The Reductive Cyclization of Keto Esters[1]

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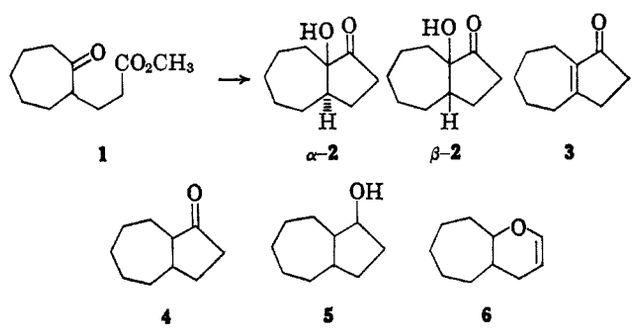
Methyl β-(2-ketocycloheptane)propionate, available from the ring enlargement of cyclohexanone with N-nitrosopyrrolidone-2, has been shown to undergo reductive cyclization upon treatment with sodium in ammonia or sodium naphthalenide in tetrahydrofuran. With sodium in ammonia as the reducing agent the 30–35% yield of volatile product includes the *cis* and *trans* isomers of 7-hydroxybicyclo[5.3.0]decan-8-one (**2**), bicyclo[5.3.0]-dec-1(7)-en-8-one (**3**), bicyclo[5.3.0]decan-8-one (**4**), 8-hydroxybicyclo[5.3.0]decane (**5**), and 4a,9a-dihydrocyclohepta[*b*]pyran (**6**). With sodium naphthalenide as the reducing agent, the 30–35% yield of volatile product is comprised mainly of the *cis* and *trans* isomers of the hydroxy ketone **2**, with one of the isomers (stereochemical designations uncertain) predominating by a ratio of 3.5:1 to 7:1. The scope and limitations of the sodium naphthalenide procedure were explored with methyl β-(2-ketocyclohexane)propionate and methyl β-(2-ketocyclopentane)propionate (to test the effect of ring size), with methyl α-(2-ketocyclohexane)acetate and methyl γ-(2-ketocyclohexane)butyrate (to test the effect of side-chain length), and with *t*-butyl β-(2-ketocycloheptane)propionate (to test the effect of the ester moiety). Only the compound containing a seven-membered ring, a three-membered side chain, and a methyl ester function (*i.e.*, **1**) gave a satisfactory yield of α-hydroxy ketone. In addition to sodium naphthalenide, various other metal and aromatic hydrocarbon combinations were also investigated. It was found that potassium naphthalenide and sodium phenanthrenide were comparable with sodium naphthalenide, that sodium biphenylide was somewhat less effective, that lithium naphthalenide was almost completely ineffective, and that sodium anthracenide failed to act as an electron-transfer reagent but instead underwent reduction to dihydroanthracene. The metal arylenide promoted reductive cyclization appears to have some utility for the preparation of the hydroazulene ring system but to be otherwise quite limited in scope.

The availability of methyl β-(2-ketocycloheptane)-propionate (**1**) and several of its ring-alkylated derivatives from the reaction of N-nitrosopyrrolidone-2 with cyclohexanone and alkylcyclohexanones[3] directed our attention to these keto esters as possible precursors to bicyclic compounds containing the hydroazulene ring system. To achieve this conversion it is necessary to generate a bond between the two carbonyl carbon atoms, a process which is known to take place under the influence of an electropositive metal. When the reaction involves the carbonyl groups of aldehydes or ketones it is known as the pinacol reduction, and when it involves the carbonyl groups of esters it is known as the acyloin condensation. Although there are but few references in the literature concerning the mixed reductive coupling of ketones with esters, a consideration of the possible mechanisms for the pinacol reduction and the acyloin condensation indicates that the mixed reaction should proceed in a comparable fashion. On this premise, an investigation of the reductive cyclization of several keto esters, principally methyl β-(2-ketocycloheptane)propionates, was undertaken.

Reductive Cyclization of Methyl β-(2-Ketocycloheptane)propionate (1) *via* Sodium in Ammonia.—Choosing a set of conditions that had been carefully worked out for acyloin condensations,[4] methyl β-(2-ketocycloheptane)propionate (**1**) was treated with sodium in a solution of ether and ammonia. From a reaction carried out with a 0.04 *M* solution of **1** and 4 g-atom equiv of sodium there was obtained, in 30–35% yield, a volatile fraction which was shown to contain at least six products including the *trans* and *cis* isomers of 7-hydroxybicyclo[5.3.0]decan-8-one (α-2 and β-2) (3.5 parts), bicyclo[5.3.0]dec-1(7)-en-8-one (**3**) (trace), bicyclo[5.3.0]decan-8-one (**4**) (1.6 parts), 8-hydroxybicyclo[5.3.0]decane (**5**) (1.0 part), and a compound tentatively identified as 4a,9a-dihydrocyclohepta[*b*]pyran (**6**) (1.6 parts). The structures of these products have been established by the methods outlined below.



The *trans* and *cis* isomers of **2** (see subsequent discussion for tentative assignments of configuration), designated for the purposes of discussion as the α and β isomers, were formed in a ratio of 3.6:1. Each isomer has an elemental analysis compatible with a $C_{10}H_{16}O_2$ formula and possesses bands in the infrared characteristic of an hydroxyl and a cyclopentanone function.[5a,b] The ultraviolet spectra of the two isomers reveals no conjugated unsaturation,[6] and the nuclear magnetic resonance (nmr) spectrum establishes the absence of vinyl protons. Upon treatment with iodine, both α-2 and β-2 lose water and form the α,β-unsaturated ketone **3**. Conversion of α-2 and β-2 to the 2,4-dinitrophenylhydrazone proceeds with loss of the hydroxyl group *via* dehydration and yields a product identical with that obtained directly from **3**. Assuming that no molecular rearrangement occurs during the dehydration

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(2) (a) Shell Oil Co. Fellow 1960–1961, Wheeler Fellow 1961–1962, and University Fellow 1962–1963. (b) Postdoctoral research associate 1965–1966.

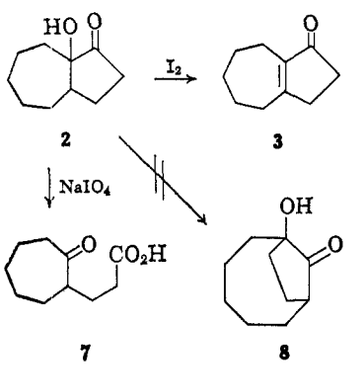
(3) C. D. Gutsche and I. Y. C. Tao, *J. Org. Chem.*, **28**, 883 (1963); **32**, 1778 (1967).

(4) J. C. Sheehan and R. C. Coderre, *J. Am. Chem. Soc.*, **75**, 3997 (1953).

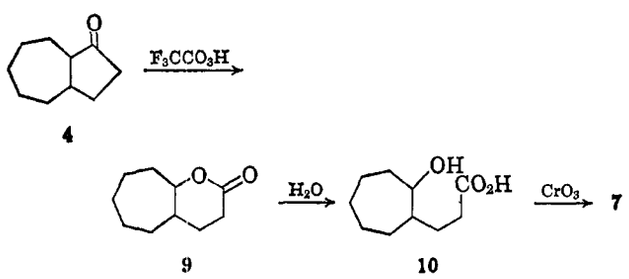
(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958: (a) p 96, (b) p 132, (c) p 34, and (d) p 114.

(6) A. E. Gillam and E. S. Stern, "An Introduction to Electronic Absorption Spectroscopy," 2nd ed, Edward Arnold Ltd., London, 1957, p 103; A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Macmillan and Co., New York, N. Y., 1964, p 55.

reactions, the formation of **3** and its derivative establishes the ring structure of α-**2** and β-**2**, for **3** is a known compound and has been prepared by an unequivocal route.[7] The unusual ease with which water is lost from **2**, however, prompted still another assay, *viz.* the oxidative conversion of **2** to β-(2-ketocycloheptane)-propionic acid (**7**) with sodium metaperiodate. The obtention of **7** from this reaction thus rules out a β-hydroxy ketone structure as well as the 1-hydroxybicyclo[5.2.1]decan-10-one (**8**) structure (which might conceivably have formed under the conditions as a result of a base-catalyzed α-hydroxy ketone rearrangement).[8]



The structure of the α,β-unsaturated ketone **3** was indicated by its infrared and ultraviolet spectral characteristics and was definitively established by comparison with material obtained *via* and independent synthesis.[7] Catalytic reduction of **3** yielded the corresponding saturated ketone **4**, a known compound, which proved to be identical with another of the products from the reductive cyclization. Finally, as a check on the absence of molecular rearrangement during its preparation, **4** was subjected to a series of degradation reactions (see the sequence **4** → **9** → **10** → **7**) to yield **7** in which the seven-membered ring is still intact.



