1-Acetyl-2-propionylferrocene was prepared as we previously reported:[1] mp 46°; nmr ($CDCl_3$) δ 1.17 (t, 3, CH_2CH_3), 2.47 (s, 3, $COCH_3$), 2.86 (m, 2, CH_2CH_3), 4.25 (s, 5, Fc), 4.58 (t, 1, Fc), 4.88 (d, 2, Fc).

1-Acetyl-2-butyrylferrocene.—To 15.0 g (0.1128 mol) of $AlCl_3$ in 100 ml of CH_2Cl_2 was added 9.4 g (0.0412 mol) of acetylferrocene and 12.0 g (0.0760 mol) of butyric anhydride in 250 ml of dry ($MgSO_4$) CH_2Cl_2 dropwise with stirring under N_2. After 4 hr the solution was cooled to 5° and hydrolyzed, and the layers were separated. The combined organic layer and ethereal wash of the aqueous layer were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The red oil which remained was chromatographed on silica gel. Elution with 25% ether in hexane produced three bands. The first band (orange) contained a trace of acetylferrocene. The second band (orange) contained 0.23 g (1.87%) of desired compound: mp 103–103.5°; nmr ($CDCl_3$) δ 1.0 (t, 3, CH_2CH_3), 1.74 (m, 2, CH_2CH_3), 2.48 (s, 3, $COCH_3$), 2.81 (t, 2, $COCH_2$), 4.27 (s, 5, Fc), 4.61 (t, 1, Fc), 4.89 (d, 2, Fc). The third band (red) contained 8.65 g (70.3%) of 1-acetyl-1′-butyrylferrocene: mp 54°; nmr ($CDCl_3$) δ 1.01 (t, 3, CH_2CH_3), 1.72 (m, 2, CH_2CH_3), 2.34 (s, 3, $COCH_3$), 2.65 (t, 2, $COCH_2$), 4.48 (t, 4, Fc), 4.74 (m, 4, Fc.)

Anal. Calcd for $C_{16}H_{18}O_2Fe$: C, 64.45; H, 6.08. Found: C, 64.32; H, 6.12. *Anal.* Calcd for $C_{16}H_{18}O_2Fe$: C, 64.45; H, 6.08. Found: C, 64.37; H, 6.04.

1-Acetyl-2-(3-methyl)butyrylferrocene.—To 16.0 g (0.120) mol) of $AlCl_3$ in 150 ml of CH_2Cl_2 was added 12.0 g (0.0996 mol) of 3-methylbutyryl chloride and 10.0 g (0.0438 mol) of acetylferrocene in 250 ml of dry CH_2Cl_2 dropwise with stirring under N_2. After 5 hr the solution was cooled to 6° and hydrolyzed, and the layers were separated. The organic layer was washed with 2 *M* Na_2CO_3 solution. The combined organic layer and ethereal wash of the aqueous layer were dried ($MgSO_4$) and the solvent was under reduced pressure. The red oil which remained was chromatographed on silica gel. Elution with 10% ether in hexane produced five bands. The first band (yellow) and the second band (orange) contained traces of some material which was not characterized. The third band (red) contained 0.90 g (9%) of starting material. The fourth band (red) contained 0.86 g (6.29%) of **27**: mp 59–60°; nmr ($CDCl_3$) δ 1.00 [d, 6, $CH(CH_3)_2$], 2.28 (m, 1, CH), 2.49 (s, 3, $COCH_3$), 2.72 (d, 2, $COCH_2$) 4.28 (s, 5, Fc), 4.62 (t, 1, Fc), 4.90 (d, 2, Fc). The fifth band (red) contained 9.85 g (72.0%) of 1-acetyl-1′-(3-methyl)butyrylferrocene: mp 76–77°; nmr ($CDCl_3$) δ 1.01 [d, 6, $CH(CH_3)_2$], 2.28 (m, 1, CH), 2.35 (s, 3, $COCH_3$), 2.55 (d, 2, $COCH_2$), 4.51 (t, 4, Fc), 4.78 (t, 4, Fc).

Anal. Calcd for $C_{17}H_{20}O_2Fe$: C, 65.40; H, 6.46. Found: C, 65.61; H, 6.48. *Anal.* Calcd for $C_{17}H_{20}O_2Fe$: C, 65.40; H, 6.46. Found: C, 65.48; H, 6.40.

