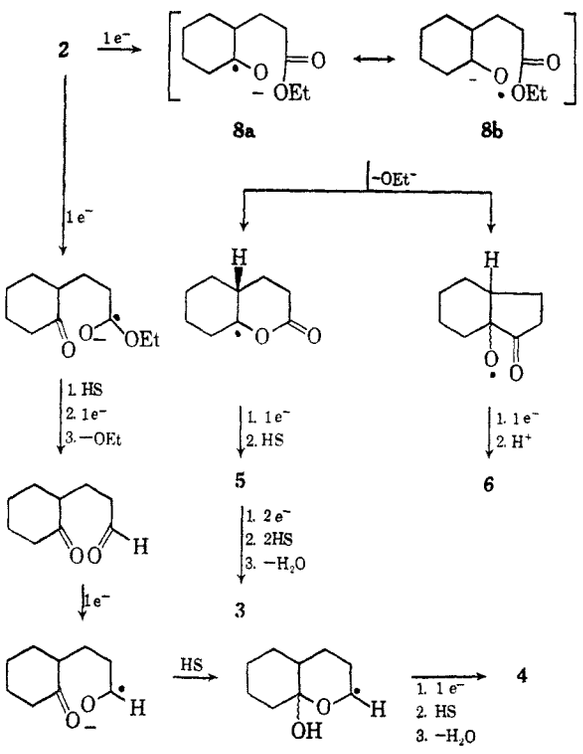
(7) (a) I. J. Borowitz and G. Gonis, *Tetrahedron Letters*, 1151 (1964); (b) I. J. Borowitz, G. Gonis, R. Kelsey, R. Rapp, and G. J. Williams, *J. Org. Chem.*, **31**, 3032 (1966); (c) S. J. Etheredge, *ibid.*, **31**, 1990 (1966). We are indebted to Professor Borowitz for providing us with generous samples of compounds **4** and **7**.

(8) This product has been characterized by Gutsche[2b] and his data support the structural assignment.

$-CH_2CH_2O-$ (distorted triplet at δ 4.22 corresponding to 2 H). Comparison with an authentic sample[7b] verified the structural assignment. The 6-ketononanolide formed in this reaction is a secondary product arising from the oxidation of **4** with Jones' reagent. Pure **4** gave a high yield of **7** on oxidation with Jones' reagent in acetone at 0°.[9]

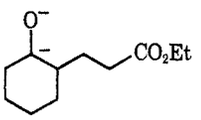
One possible rationalization for the products formed in this reaction is shown in Scheme II. It is particu-

SCHEME II



larly interesting that the reducing metal employed in the reduction of keto esters of type **2** plays a major role in determining the products of the reduction. Although the exact product distribution was quite erratic from run to run, in no case have we obtained appreciable quantities of **6** or its further reduction products. When sodium is used as the reducing agent the predominant products arise from the formation of a new carbon–carbon bond.[2b] In contrast, the use of lithium leads to predominant formation of a new carbon–oxygen bond. In both cases the major products of the reaction can be readily explained by an initial one electron reduction to produce radical anion **8**. Although there are no data available with which to compare the ease of reduction of aliphatic ketones and esters, in the aromatic series the ketones are more readily reduced than the esters[10] and this is in agreement with preferential formation of the ketone radical anion. A radical anion such as **8** is capable of undergoing further reaction at either carbon or oxygen (an ambident anion[11]). It has been well established that in the reactions of ambident ions[12] (*e.g.*, the anions of phenols, pyrroles, nitro compounds, enols, etc.) the nature of the cation plays an important part in determining the products of the reaction. It is generally accepted that lithium salts are more highly associated than salts of other alkali metals and it is possible that in the reduction of **2** with lithium the radical anion exists chiefly as an ion pair (particularly at the relatively high concentrations used in this study) and leads to preferential reaction at oxygen.[13,14] There is, however, little information about the importance of ion pairs or reactions of ambident anions in liquid ammonia solution.

A second possibility for the difference in products under the different reaction conditions would be that lithium, with its higher reducing potential, leads to formation of a dianion such as **9**, which undergoes



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preferential reaction at oxygen. The only evidence in the literature which bears on the reactivities of 1,2-dianions such as **9** is the studies on the alkylation and acylation of dialkali salts of diarylketones.[15] When these reactions are carried out with the dilithium, disodium, and dipotassium salts in liquid ammonia, the reaction takes place exclusively at carbon. Furthermore, the reaction fails with ketones other than those of the diaryl type.[15d] Only when ether was used as a solvent does any reaction occur at oxygen.[15a] It is obvious, however, that considerably more information about dissolving metal reductions is necessary before processes of the type discussed in this paper can be thoroughly understood.

Experimental Section[16]

Reduction of Ethyl 3-(2-Ketocyclohexyl)propionate with Lithium–Liquid Ammonia.—To a refluxing solution of 7.51 g (1.08 g-atoms) of lithium in 2 l. of liquid ammonia (distilled from sodium) was added, with stirring and under nitrogen, a solution of 51.05 g (0.257 mole) of **2**[17] in 200 ml of anhydrous ether over

(9) Jones' reagent appears to provide a convenient method for the oxidative cleavage of enol ether double bonds. Further examples of the utility of this method will be provided at a later date.