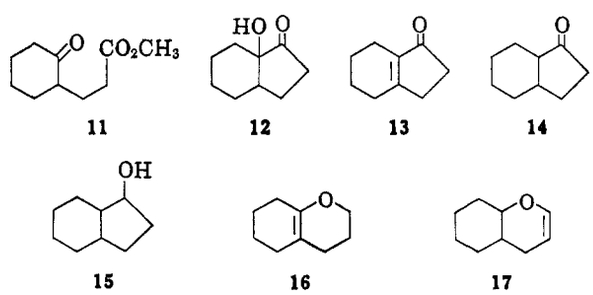
The structure of the saturated alcohol **5** is confirmed by an elemental analysis compatible with a $C_{10}H_{18}O$ formula, an infrared absorption characteristic for a hydroxyl group,[5a] and an nmr spectrum lacking vinyl proton resonances but containing a resonance characteristic for an hydroxyl group.[9a] Upon treatment with chromic acid, **5** is converted to the saturated ketone **4** which, in turn, can be reconverted to **5** upon treatment with sodium borohydride. The isomer of **5** obtained from the reductive cyclization has the same retention time on the vapor phase chromatography (vpc) column as the isomer obtained by sodium borohydride reduction of **4**; presumably, they are configurationally as well as structurally identical.

The structure of **6** has been tentatively established on the basis of an elemental analysis compatible with a $C_{10}H_{16}O$ formula, infrared absorptions characteristic of an olefin and an ether,[5c,d] and an nmr spectrum showing the presence of two vinyl protons and a proton α to an ether oxygen function.[9b]

Variations in the experimental procedures in the sodium in ammonia reduction led to certain changes in the ratio of products formed. In the initial experiments ammonia was used directly from the tank without purification. It was subsequently found, however, that a pretreatment of the ammonia with sodium (to remove water and other impurities) resulted in a somewhat better yield of **2** (25% compared with 17%) and a reduced amount of **5**.[10] Increasing the ratio of gram-atom equivalents of sodium to mole equivalents of keto ester from 2 to 4 increased the amount of **2**, but increases beyond this ratio diminished the amount of **2** and increased the amount of **4** and **5**. When the concentration of keto ester was reduced from 0.04 *M* (the concentration used in most of the experiments) to 0.004 *M*, the major product was the saturated ketone **4**, obtained in 45% yield. Unfortunately, however, this reaction is rather impractical from the preparative standpoint because of the large volumes of ammonia and ether that are required for small amounts of reactants.

Reductive Cyclization of Methyl β-(2-Ketocyclohexane)propionate (11) *via* Sodium in Ammonia.—Employing the conditions for the sodium in ammonia reaction that were used for the reductive cyclization of **1**, the reaction of methyl β-(2-ketocyclohexane)-propionate (**11**) yielded 37% of a volatile product which contained at least five components including 6-hydroxybicyclo[4.3.0]nonan-7-one (**12**) (5.5 parts), bicyclo[4.3.0]non-1(6)-en-7-one (**13**) (1.5 parts), bicyclo[4.3.0]nonan-7-one (**14**) (trace), and two other materials designated as olefin A (1 part) and olefin B (1 part). The structures of these products were assigned on the basis of the following data.

The major product of the cyclization, formed in 20% yield, is assigned the structure of the hydroxy ketone **12** on the basis of an elemental analysis compatible with a $C_9H_{14}O_2$ formula, infrared absorptions characteristic of an hydroxyl and a cyclopentanone function,[5a,b] and its facile dehydration to the α,β-unsaturated ketone **13**. An authentic sample of **13**, a known compound,[11] was prepared by a Stobbe condensation of cyclohexanone with diethyl succinate followed by acid-catalyzed



(7) N. Jones, H. T. Taylor, and E. Rudd, *J. Chem. Soc.*, 1324 (1961).

(8) Y. Mazur and M. Nussim, *Tetrahedron Letters*, No. 22, 817 (1961).

(9) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Vol. 1, Varian Associates, Palo Alto, Calif., 1962: (a) see isopropyl alcohol (spectrum 44) and (b) see dihydropyran (spectrum 111).

(10) H. L. Dryden, Br. B. M. Webber, R. R. Burtner, and J. A. Cella [*J. Org. Chem.*, **26**, 3237 (1961)] found that undistilled ammonia contains traces of iron and other transition metals which may exert catalytic effects on certain of the reactions taking place in the presence of sodium.

(11) W. S. Johnson, C. E. Davis, R. H. Hunt, and G. Stork, *J. Am. Chem. Soc.*, **70**, 3021 (1948).

cyclization. The product proved to be identical with the dehydration product from **12** and to be identical (by vpc retention time comparison) with one of the minor products in the mixture from reductive cyclization. Catalytic reduction of the authentic sample of **13** yields the corresponding saturated ketone **14** which also was shown to be identical (by vpc retention time comparison) with one of the minor products in the mixture from reductive cyclization.

Olefin A and olefin B, obtained as low-boiling components, have elemental analyses compatible with a $C_9H_{14}O$ formula and infrared absorptions characteristic of olefinic and ether moieties.[5c,d] The nmr spectrum of olefin A possesses no resonances from vinyl protons but shows bands characteristic for a pair of hydrogens adjacent to an ether oxygen,[9b] commensurate with structure **16**. The nmr spectrum of olefin B shows bands characteristic for a pair of vinyl protons; although the presence of a resonance from a bridgehead hydrogen adjacent to the ether oxygen is equivocal, structure **17** is felt to be the most likely one for this material. More extensive work in this series, carried on in another laboratory,[12] has supported this contention.

Under high-dilution conditions the sodium in ammonia method yielded 38% of a volatile product from **11**, the major constituent of which (56%) was bicyclo-[4.3.0]nonan-7-one (**15**).

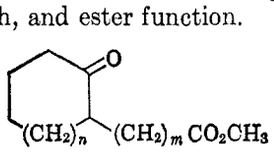
Reductive Cyclization of Methyl β-(2-Ketocycloheptane)propionate *via* Sodium Arylenides in Tetrahydrofuran.—With sodium and ammonia as the cyclization agent the anticipated α-hydroxy ketone is accompanied by rather large amounts of other products, including the α,β-unsaturated ketone, the saturated ketone, and the saturated alcohol. On the premise that the products of over reduction might be minimized by providing the keto ester with electrons at a lower potential, naphthalene rather than ammonia was investigated as an electron-solvating agent. Sodium is known to readily transfer an electron to naphthalene to form a radical anion[13] which, under certain circumstances, can pass the added electron along to other entities in the system. Thus, the naphthalenide radical anion has been used as a polymerization initiator[14] and as a reagent for effecting the Wurtz coupling reaction of alkyl halides.[15] It has been reported to fail as a acyloin-condensing agent,[15c] but fortunately this was unknown to us at the inception of our work.

When a tetrahydrofuran solution of sodium naphthalenide was treated with the keto ester **1**, reductive cyclization occurred, and a mixture qualitatively comparable with that from the sodium in ammonia method was obtained. However, the amount of hydroxy ketone **2** was considerably increased, in apparent support of the rationale for the experiment. A series of runs was carried out with varying ratios of reactants, and it was established that a useful ratio is 4 g-atoms of sodium, 2–4 moles of naphthalene, and 1 mole of keto ester. Under these conditions a 30–35% yield of volatile product is obtained which consists almost entirely of a mixture of α-**2** and β-**2** with the former predominating by a factor of *ca.* 4. When the keto ester **11** was treated under comparable conditions, however, only an 11% yield of volatile product is obtained which consists of 76% **12** and 17% **14**.

In the hope of finding a correlation between the electron affinity of the aromatic hydrocarbon employed and its efficiency as a reductive cyclizing reagent, several additional compounds were tested. Phenanthrene and biphenyl behaved qualitatively like naphthalene and produced the hydroxy ketones α-**2** and β-**2** in yields of 36 and 10–25%, respectively. Anthracene, however, underwent reduction under the conditions of the reaction and yielded dihydroanthracene, the hydrogen presumably being supplied by the keto ester; consequently, no cyclization products whatsoever were obtained. The failure of sodium anthracenide to act as an electron-transfer reagent is in accord with the greater electron affinity of anthracene compared with naphthalene.[16]

A few experiments with metals other than sodium were also carried out. When potassium naphthalenide was used, the results remained essentially unaltered from those with sodium naphthalenide; the yield of volatile product was 36%, and the ratio of α-**2** to β-**2** was 3.3. With lithium naphthalenide, on the other hand, only a 2% yield of hydroxy ketone was obtained, and the remainder of the product consisted of high-boiling materials.