Registry No.—**1**, 12766-52-8; **2**, 12766-58-4; **3**, 12766-62-0; **4**, 12766-65-3; **5**, 12766-54-0; **6**, 12766-59-5; **7**, 12766-63-1; **8**, 12766-51-7; **9**, 12766-57-3; **10**, 12766-61-9; **11**, 12766-50-6; ferrocobenzoquinone, 12766-53-9; 1,2-α-ketotetramethyleneferrocene, 12766-55-1; 1,2-diacetylferrocene, 12766-56-2; 1-acetyl-2-propionylferrocene, 12766-60-8; 1-acetyl-2-butyrylferrocene, 12766-64-2; 1-acetyl-2-(3-methyl)butyrylferrocene, 12766-66-4.

Competitive Metal Hydride Reductions of β-Phorone with Cyclic Ketones

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Competitive reductions with lithium aluminum tri-*tert*-butoxyhydride of β-phorone, a nonconjugated enone, and a number of cyclic saturated ketones and conjugated enones having varied steric environments were studied. The nonconjugated enone was found to be less reactive than cyclic saturated ketones, but more reactive than the conjugated enones. Steric and torsional factors are involved, but apparently not in a major way, in determining relative reactivities in these experiments.

The greater reactivity toward metal hydride reduction of cyclic saturated ketones as compared with cyclic conjugated enones has been recognized, and selective reductions have been successfully carried out with steroids. For example, reduction of androst-4-ene-3,17-dione (**1**) with lithium aluminum tri-*tert*-butoxyhydride (LATH)[2] occurred at C-17 in preference to reduction at C-3.[3] A similar result with the same substrate was obtained with sodium borohydride in methanol, giving 17β-hydroxyandrost-4-en-3-one.[4] With six-membered ring ketones, similar large reactivity differences were encountered in intermolecular competition studies with lithium aluminum hydride and LATH.[5] The α,β-unsaturated ketones were consistently less reactive than their saturated competitors, even when steric or torsional[6] factors would have disfavored the latter. A similar observation was made in the reduction of the steroid prednisone-BMD with LATH.[7] The strongly hindered C-11 carbonyl group was reduced in preference to the conjugated carbonyl group at C-3. The greater selectivity of LATH over $LiAlH_4$ was also noted.[5,8]

A consideration of the steric and torsional factors conceivably involved in the reduction of various cyclohexanones and conjugated cyclohexenones led to the conclusion that these factors could not explain the observed reactivity differences between the two types of substrates, and an explanation was suggested in which the major factor was the stability of the conjugated enone system.[5] If the reduced reactivity of conjugated enones is due to the intrinsic stability of the conjugated π system, then there should be a marked difference in reactivity between conjugated and nonconjugated enones, with the latter being the more reactive.

This paper reports the results of competitive LATH reductions of the nonconjugated ketone 3,5,5-trimethylcyclohex-3-enone (β-phorone, **2**) with saturated and conjugated enone systems of varying steric com-

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(1) Undergraduate research participant, 1971–1972.

(2) Lithium aluminum tri-*tert*-butoxyhydride is also commonly called lithium tri-*tert*-butoxyaluminohydride. However, we now prefer the former name because of its similarity to the name lithium aluminum hydride.

(3) J. Fajkoš, *Collect. Czech. Chem. Commun.*, **24**, 2284 (1959).

(4) J. K. Norymberski and G. F. Woods, *Chem. Ind.* (*London*), 518 (1954).

(5) H. Haubenstock, *J. Org. Chem.*, **37**, 656 (1972).

(6) (a) M. Chérest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2199 (1968); M. Chérest and H. Felkin, *ibid.*, 2205 (1968). (b) For a recent and thorough discussion of stereochemical factors involved in metal hydride reductions of alkylcyclohexanones, see E. L. Eliel and Y. Senda, *Tetrahedron*, **26**, 2411 (1970).

(7) J. A. Zderic and J. Iriarte, *J. Org. Chem.*, **27**, 1756 (1962).

(8) H. Haubenstock and E. L. Eliel, *J. Amer. Chem. Soc.*, **84**, 2363 (1962).