(10) P. Zuman, "Organic Polarographic Analysis," The Macmillan Co., New York, N. Y., 1964, p 105.

(11) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955).

(12) For a recent review, see R. Gompper, *Angew. Chem. Intern. Ed, Engl.*, **3**, 560 (1964).

(13) N. Kornblum, R. Seltzer, and P. Haberfield, *J. Am. Chem. Soc.*, **85**, 1148 (1963). These authors have suggested that, contrary to previous postulates, ion-pair formation leads to predominant alkylation at oxygen in the alkylation of phenol salts and enolate anions.

(14) For evidence that ion pairs are important in the reactions of aromatic radical anions, see A. Krapcho and A. A. Bothner-By, *J. Am. Chem. Soc.*, **81**, 3658 (1961).

(15) (a) W. Schlenk and E. Bergman, *Ann.*, **464**, 28 (1928); (b) P. J. Hamrick, Jr. and C. R. Hauser, *J. Am. Chem. Soc.*, **81**, 493 (1959); (c) D. V. Ioffe, *J. Gen. Chem. USSR*, **34**, 3960 (1964); (d) J. A. Gautier, M. Miocque, C. Fauran, and M. d'Engenieres, *Bull. Soc. Chim. France*, 3162 (1965); (e) S. Selman and J. F. Eastham, *J. Org. Chem.*, **30**, 3804 (1965); (f) E. L. Anderson and J. E. Casey, Jr., *ibid.*, **30**, 3959 (1965).

(16) All boiling points are uncorrected. The infrared spectra were recorded on a Beckman IR-8 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 instrument using tetramethylsilane as an internal standard. The mass spectra were determined on a Nuclides Analysis Associates Model 12-90-G mass spectrometer. Gas chromatography studies utilized an Aerograph A-90-P or F & M Model 700 gas chromatograph and a Beckman 10-in. recorder equipped with a Disc Integrator. Unless otherwise stated, magnesium sulfate was employed as the drying agent. Microanalyses were performed by Hufmann Laboratories.

(17) G. Stork, A. Brizzolara, H. Landesman, J. Szmuskovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

a period of 30 min. After the addition was complete, the mixture was stirred at reflux for an additional 30 min, cooled in a Dry Ice bath, and excess lithium was destroyed by the addition of solid ammonium chloride. The ammonia was allowed to evaporate overnight, methylene chloride was added, and the mixture was acidified with 3% hydrochloric acid. The methylene chloride was separated and the aqueous layer extracted with additional methylene chloride. The combined organic layer was washed with saturated sodium bicarbonate solution, brine, and dried. Removal of the solvent afforded 38.99 g of crude product which was dissolved in 300 ml of acetone and 20 ml of a 2.67 *M* solution of chromium trioxide in aqueous sulfuric acid[4] was added dropwise. Work-up in the usual manner afforded 27.13 g of crude neutral product. Vpc analysis[18] indicated the presence of 60% **3**, 22% **4**, 8% **5**, 8% **6**, and 2% **7** of the total vpc volatile material.

On standing a small amount of crystalline material separated from the crude product and was collected and recrystallized from ether to afford white prisms, mp 69–71°. Further purification by sublimation at 60–65° (0.02 mm) afforded the pure product, mp 69.5–71°, which was identified as **6-ketononanolide** (**7**). The product exhibited infrared absorption[19] at 1730 (lactone carbonyl), 1708 (ketone), and 1210 cm^{-1} (C–O), nmr absorption[19] at δ 4.22 (2 H, distorted triplet, $-CH_2CH_2O$), 2.24 (8 H, multiplet), and 1.75 (4 H, multiplet), and an ultraviolet absorption maximum at λ_{max}^{EtOH} 280 mμ (ϵ 36).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29; mol wt, 170. Found: C, 63.40; H, 8.17; mol wt, 170 (mass spectral).

(18) A 5 ft × 0.25 in. column packed with GE-SF-96 on 60–80 mesh firebrick was employed.

(19) Determined as a solution in carbon tetrachloride.

The compound was identical (infrared spectrum and mixture melting point) with an authentic sample of **7**.

A small portion of the crude product was distilled to afford a low-boiling fraction [bp 80–83° (16 mm)] which was shown by vpc[18] to be a mixture of **3** (first eluted) and **4**. Separation by preparative vpc afforded the pure compounds. *trans*-4H-4a,-5,6,7,8,8a-Hexahydro-1-benzopyran (**3**) was obtained as a colorless liquid which exhibits infrared absorption[19] at 3080 (olefinic hydrogens) and 1650 cm^{-1} (enol ether double bond) and nmr absorption[19] at δ 6.26 (1 H, doublet, J = 6 cps, $-CH{=}CHO-$), 4.54 (1 H, multiplet, $OCH{=}CHCH_2$), 3.35 (1 H, br, half-band width 17 cps, OCH), and unresolved absorption in the region 2.20–1.00 (11 H).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21; mol wt, 138. Found: C, 78.25; H, 10.23; mol wt, 138 (mass spectral).