Scope and Limitations of Reductive Cyclization *via* Sodium Naphthalenide.—Having ascertained the optimum conditions for the reductive cyclization of methyl β-(2-ketocycloheptane)propionate (**1**) *via* sodium naphthalenide, it was of interest to determine to what extent the method could tolerate structural variations in the keto ester. Accordingly, experiments were carried out to assess the effect of changes in ring size, side-chain length, and ester function.



1, $n=2$; $m=2$
11, $n=1$; $m=2$
18, $n=0$; $m=2$
19, $n=1$; $m=1$
20, $n=1$; $m=3$

When the sodium naphthalenide procedure was applied to the six-membered keto ester, methyl β-(2-

(12) R. G. Carlson and R. G. Blecke [*J. Org. Chem.*, in press] have studied the reductive cyclization of compound **11** *via* sodium and lithium in liquid ammonia. Under their conditions, not significantly different from those described in this paper, products **12**, **16**, and **17** were obtained but in quite different ratios. The explanation for this disparity of results is not apparent, although it has been noted by both groups of investigators that the reductive cyclization tends to be capricious.

(13) N. D. Scott, J. F. Walker, and V. L. Hensley, *J. Am. Chem. Soc.*, **58**, 442 (1936); A. Jeanes and R. Adams, *ibid.*, **59**, 2608 (1937); J. F. Walker and N. D. Scott, *ibid.*, **60**, 951 (1938); T. L. Chu and S. Chi-Yu, *ibid.*, **76**, 3367 (1954); T. R. Tuttle, R. L. Ward, and S. I. Weissman, *J. Chem. Phys.*, **25**, 189 (1956); R. L. Ward and S. I. Weissman, *J. Am. Chem. Soc.*, **79**, 2086 (1957).

(14) D. Lipkin, D. E. Paul, J. Townsend, and S. I. Weissman, *Science*, **117**, 534 (1953); M. Szwarc, *Nature*, **178**, 1168 (1956); M. Szwarc, M. Levy, and R. Milkovich, *J. Am. Chem. Soc.*, **78**, 2656 (1956); G. J. Hoijtink, *Chem. Weekblad*, **56**, 55 (1960); A. V. Tobolsky and D. B. Hartley, *J. Am. Chem. Soc.*, **84**, 1391 (1962).

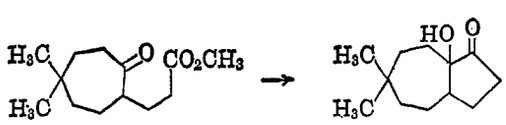
(15) (a) N. D. Scott and J. F. Walker, U. S. Patent 2,150,039 (March 7, 1939); (b) M. Szwarc, *Macromol. Chem.*, **35**, 132 (1959); (c) H. Gusten and L. Horner, *Angew. Chem.*, **74**, 455 (1962); L. Horner and H. Gusten, *Ann.*, **652**, 99 (1962).

(16) See E. de Boer, *Advan. Organometal. Chem.*, **2**, 115 (1964), for a review which includes data on the electron affinities of aromatic hydrocarbons (pp 119–127).

ketocyclohexane)propionate (**11**), the hydroxy ketone **12** was obtained in only 9% yield. When the five-membered keto ester, methyl β-(2-ketocyclopentane)-propionate (**18**), was used, the corresponding hydroxy ketone was obtained in but 2% yield. Thus, the seven-membered keto ester proves to react much more effectively in the reductive cyclization than its lower homologs. The effect of side-chain length was demonstrated by subjecting methyl α-(2-ketocyclohexane)-acetate (**19**), methyl β-(2-ketocyclohexane)propionate (**11**), and methyl γ-(2-ketocyclohexane)butyrate (**20**) to reductive cyclization with sodium naphthalenide. Of these, only the three-membered side-chain compound, **11**, yielded a significant amount of hydroxy ketone (see above); the four-membered side-chain compound, **18**, yielded only 2% of hydroxy ketone, and the two-membered side-chain compound yielded none whatsoever. Thus, the three-membered side-chain compounds prove to react more effectively in the reductive cyclization than either the lower or higher homologs.

On the premise that the high-boiling material produced in the cyclization might be the result of intermolecular acyloin condensation, an ester of increased steric bulk was investigated in the hope that such condensation might be curtailed. The *t*-butyl ester corresponding to **1** was prepared (by hydrolysis to the keto carboxylic acid followed by treatment with isobutylene and sulfuric acid[17]) and subjected to reductive cyclization with sodium naphthalenide. The hydroxy ketone **2** was obtained in only 18% yield.

That the reaction possesses at least some generality within the methyl β-(2-ketocycloheptane)propionate series, however, was demonstrated by the reductive cyclization of methyl β-(4,4-dimethyl-2-ketocycloheptane)propionate (**21**) to 4,4-dimethyl-7-hydroxy-8-ketobicyclo[5.3.0]decane (**22**) in 27% yield.



21 **22**

Discussion of Results.—The reduction of the carbonyl function by means of electrons supplied by metals is the basis for a variety of preparative methods in organic chemistry. In the presence of sufficiently strong proton donors, metals such as zinc have the capacity for reducing aldehydes and ketones to the corresponding methyl or methylene function (Clemmensen reduction); in the presence of weaker proton donors, the reduction usually proceeds only to the alcohol (*e.g.*, Bouveault–Blanc reduction of esters); with very weak proton donors or under aprotic conditions, the reduction frequently proceeds in a bimolecular fashion to give a coupling product. Representative of this last variety are the pinacol and acyloin reductions, and it is with these that the present discussion is primarily concerned. Both the pinacol reduction[18] and the acyloin condensation[19] are generally regarded as proceeding *via* a free-radical coupling mechanism.[20] That radical anions (ketyls) do exist in solutions containing ketones and alkali metals has been demonstrated by a variety of techniques, most recently by electron spin resonance measurements on ketones such as benzophenone and di-*t*-butyl ketone.[21] It is a reasonable postulate, therefore, that pinacols arise simply by the coupling of two ketyl species. However, an alternative mechanism involving the formation of a dianion (*e.g.*, addition of an electron to the ketyl) followed by nucleophilic attack on the parent ketone might also be advanced on the basis of the following observations. (a) Disodium benzophenone reacts more rapidly than monosodium benzophenone with ethyl iodide.[22] (b) Olefins react at the dropping mercury electrode to take up the first electron in a reversible, rate-determining step and a second electron in a rapid, irreversible step;[23] carbonyl compounds may possibly behave in a comparable fashion.

The reductive cyclization of keto esters such as **1** is assumed to be initiated by the addition of an electron to the ketone carbonyl group. Although redox potentials for aliphatic esters have not been reported, the esters of aromatic carboxylic acids are known to be less easily reduced than their ketonic counterparts.[24] On the premise that it is easier to add a second electron to the ketone radical anion (to give a ketone dianion) than to add an electron to the carbomethoxy group (to give a diketyl species), it is postulated that the coupling step proceeds *via* a nucleophilic displacement by the ketone dianion on the carbonyl group of the ester. Consistent with this interpretation, although providing no compelling support for it, is the observation that the yield of cyclization product diminishes as the hindrance around the ester carbonyl increases (*e.g.*, the *t*-butyl ester corresponding to **1** gives an 18% yield of **2**, while the methyl ester (**1**) gives a 30–35% yield of product). The sodium surface effect, advanced in explanation for the excellent yields of medium-ring acyloins from dibasic esters,[25] appears to play no part in the present reaction. Although sodium naphthalenide has been shown to be ineffective in the acyloin condensation,[15c] the keto ester **1** undergoes reductive cyclization in sodium naphthalenide solutions containing no undissolved sodium.

Regardless of the sequence of electron transfers and bond making processes, the product resulting from the two-electron reduction is the anion of the α-hydroxy ketone (see Scheme I). Under the conditions of the sodium naphthalenide experiment, this may be sufficiently stable to survive without alteration until the reaction mixture is hydrolyzed (however, see following discussion). Under the conditions of the sodium in ammonia experiment, however, a certain fraction of this intermediate is converted to other compounds including the α,β-unsaturated ketone, the saturated

(17) W. S. Johnson, A. L. McCloskey, and D. A. Dunnigan, *J. Am. Chem. Soc.*, **72**, 514 (1950).

(18) See R. C. Fuson, *Record Chem. Progr. Kresge-Hooker Sci. Lib.*, **12**, 1 (1951), for a review of the pinacol reduction.

(19) See S. M. McElvain, *Org. Reactions*, **4**, 256 (1940), and K. T. Finley, *Chem. Rev.*, **64**, 573 (1964), for reviews of the acyloin condensation.

(20) (a) M. S. Kharasch, E. Sternfeld, and F. R. Mayo, *J. Org. Chem.*, **5**, 362 (1940). (b) E. Van Heyningen, *J. Am. Chem. Soc.*, **74**, 4861 (1952); **77**, 4016 (1955).

(21) N. Hirota and S. I. Weissman, *ibid.*, **82**, 4424 (1960); **83**, 3533 (1961).

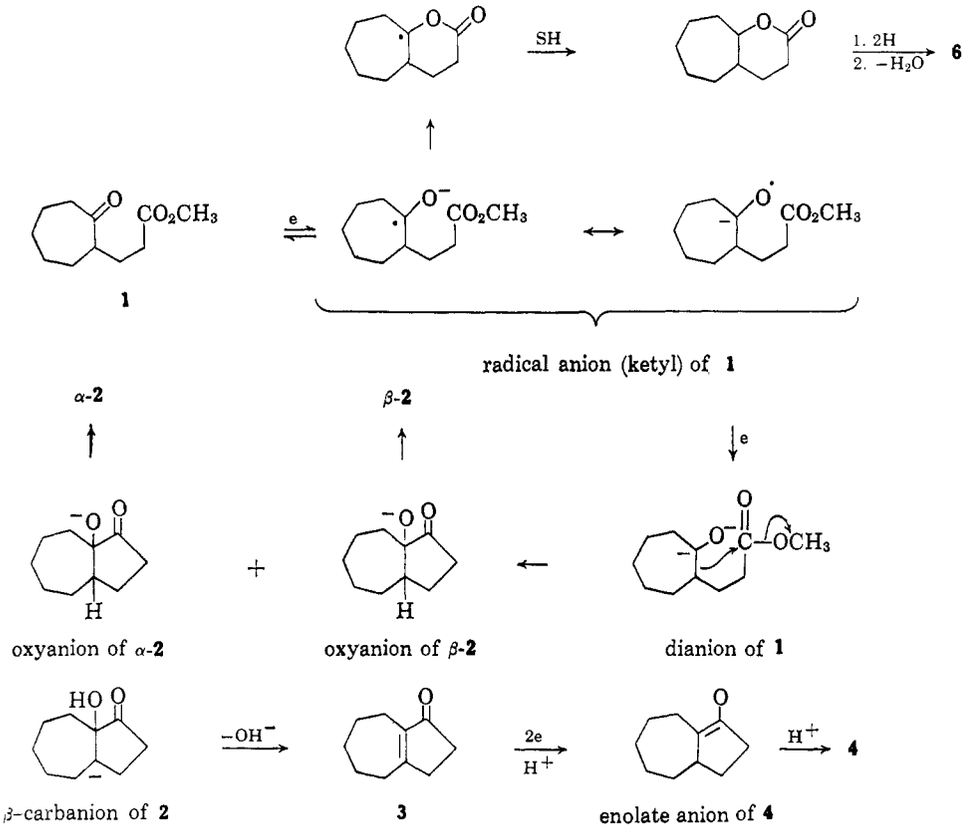
(22) C. B. Wooster and W. E. Holland, *ibid.*, **56**, 2438 (1934).

(23) H. A. Laitinen and S. Wawzonek, *ibid.*, **64**, 1765, 2365 (1942).

(24) See O. H. Muller in "Technique of Organic Chemistry," Vol. I, 3rd ed, A. Weissberger, Ed., John Wiley and Sons, Inc., New York, N. Y., 1960, p 3278.

(25) V. Prelog, *J. Chem. Soc.*, 420 (1950).

SCHEME I
PATHWAYS FOR PRODUCT FORMATION BY REDUCTIVE CYCLIZATION OF METHYL β-(2-KETOCYCLOHEPTANE)PROPIONATES



ketone, and the saturated alcohol. The α,β-unsaturated ketone may form *via* protonation to **2** followed by base-catalyzed elimination of hydroxide to yield **3**. However, the α-hydroxy ketone is so much stronger an acid than any of the other substances in the reaction mixture that the equilibrium concentration of **2** must be exceedingly small. If **3** is a component in the reaction mixture, the formation of the saturated ketone **4** can be interpreted as the product of a conjugate reduction reaction.[26,27a] Examples are known, however, of the removal of the hydroxyl, acyloxy, or aroyloxy group α to a ketone by means of metal reduction,[27b,28] so the α,β-unsaturated ketone is not necessarily an intermediate in the formation of **4**. The saturated alcohol **5** must be the result of reduction of the ketone **4**, a process for which numerous examples are known.[27c]

In addition to the several carbocyclic products formed from **1**, a heterocyclic compound is formed to which the structure **6** has been assigned. This may be interpreted as the result of attack by the ketone oxygen of **1** (either in the radical anion or the dianion form) on the carbomethoxy group to yield a lactone which then suffers further reduction and dehydration to yield **6** as illustrated in Scheme I.

The use of sodium naphthalenide in place of sodium in ammonia for the reductive cyclization results in larger amounts of α-hydroxy ketone and smaller amounts of other reduction products; whether or not this is due to a change in reduction potential of the electron donor is uncertain. Several observations, in fact, suggest that other factors may be equally if not more important. When a mixture containing α-**2** and β-**2** is treated with sodium naphthalenide, a significant amount of the saturated ketone **4** is formed, arising apparently from the β isomer which disappears from the reaction mixture much more rapidly than the α isomer. Similar differences between epimers have been observed in metal and ammonia cleavages of α-ketol derivatives in the steroids, where it has been demonstrated that an axial hydroxyl is more easily replaced than an equatorial hydroxyl.[28e] Thus, the improved yield of hydroxy ketone and the diminished amount of other reduction products may be a function of the α-**2** to β-**2** ratio, and this is probably not dependent upon the reduction potential of the electron donor but, rather, on various steric factors. There is a significant difference in the apparent α-**2** to β-**2** ratio for reactions effected with metal arylenides compared with sodium in tetrahydrofuran where no ammonia or aromatic hydrocarbon is available for electron solvation. In the metal arylenide reactions the ratio is 3.5:1 to 7:1; in the sodium in tetrahydrofuran reaction, however, the ratio is only *ca.* 0.6–0.95, the lower value being obtained after 7.5 hr (25% unreacted starting material) and the higher value after 17 hr (no unreacted starting material). The increase in the ratio is interpreted as a selective removal of the β isomer (see above) in a process which is slower than the initial cyclization step and which may be more dependent than the initial cyclization step on the reduction potential of the electron donor. On the basis of these observations it is postu-

(26) A. J. Birch and D. Phill, *Quart. Rev.*, (London), **4**, 69 (1950).

(27) H. Smith, "Organic Reactions in Liquid Ammonia," Vol. 1, part 2, John Wiley and Sons, Inc., New York, N. Y., 1963: (a) see p 231 for review of this type of reaction, (b) p 179, and (c) p 216.

(28) (a) W. T. Smith, Jr., *J. Am. Chem. Soc.*, **73**, 1883 (1951); (b) C. Amendolla, G. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, 1226 (1954); (c) D. H. R. Barton and C. H. Robinson, *ibid.*, 3045 (1954); (d) A. Zürcher, H. Heuser, O. Jeger, and P. Geistlich, *Helv. Chim. Acta*, **37**, 1562 (1954); (e) J. Elks, G. H. Phillips, T. Walker, and L. J. Wyman, *J. Chem. Soc.*, 4330 (1956); (f) E. S. Rothman and M. E. Wall, *J. Am. Chem. Soc.*, **79**, 3228 (1957).

lated that (a) the *instantaneous* ratio of α-2 to β-2 is a function of the size of the electron donor, and it increases as the size of the electron donor increases; thus, the instantaneous ratio is postulated to increase in going from sodium in tetrahydrofuran to sodium in ammonia to sodium naphthalenide, (b) the *observed* ratio of α-2 to β-2 is a function of the relative rates at which the two isomers undergo further reaction, the β isomer having been demonstrated to be the more reactive, and (c) the rate at which the α and β isomers undergo further reaction is a function of the reduction potential of the electron donor and increases from sodium naphthalenide to sodium in ammonia to sodium in tetrahydrofuran. Thus, the difference in the product distribution when sodium naphthalenide and sodium in ammonia are employed may be partly due to a difference in reduction potentials but may also be a function of the relative proportions in which the α-hydroxy ketones are initially formed.