5,6,7,8-Tetrahydrochroman (**4**) was obtained as a colorless liquid which exhibits infrared absorption[19] at 1698 cm^{-1} (enol ether double bond) and nmr absorption[19] at δ 3.83 (2 H, distorted triplet, $-CH_2O-$) and unresolved absorption in the region 2.40–1.42 (12 H). The compound was identical (infrared spectrum and vpc retention time) with an authentic sample.[7]

The remaining compounds were obtained from the residue of the above distillation by preparative vpc. *trans*-Octahydrocoumarin (**5**) was identified by comparison with an authentic sample.[6c] 6-Hydroxybicyclo[4.3.0]nonan-7-one[2b] was obtained as a colorless liquid which exhibited infrared absorption[19] at 3500–3200 (hydroxyl) and 1740 cm^{-1} (cyclopentanone carbonyl) and nmr absorption[19] at δ 3.58 (1 H, singlet, –OH) and complex absorption in the region 2.45–1.30 (13 H).

Registry No.—**2**, 4095-02-7; **3**, 14072-77-6; **4**, 7106-07-2; **5**, 14072-79-8; **6**, 14072-80-1; **7**, 13030-92-7.

The Structure of Dicyclopentadienedicarboxylic Acid and Its Dihydro and Tetrahydro Derivatives

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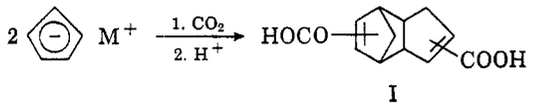
Carbonation of the sodium salt of cyclopentadiene produces a single dimeric acid (II) as the main product. Hydrogenation of II with 1 mole of hydrogen gives 8,9-dihydrodicyclopentadiene-9-*endo*-dicarboxylic acid and with 2 moles of hydrogen 8,9,3,4-tetrahydrodicyclopentadiene-9-*endo*-3-*exo*-dicarboxylic acid (VI) is obtained. The diacid chloride of VI cyclizes thermally with elimination of hydrochloric acid to the acyl chloride of VIa.

Dicyclopentadienedicarboxylic acid (I) was first prepared by Thiele[1] through carbonation of cyclopentadienylpotassium accompanied by spontaneous



I

dimerization. It has also been prepared by carbonation of the corresponding cyclopentadienylsodium,[2–4] or Grignard reagent[5] and by the reaction of amylsodium on bicyclo[2.2.1]heptadiene.[6] Most of the synthetic procedures have a common feature, namely a solid state (suspended particles) dimerization which appears to be stereospecific. Several different melting points for the dimer acid have been reported covering the range between 200 and 212° because its melting process is decomposition induced and depends on the thermal history of the sample just prior to melting and also on the melting point apparatus used. Earlier structures postulated by Alder[7] were discarded when more recent spectroscopic[8,9] and proton magnetic resonance (pmr)[10] data established that the carboxyl groups of the dimer acid are conjugated with the double bonds. Alder[7] also postulated the *endo* configuration for the dimer by analogy with the adduct[11] of cyclopentadiene carboxylate with maleic anhydride and Peters[9b] obtained ultraviolet data which renders some support for the *endo* configuration, but chemical evidence to this effect is lacking. In addition to the existing uncertainty for the configuration (*endo* or *exo*) of the dicyclopentadiene skeleton, the position of the two carboxyl groups has not been established and attempts[12] to determine their position by a Schmidt or

(1) J. Thiele, *Ber.*, **33**, 666 (1900); **34**, 68 (1901).

(2) H. K. Wiese, U. S. Patent 2,781,395 (1957).

(3) C. A. Cohen and L. A. Mikeska, U. S. Patent 2,716,662 (1955) and Reissue 24,123 (1956).

(4) K. Ziegler, H. E. Kühlhorn, and K. Hafner, *Ber.*, **89**, 434 (1956).

(5) C. Courtot, *Ann. Chim.*, **4**, 75 (1915).

(6) R. A. Finnegan and R. S. McNees, *Tetrahedron Letters*, No. 17, 755 (1962).

(7) K. Alder, F. H. Flock, A. Hausweiler, and R. Reeber, *Ber.*, **87**, 1752 (1954).

(8) O. C. Slotterbeck and H. K. Wiese, U. S. Patent 2,818,430 (1957).

(9) (a) D. Peters, *J. Chem. Soc.*, 1761 (1959); (b) 1042 (1961).

(10) H. K. Wiese, Esso Research and Engineering Co., Linden, N. J., private communication.

(11) K. Alder and G. Stein, *Ann.*, **514**, 2 (1934).

(12) R. J. Day, Thesis, University Microfilms Inc., Ann Arbor, Mich.