The stereochemical assignments to α-2 and β-2 are based on the relative ease with which these two compounds undergo reductive dehydroxylation and on the premise that the conversion of the oxyanion of 2 to the β-carbanion of 2 (see Scheme I) is intramolecular. If the latter is true, only the isomer in which the oxygen is *cis* to the β-hydrogen can engage in an intramolecular proton shift. Accordingly, the isomer which undergoes reductive dehydroxylation (*i.e.*, β-2) is assigned the *cis* configuration. Attempts to substantiate this assignment by comparisons of the infrared and nmr spectra of α-2 and β-2 were quite inconclusive, and it is probable that chemical methods or an X-ray crystallographic determination must be resorted to.

The reactions described in this paper add to the very few known examples of acyloin-type condensations between ketones and esters, and they represent the first examples of the reductive cyclization of keto esters. The scarcity of related examples may stem from general disinterest in the reaction but may also be due to the apparently very special circumstances that are necessary for such reactions to take place. Even in the intramolecular systems studied, only the compound containing a cycloheptanone ring, a three-membered side chain, and a methyl ester function furnished product in reasonable yield. Although the method has some preparative utility in the construction of certain hydroazulene systems, it appears that it will require further study and alterations if it is to find application in other systems.

Experimental Section[29]

Reductive Cyclization of Methyl β-(2-Ketocycloheptane)propionate (1). A. With Sodium in Liquid Ammonia under Standard Conditions.—To a solution of 600 ml of anhydrous ether and 900 ml of anhydrous liquid ammonia (distilled from sodium) contained in a 3-l. flask was added 5.52 g (0.24 g-atom) of sodium metal. The system was swept with nitrogen for 0.5 hr, and to the efficiently stirred solution 11.9 g (0.06 mole) of methyl β-(2-ketocycloheptane)propionate in 600 ml of ether was added over a period of 2 hr. The mixture was allowed to warm slowly to room temperature during which time (19.5 hr) the ammonia and some of the ether was carried off in the nitrogen stream. To the residue 6 ml of absolute methanol in 200 ml of ether was added. After stirring for 0.5 hr the reaction mixture was acidified with 150 ml of 5% hydrochloric acid and the product was worked-up to yield 4.0 g of a colorless liquid after distillation through a 4-in. Vigreux column, bp 64–100° (1 mm). Analysis by vpc indicated that five major products and one minor product were present; these were identified as the α and β isomers of 7-hydroxybicyclo[5.3.0]decan-8-one (2) (3.5 parts), bicyclo[5.3.0]dec-1(7)-en-8-one (3) (trace), bicyclo[5.3.0]decan-8-one (4) (1.6 parts), 8-hydroxybicyclo[5.3.0]decane (5) (1.0 part), and 4a,9a-dihydrocyclohepta[*b*]pyran (6) (1.6 parts).

B. With Sodium in Ammonia under High-Dilution Conditions.—To a solution of 600 ml of anhydrous ether and 900 ml of anhydrous liquid ammonia (distilled from sodium) was added 0.56 g (0.024 g-atom) of sodium metal followed by 1.2 g (0.006 mole) of keto ester 1 under the conditions described above. After the ammonia had been removed, 2 ml of absolute methanol in 200 ml of ether was added, and the product was worked-up to give, after distillation through a 4-in. Vigreux column, 0.42 g (45%) of bicyclo[5.3.0]decan-8-one (4) as a colorless oil, bp 64–66° (0.25 mm).

C. With Metal Arylenides in Tetrahydrofuran under Standard Conditions.—To 300 ml of tetrahydrofuran (Du Pont product, dried over sodium hydride and distilled from sodium hydride in an atmosphere of nitrogen) was added 11.4 g (0.089 mole) of naphthalene (Eastman White Label grade, dried over alumina under vacuum) and 2.05 g (0.089 g-atom) of sodium metal. The reaction between the sodium and naphthalene commenced within 10 min as evidenced by the formation of a green color. The solution was stirred at room temperature for 1 hr and was then treated with a solution of 4.4 g (0.022 mole) of methyl β-(2-ketocycloheptane)propionate in 100 ml of dry tetrahydrofuran, added dropwise over a period of 2 hr. The reaction mixture was stirred an additional 6 hr and was then neutralized with 6 g (0.1 mole) of glacial acetic acid in 20 ml of tetrahydrofuran. The nitrogen source was disconnected, and the pale yellow reaction mixture was filtered and concentrated to give a yellow, semisolid residue which was dissolved in petroleum ether (bp 63–69°) and passed through a 1 × 12 in. column of alumina (Alcoa, grade F-20). Elution with 800–1000 ml of petroleum ether removed the naphthalene, and elution with 400 ml of absolute methanol removed the other products from the column. Distillation of the latter in a short-path apparatus (air bath temperature 75–135° at 0.3 mm) yielded 1.43 g (34%) of a pale yellow semisolid which was shown by vpc analysis to consist of 97% of the α and β isomers of 7-hydroxy-bicyclo[5.3.0]decan-8-one (2) and 3% of bicyclo[5.3.0]decan-8-one (4). The crude product from a run using 15.0 g of keto ester 1 yielded 0.5 g (4%) of bicyclo[5.3.0]decan-8-one (4), 2.1 g (17%) after distillation of the alumina chromatographed fraction) of the α isomer of 7-hydroxybicyclo[5.3.0]decan-8-one (2) as a solid, mp 40–43°, and 1.0 g (8%) (after distillation of the alumina chromatographed fraction) of a mixture of 2 and bicyclo[5.3.0]dec-1(7)-8-one (3). The olefin 3 is thought, in this instance, to arise during the work-up and chromatographic operations and not to be a significant component of the original product mixture. The isolated material, then, corresponds to *ca.* a 25% yield of α-hydroxy ketone (2). This is a somewhat lower figure than is indicated by vpc analysis and may be partly attributable to mechanical losses. As an alternative to purification by column chromatography, the naphthalene can be removed from the crude product by steam distillation.

(29) All melting points are corrected; all boiling points are uncorrected. The infrared spectra were measured on Perkin-Elmer Model 21 and Infracord instruments. The nmr spectra were measured on a Varian HA-60 and A-60 spectrometer; carbon tetrachloride was used as solvent; and the resonances are expressed in parts per million downfield shift from tetramethylsilane, present as an internal reference. Vpc analyses were performed on (a) a Perkin-Elmer Model 154B instrument containing a 0.25 in. × 6 ft column packed with 5% by weight of Dow-Corning No. 710 silicone oil on 30–60 mesh firebrick, (b) F & M Model 720 instrument containing a 0.25 in. × 16 ft column packed with 0.5% by weight of Dow-Corning No. 710 silicone oil on 110 mesh Superbrite glass beads (a product of Minnesota Mining and Manufacturing Co., St. Paul, Minn.), and (c) a homemade instrument containing a 0.25 in. × 16 ft column packed with 15% by weight of A3 neopentyl glycol sebacate on 40–50 mesh, Type ABS "Anakrom" (a product of Analytical Engineering Laboratory, Inc., Hamden, Conn.). The percentage compositions of mixtures analyzed by vpc was calculated fron peak area measurements and are uncorrected for differences in heat capacities. The short-path distillation apparatus consisted of a two-bulb unit blown from 8- to 10-mm-diameter glass tubing, the end bulb containing the sample and being heated in an electrically controlled air bath and the second bulb acting as a collector and being cooled by air or by pieces of wet cotton wrapped around it. Microanalyses were performed by Dr. Josef Zak, Mikroanalytisches Laboratorium, Vienna, Austria.

Employing the general procedure described above, the effects of (a) changes in ratios of reactants, (b) changes in temperature, (c) changes in the metal, and (d) changes in the aromatic hydrocarbon were investigated. The results are shown in Table I.

TABLE I

REDUCTIVE CYCLIZATION OF METHYL β-(2-KETOCYCLOHEPTANE)PROPIONATE WITH METAL ARYLENIDES

Metal	Hydrocarbon	Ratio of metal: hydrocarbon: keto ester	Temp, °C	Yield of volatile product, %	Ratio of α-2:β-2
Sodium	Naphthalene	1:2:4	25	16	2.6
Sodium	Naphthalene	1:3:4	25	29	3.9
Sodium	Naphthalene	1:4:4	25	36	5.8
Sodium	Naphthalene	1:8:4	25	13	5.4
Sodium	Naphthalene	1:4:4	Reflux	0	
Sodium	Naphthalene	1:4:4	0–5	31	6.9
Sodium	Phenanthrene	1:4:4	25	36	3.9
Sodium	Biphenyl	1:4:4	25	25	7.0
Sodium	Anthracene	1:2:4	25	0[a]	...
Potassium	Naphthalene	1:4:4	25	36	3.3
Lithium	Naphthalene	1:4:4	25	2.5	2.1

[a] The volatile product consisted of dihydroanthracene (71% yield) and starting keto ester (11%).

D. With Sodium Naphthalenide in Tetrahydrofuran under High-Dilution Conditions.—To 1000 ml of tetrahydrofuran was added 11.4 g (0.089 mole) of naphthalene, 2.05 g (0.089 g-atom) of sodium, and 4.4 g (0.022 mole) of keto ester (in 100 ml of tetrahydrofuran) according to the procedure described above. The distilled product consisted of 1.26 g (31.5%) of a yellow liquid which was shown by vpc analysis to contain mainly the α-hydroxy ketone **2** (α:β ratio, 4.6).

E. With Sodium in Tetrahydrofuran.—To 300 ml of tetrahydrofuran in a system filled with nitrogen 2.05 g (0.089 g-atom) of sodium was added. To the stirred mixture was added, over a period of 4.5 hr a solution of 4.4 g (0.022 mole) of keto ester **1** in 100 ml of tetrahydrofuran. After an additional 3 hr of stirring, the mixture was neutralized with 6 g (0.1 mole) of glacial acetic acid in 20 ml of tetrahydrofuran. The distilled product consisted of 1.31 g of a pale yellow liquid which was shown by vpc analysis to contain starting keto ester **1** (2.0 parts), the α isomer of the hydroxy ketone **2** (2.0 parts), the β isomer of the hydroxy ketone **2** (3.1 parts), and 8-hydroxybicyclo[5.3.0]decane (**5**) (1.0 part). A reaction carried out in a similar fashion but for a total of 23 hr yielded 1.58 g of distilled product which was shown by vpc analysis to contain α-**2** (1.0 part), β-**2** (1.1 part), and an uncharacterized higher boiling fraction (1.9 parts).

Proof of Structure of Products from Reductive Cyclization of Methyl β-(2-Ketocycloheptane)propionate (1). A. α-Epimer of 7-Hydroxybicyclo[5.3.0]decan-8-one (α-2).—This compound is most readily obtained from the reductive cyclization with sodium naphthalenide in tetrahydrofuran and can be recrystallized from petroleum ether (bp 62–69°) to yield colorless needles, mp 44.5–45.5°, ν^{KBr} 3520 (hydroxyl) and 1740 cm^{-1} (cyclopentanone carbonyl), and nmr (in CCl_4) one-proton singlet at 2.68 ppm which changes position as a function of concentration and which disappears upon addition of D_2O (O*H*) and 15-proton multiplet from 1 to 2.4 ppm (remaining protons).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.38; H, 9.59. Found: C, 71.38; H, 9.43.

Treatment of α-**2** with 2,4-dinitrophenylhydrazine under the usual acid-catalyzed conditions for hydrazone formation yielded the 2,4-dinitrophenylhydrazone of bicyclo[5.3.0]dec-1-en-8-one (**3**), mp 231.5–232° dec, as indicated by the nondepression in the melting point when it was admixed with an authentic sample, mp 233–233.5° dec.

Periodate cleavage of **2** was carried out by dissolving an 0.8-g sample in 30 ml of methanol and 20 ml of water and treating the solution with 60 ml of 0.2 *M* sodium metaperiodate solution.[30] The mixture was stirred at room temperature for 2 hr, made basic with 0.5 *M* sodium hydroxide solution, and the unreacted material was removed by ether extraction. The base-soluble fraction was converted to the free acid, treated with diazomethane, and distilled through a short-path apparatus to yield 0.47 g (50%) of methyl β-(2-ketocycloheptane)propionate, identified by vpc and infrared comparison with authentic material.

B. β Epimer of 7-Hydroxybicyclo[5.3.0]decan-8-one (β-2).—This compound is most readily obtained from the reductive cyclization with sodium in tetrahydrofuran by means of preparative vpc. The crude product, after crystallization from petroleum ether (bp 63–69°), yields colorless plates, mp 74–75°, ν^{KBr} 3520 (hydroxyl) and 1740 cm^{-1} (cyclopentanone carbonyl), and nmr (in CCl_4) one-proton singlet at 2.8 ppm (O*H*) and 15-proton multiplet at 1.2–2.5 ppm (remaining protons).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.40; H, 9.60.

Treatment of β-**2** with 2,4-dinitrophenylhydrazine under the usual acid-catalyzed conditions for hydrazone formation yielded the 2,4-dinitrophenylhydrazone of bicyclo[5.3.0]dec-1-en-8-one (**3**), mp 230–231° dec, as indicated by the nondepression in the melting point when it was admixed with an authentic sample, mp 233–233.5° dec.

C. Bicyclo[5.3.0]dec-1(7)-en-8-one (3).—This material was present in only very small amounts in all of the reductive cyclization mixtures; it was identified on the basis of vpc comparisons with authentic material prepared by the procedure of Jones, *et al.*[7] An 18.5-g sample of freshly distilled β-chloropropionyl chloride was treated with cycloheptene in the presence of aluminum chloride to yield 6.5 g of an oil, bp 84–106° (5 mm) which was cyclized with phosphoric acid–formic acid to give 1.8 g of bicyclo[5.3.0]dec-1(7)-en-8-one as a colorless oil, bp 104–106° (5 mm), ν^{liquid} 1705 (cyclopentenone carbonyl) and 1645 cm^{-1} (olefin), λ_{max}^{EtOH} 234 mμ (ε 17,000), and nmr (in CCl_4) seven-proton multiplet at 2.0–2.5 ppm and seven-proton multiplet at 1.4–1.8 ppm. The α,β-unsaturated ketone was also obtained by dehydration of the α-ketols. A 1.42-g sample of a mixture containing α-**2** and β-**2** in a ratio of 6:1 was dissolved in 80 ml of dry thiophene-free benzene and treated with a crystal of iodine. The mixture was refluxed for 4 hr in a system equipped with a water separator. The product was distilled through a short-path apparatus to yield 1.03 g of a yellow oil which was shown by vpc analysis and by infrared and ultraviolet spectra comparisons to be identical with bicyclo[5.3.0]dec-1(7)-en-8-one.

D. Bicyclo[5.3.0]decan-8-one (4).—This compound was most readily prepared by the reductive cyclization with sodium in ammonia under high-dilution conditions from which it was obtained as a colorless oil, bp 64–66° (0.25 mm), ν^{liquid} 1745 cm^{-1} (cyclopentanone carbonyl), and nmr (neat) multiplet at 1.0–2.5 ppm.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.55; H, 11.00.

An authentic sample of **4** was obtained by treating a 0.268-g sample of bicyclo[5.3.0]dec-1-en-8-one, prepared as described above, with hydrogen in the presence of a 5% palladium-on-charcoal catalyst. The distilled product consisted of 0.2 g of a colorless oil. The 2,4-dinitrophenylhydrazone of bicyclo[5.3.0]-decan-8-one, obtained as orange needles after recrystallization from ethanol–ethyl acetate, mp 189–190.5° dec, showed no depression in the melting point when admixed with the 2,4-dinitrophenylhydrazone obtained from the reductive cyclization product, mp 189–190.5° dec.

Anal. Calcd for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.07. Found: C, 57.77; H, 5.86.

The semicarbazone of bicyclo[5.3.0]decan-8-one, obtained as colorless needles after recrystallization from aqueous ethanol, mp 220–221° dec, showed no depression in the melting point when admixed with the semicarbazone obtained from the reductive cyclization product, mp 221–222° dec.

Bicyclo[5.3.0]decan-8-one was also obtained from bicyclo[5.3.0]dec-1(7)-en-8-one by reduction with sodium naphthalenide To 75 ml of tetrahydrofuran was added 0.7 g (0.03 g-atom) of sodium and 3.9 g (0.03 mole) of naphthalene. To this was added, over a period of 1.75 hr, a solution of 1.0 g of a mixture containing 72% of the unsaturated ketone **3** and 28% of the saturated ketone **4** in 25 ml of tetrahydrofuran. The mixture was stirred for 6.5 hr and then worked up in the usual fashion to give 0.45 g of a colorless liquid, bp 85–100° (0.3 mm). Analysis by vpc showed the product to consist of 35% of the unsaturated ketone **3** and 65% of the saturated ketone **4**. While it is conceivable that only the unsaturated ketone suffered conversion

(30) J. R. Dyer, *Methods Biochem. Anal.*, **3**, 111 (1956).

to nonvolatile material and that there was no net conversion of **3** to **4**, this seems unlikely.

Additional structure proof was provided by the conversion of **4** to the keto ester **1**. A 2.4-g sample of **4** was treated with peroxytrifluoroacetic acid according to the directions of Emmons and Lucas.[31] The resulting lactone (1.7 g) was refluxed with 20 ml of 1.2 *N* alcoholic sodium hydroxide solution for 1.5 hr, and the sodium salt of the hydroxy acid was oxidized with chromium trioxide–pyridine complex as described by Sarett, *et al.*[32] The keto acid formed from the oxidation was treated with diazomethane, and the product was distilled through a short-path apparatus to give 0.2 g of methyl β-(2-ketocycloheptane)-propionate, identified by comparison of the infrared spectrum with that of an authentic sample and by the preparation of a semicarbazone, mp 113.5–114.5°, which showed no depression upon admixture with the semicarbazone of an authentic sample, mp 114.5–115°.

E. 8-Hydroxybicyclo[5.3.0]decane (5).—A 1.0-g sample comprised of a 1:1 mixture of bicyclo[5.3.0]decan-8-one (**4**) and 8-hydroxybicyclo[5.3.0]decane (**5**) (extremely difficultly separable on the vpc column) was treated with 0.12 g of sodium borohydride[33] in 4 ml of 1.2 *N* sodium hydroxide solution. After 48 hr at room temperature, the mixture was processed to give, after distillation, 0.66 g of **5** which was further purified by passage through a vpc column: $\tilde{\nu}^{\text{liquid}}$ 3420 cm^{-1} (hydroxyl), nmr (neat) one-proton singlet at 3.3 ppm (O*H*) and 17-proton multiplet at 1.0–2.1 ppm (remaining protons).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.45; H, 11.42.

Employing the method of Brown and Garg,[34] a 1.0-g sample of **5** was oxidized with potassium dichromate and sulfuric acid to give, after distillation through a short-path apparatus, 0.6 g of **4** as a colorless oil identical in its vpc and infrared characteristics with samples of **4** obtained from other sources (see above).

F. 4a,9a-Dihydrocyclohepta[*b*]pyran (6) was isolated *via* vpc as a colorless liquid: $\tilde{\nu}^{\text{liquid}}$ 1645 (olefin), 1230, and 1080 cm^{-1} (ether); nmr (neat) one-proton doublet at 6.2 ppm ($\overset{H}{O}$>C=C), one-proton quadruplet at 4.45 ppm (OC=C*H*), one-proton multiplet at 4.0 ppm (HCOC=C), two-proton multiplet at 3.55 ppm (=CCH_2), and multiplet at 1.0–2.5 ppm (remaining protons).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.58; H, 10.48.

Reductive Cleavage of 7-Hydroxybicyclo[5.3.0]decan-8-one (2).—A 3.0-g sample containing 76% of the α epimer of **2**, 16% of the β epimer of **2**, and 8% of bicyclo[5.3.0]decan-8-one (**4**) was added, over a period of 3.5 hr, to a stirred solution of 1.68 g (0.073 g-atom) of sodium and 9.3 g (0.073 mole) of naphthalene in 300 ml of tetrahydrofuran. After an additional 6 hr of stirring, the mixture was neutralized with 4.8 g (0.08 mole) of glacial acetic acid in 20 ml of tetrahydrofuran. The product was obtained in the usual fashion and consisted, after distillation through a short-path apparatus, of 2.48 g of a yellow oil. Analysis by vpc indicated the composition of the mixture to be 75% of the α epimer of **2**, 21% of **4**, and no more than 4% of the β epimer of **2**.

Reductive Cyclization of *t*-Butyl β-(2-Ketocycloheptane)-propionate.—A 20-g sample of methyl β-(2-ketocycloheptane)-propionate was saponified with aqueous alcoholic potassium hydroxide to yield 15.3 g of β-(2-ketocycloheptane)propionic acid as a pale yellow liquid. Following the general procedure of Johnson, *et al.*,[17] the crude acid was dissolved in 150 ml of dichloromethane (dried over Linde Molecular Sieve 5A), 2 ml of concentrated sulfuric acid was added, and isobutene was bubbled through the stirred solution for 3 hr. The reaction mixture was allowed to remain at room temperature for 92 hr and was then neutralized and worked up to give, after distillation of the crude product through a 4-in. Vigreux column, 7.8 g (39%) of *t*-butyl β-(2-ketocycloheptane)propionate as a colorless liquid, bp 130–132° (0.5 mm), $\tilde{\nu}^{\text{liquid}}$ 1740 ester carbonyl) and 1705 cm^{-1} (cycloheptanone carbonyl), and nmr (in CCl_4) nine-proton singlet at 1.40 ppm (*t*-butyl group).

A 2.05-g sample of the *t*-butyl ester was subjected to reductive cyclization with sodium naphthalenide in tetrahydrofuran according to the procedure described above. The product, after distillation through a short-path apparatus, consisted of 0.72 g of a semisolid which was shown by vpc analysis to contain the α and β epimers of 7-hydroxybicyclo[5.3.0]decan-8-one in a ratio of 6.8:1 (18% yield of combined epimers) and only trace amounts of starting keto ester and bicyclo[5.3.0]decan-8-one.

Reductive Cyclization of Methyl β-(2-Ketocyclohexane)-propionate (11). A. With Sodium in Liquid Ammonia under Standard Conditions.—Following the procedure described above for the reductive cyclization of methyl β-(2-ketocycloheptane)-propionate, an 11.1-g (0.06 mole) sample of methyl β-(2-ketocyclohexane)propionate (**11**) afforded, after distillation of the crude product through a 4-in. Vigreux column, 3.5 g of a colorless oil, bp 80–120° (0.2 mm). Analysis by vpc indicated that the mixture contained 5.5 parts of 6-hydroxybicyclo[4.3.0]nonan-7-one (**12**), small amounts of bicyclo[4.3.0]nonan-7-one (**14**), 1.5 parts of bicyclo[4.3.0]non-1(6)-en-7-one (**13**), 1 part of olefin A (**16**), and 1 part of olefin B (**17**).

B. With Sodium in Liquid Ammonia under High-Dilution Conditions.—Following the procedure described above for the reductive cyclization of **1** under high dilution conditions with sodium in ammonia, a 1.11 g (0.006 mole) sample of methyl β-(2-ketocyclohexane)propionate (**11**) afforded, after distillation of the crude product through a short-path apparatus, 0.35 g of a colorless liquid. Analysis by vpc indicated the mixture to contain 1.0 part of **12**, 4.3 parts of **14**, 1.1 part of 7-hydroxybicyclo-[4.3.0]nonane (**15**), and 17% of unidentified lower boiling products.

C. With Sodium Naphthalenide in Tetrahydrofuran.—Following the procedure described above for the reductive cyclization of **1** with sodium naphthalenide in tetrahydrofuran, a 4.1-g (0.022 mole) sample of methyl β-(2-ketocyclohexane)propionate gave, after distillation of the crude product through a short-path apparatus, 0.42 g of a yellow liquid. Analysis by vpc indicated that the product consisted of 7 parts of unreacted keto ester **11**, 10.9 parts of **12** (9% over-all yield from **11**), and 2.4 parts of bicyclo[4.3.0]nonan-7-one (**14**).

Proof of Structure of Products from Reductive Cyclization of Methyl β-(2-Ketocyclohexane)propionate. A. 6-Hydroxybicyclo-[4.3.0]nonan-7-one (12) was isolated by preparative-scale vpc from the reductive cyclization with sodium in ammonia and with sodium naphthalenide in tetrahydrofuran and was obtained as a colorless oil, $\tilde{\nu}^{\text{liquid}}$ 3500 (hydroxyl) and 1740 cm^{-1} (cyclopentanone carbonyl).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.45; H, 9.06.

Treatment of **12** with 2,4-dinitrophenylhydrazine under the usual acid-catalyzed conditions for hydrazone formation yielded the 2,4-dinitrophenylhydrazone of bicyclo[4.3.0]non-1-en-7-one, mp 234–234.5° dec, as indicated by the nondepression in the melting point when it was admixed with an authentic sample (see below).

B. Bicyclo[4.3.0]nonan-7-one (13) was synthesized by an independent route according to the procedure of Johnson, *et al.*[11] Cyclohexanone was converted, *via* a Stobbe condensation followed by acid-catalyzed decarboxylation, to β-(1-cyclohexenyl)propionic acid which was cyclized to bicyclo[4.3.0]non-1-en-7-one. The 2,4-dinitrophenylhydrazone of this product was obtained as violet crystals, mp 232–233° dec. Hydrogenation of **13** yielded bicyclo[4.3.0]nonan-7-one as a colorless oil, $\tilde{\nu}^{\text{liquid}}$ 1745 cm^{-1} (cyclopentanone carbonyl), which was used to establish the presence of the saturated ketone in the reductive cyclization mixture by means of the vpc enrichment technique.

C. 7-Hydroxybicyclo[4.3.0]nonane (15) was prepared by a sodium borohydride reduction of bicyclo[4.3.0]nonan-7-one and was obtained as a colorless oil, $\tilde{\nu}^{\text{liquid}}$ 3450 cm^{-1} (hydroxyl). It was used to establish the presence of this compound as a constituent in the reductive cyclization mixture by means of the vpc enrichment technique.

D. Olefin A (16) was separated by vpc and obtained as a colorless oil: $\tilde{\nu}^{\text{liquid}}$ 1660 (olefin), 1250, and 910 cm^{-1} (ether); and nmr (in CCl_4) two-proton triplet at 3.84 ppm (=COCH_2) and 12-proton multiplet at 1.4–2.2 ppm (remaining protons).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.19; H, 10.34.

E. Olefin B (17) was separated by vpc and obtained as a colorless oil: $\tilde{\nu}^{\text{liquid}}$ 1695 (olefin), 1240, and 910 cm^{-1} (ether); and nmr (in CCl_4) one-proton doublet at 6.2 ppm ($\overset{H}{O}$>C=C), one-proton multiplet at 4.5 ppm (OC=C*H*), one-proton multi-

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plet at 3.3 ppm (indistinct) (*H*COC=C), and multiplet at 0.8–2.2 ppm (remaining protons).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.48; H, 10.20.

Reductive Cyclization of Methyl γ-(2-Ketocyclohexane)butyrate (20).—A 4.14-g (0.022 mole) sample of methyl γ-(2-ketocyclohexane)butyrate[35] was subjected to reductive cyclization with sodium naphthalenide in tetrahyrofuran according to the conditions described above. The crude product was distilled through a short-path apparatus to yield 0.71 g of a pale yellow liquid which was shown by vpc analysis to contain unreacted starting material and 11% of 6-hydroxybicyclo[4.4.0]decan-7-one. The hydroxy ketone was separated by means of preparative-scale vpc and obtained as a colorless oil, $\tilde{\nu}^{\text{liquid}}$ 3600 (hydroxyl) and 1720 cm^{-1} (cyclohexanone carbonyl).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.04; H, 9.98.

Reductive Cyclization of Methyl β-(2-Ketocyclopentane)-propionate (18).—A 3.78-g (0.022 mole) sample of methyl β-(2-ketocyclopentane)propionate[36] was subjected to reductive cyclization with sodium naphthalenide in tetrahydrofuran according to the conditions described above. The crude product was distilled through a short-path apparatus to give 0.31 g of a yellow liquid which was shown by vpc analysis to contain a small amount of unreacted starting material, 30% of 5-hydroxybicyclo[3.3.0]octan-6-one, and 70% of unidentified higher boiling materials. A small sample of the hydroxy ketone was separated by means of vpc and was obtained as a colorless oil, $\tilde{\nu}^{\text{liquid}}$ 3520 (hydroxyl) and 1740 cm^{-1} (cyclopentanone carbonyl).

Reductive Cyclization of Methyl β-(4,4-Dimethyl-2-ketocycloheptane)propionate (21).—Following the procedure described above, a sodium naphthalenide solution was prepared from 600 ml of tetrahydrofuran, 15.9 g (0.124 mole) of naphthalene, and 2.85 g (0.124 g-atom) of sodium. To this was added, over a period of 1 hr, 7.0 g (0.03 mole) of methyl β-(4,4-dimethyl-2-ketocycloheptane)propionate (21) in 30 ml of tetrahydrofuran. The reaction mixture was allowed to stand overnight and was then processed in the previously described fashion to yield, after chromatography over alumina, 1.60 g (27%) of 4,4-dimethyl-7-hydroxy-8-ketobicyclo[5.3.0]decane (22). Recrystallization from petroleum ether furnished colorless crystals: bp 99–101° (0.07 mm); mp 59.5–60.5°; $\tilde{\nu}^{\text{KBr}}$ 3400 (hydroxyl) and 1745 cm^{-1} (cyclopentanone carbonyl); and nmr (in CCl_4) one-proton multiplet at 3.66 ppm (hydroxyl), six-proton unsymmetrial triplet at 0.90, 0.96, and 1.0 ppm (methyl groups), and 13-proton multiplet from 1.2 to 2.6 ppm (remaining protons) (the multiplets of the hydroxyl and methyl resonances suggest that the compound is not a pure stereoisomer but probably a mixture of the two epimeric forms).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.48; H, 10.25. Found: C, 73.70; H, 10.12.

Treatment of 22 with 2,4-dinitrophenylhydrazone under the usual acid-catalyzed conditions for hydrazone formation yielded the 2,4-dinitrophenylhydrazone of 4,4-dimethylbicyclo[5.3.0]dec-1-en-8-one, mp 196–197° after recrystallization from ethanol.

Anal. Calcd for $C_{18}H_{22}N_4O_4$: C, 60.32; H, 6.19. Found: C, 60.68; H, 6.33.

Registry No.—**1**, 10407-26-8; α-**2**, 10407-27-9; β-**2**, 10407-28-0; **3**, 769-32-4; **4**, 10407-30-4; **5**, 10407-31-5; **6**, 10407-32-6; **11**, 10407-33-7; **12**, 10421-80-4; **16**, 7106-07-2; **17**, 10407-35-9; **18**, 10407-36-0; **20**, 1205-19-2; **21**, 10407-38-2; **22**, 10407-39-3; 2,4-dinitrophenylhydrazone of 4,4-dimethylbicyclo[5.3.0]dec-1-en-8-one, 10407-40-6; *t*-butyl β-(2-ketocycloheptane)-propionate, 10407-41-7; 6-hydroxybicyclo[4.4.0]decan-7-one, 10407-42-8; 5-hydroxybicyclo[3.3.0]octan-6-one, 10407-43-9.

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Syntheses of Optically Active α-Amino Acids from α-Keto Acids by Hydrogenolytic Asymmetric Transamination[1]

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Sodium α-phenylglycinate was found to be hydrogenolyzed easily to ammonia and phenylacetic acid using palladium as the catalyst. By using this reaction, asymmetric syntheses of α-amino acids from their corresponding α-keto acids with optically active α-phenylglycine in aqueous alkaline solution were investigated. Optically active alanine, α-amino-*n*-butyric acid, glutamic acid, and aspartic acid were synthesized. Optical purities of these synthesized amino acids were in the 40–60% range.

Several asymmetric syntheses of α-amino acids have been reported. However, a few studies have been made on the nonenzymatic synthesis of optically active amino acids from their corresponding α-keto acids.[2-8] Octopine was first synthesized from L-arginine and pyruvic acid.[2] Later the synthesized octopine was found to be isooctopine.[3,9] A pyridoxal–copper(II) complex catalyzed reaction of α-ketoglutaric acid with L-alanine and L-phenylalanine was reported by Longenecker and Snell.[4] Hiskey and Northrop[5a] reported the formation of optically active α-amino acids (optical purity 12–80%) by hydrogenation and hydrogenolysis of the Schiff base of α-keto acids with (+)- and (−)-α-methylbenzylamine. They also reported the synthesis of alanylalanine[5b] from the Schiff base of pyruvyl-(*S*)-alanine with benzylamine by catalytic hydrogenation. Kanai and Mitsui[6] synthesized optically active phenylglycine using the Hiskey reaction. Harada and Matsumoto[7] studied various Hiskey-type reactions and proposed possible steric courses for the syntheses. They also reported the syntheses of optically active amino acids by catalytic hydrogenation of the oximes of the Schiff bases of *l*-menthyl esters of α-keto acids with benzylamine.[8]

In the previous communication of this investigation,[10] it was reported that several amino acids were

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