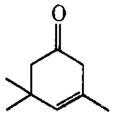
TABLE I

COMPETITIVE REDUCTIONS OF KETONE PAIRS WITH LATH

Entry	Ketone pair (mol)	Mol of LATH	Reduction, %	Ketone composition^{a} of product		
					Calcd, %	Found, %
1	**2**^{b} (0.030), **3**^{c} (0.030)	0.015^{d}	**2** (0);^{e} **3** (43)	**3**	36	39
2	**2**^{f} (0.025), **4**^{g} (0.031)	0.015^{d}	**2** (0); **4** (40, 41^{h,i})	**4**	38	39, 40^{h}
3	**2**^{j} (0.012), **5**^{k} (0.013)	0.0066^{l}	**2** (13); **5** (29)	**5**	45	47
4	**2**^{j} (0.029), **6**^{c} (0.030)	0.0149^{d}	**2** (28); **6** (17)	**6**	53	52
5	**2**^{m} (0.026), **7**^{g} (0.028)	0.0149^{d}	**2** (38); **7** (3)	**7**	58	56

^{a} Ketone composition is normalized to 100%. ^{b} **2** was 99% pure. ^{c} Ketones were dissolved in 70 ml of THF. ^{d} In 50 ml of THF. ^{e} Trace quantities of alcohol product were neglected. ^{f} **2** was 82% pure. ^{g} Ketones in 75 ml of THF. ^{h} Analysis of hydrogenated product. ^{i} *cis*- and *trans*-3-methylcyclohexanol peaks overlap. ^{j} **2** was 95% pure. ^{k} Ketones in 30 ml of THF. ^{l} In 22 ml of THF. ^{m} **2** was 87% pure.

plexities. In these experiments, **2** competed for a limited quantity of LATH added inversely to **2** and one of the other ketone substrates 3 to 7 in tetrahydrofuran (THF) solution.



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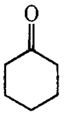

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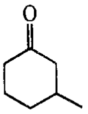

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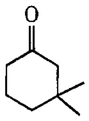

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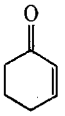

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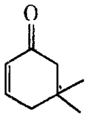

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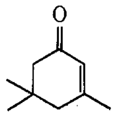

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The results obtained from these experiments are summarized in Table I.

Results and Discussion

The extent of reduction for each competitive ketone pair is listed in Table I. A few pertinent comments are necessary before discussing the data. β-Phorone (**2**) isomerizes slowly to isophorone (**8**), even when kept refrigerated. It was therefore necessary to analyze **2** at the time the competition experiment was carried out. The purity of **2** used in each experiment is recorded in Table I, and the remaining material in each case is isophorone. This did not cause any serious difficulty, since the purities of **2** were usually quite good, and also because **8** is reduced by LATH extremely slowly. Note that the moles of **2** in each entry are the corrected values. In Table I, the normalized per cent of remaining unreacted ketone (**3** to **7**) is listed for each entry. For example, in entry 1 the product contained 39% **3** and 61% unreacted **2**. Actually, in these reductions unreacted **2** was partially or completely isomerized to **8** during alkaline hydrolysis. In the calculations, account was taken of the amount of **8** present in the original reaction mixture. The unreacted ketone composition is an important analytical check for each experiment. The calculated values are based on the extent of reduction of each ketone pair, and it can be seen from Table I that the calculated and found ketone composition values are in excellent agreement in all cases. Sensitivity factors derived from standard mixtures were used in these glpc analyses and were calculated as previously described.[5]

In the experiment using ketone **4** (entry 2, Table I) two experimental variations from the normal runs were made. An aliquot was removed from the reaction mixture 26 min after addition of the LATH. This was analyzed in addition to the major portion of the product, which was hydrolyzed 200 min after LATH addition. The results were identical in both cases (40% reduction of **4**), showing that, after reaction was complete, no further change in product composition occurred. Secondly, part of the reaction product was hydrogenated over 0.2 g of 10% palladium on carbon. Analysis of the hydrogenated product gave identical results with that of the nonhydrogenated product.

The data in Table I point to three basic conclusions. First, the conjugated enones studied, **6** and **7**, are less reactive than the nonconjugated ketone **2**, as seen from entries 4 and 5, Table I. Second, the C=C double bond in **2** does lower the reactivity of **2** relative to the saturated ketones **3**, **4**, and **5** (entries 1, 2, and 3, Table I). Third, steric or torsional factors are involved in comparisons of reactivity among the cyclohexanones.[6b] Thus, while **2** could not compete with ketones **3** and **4** (entries 1 and 2), introduction of the second methyl group in ketone **5** lowered its reactivity to the extent that 13% reduction of **2** was observed (entry 3, Table I). It should be noted that in ketone **5** one methyl group must be in an axial position in the chair form.[9] Similarly, while ketone **6** was reduced to an extent of 17%, ketone **7** was only 3% reduced, owing to the effect of the added methyl group.

It is rather striking that the conjugated enone **6**, without alkyl substituents, is less reactive than β-phorone, with three alkyl substituents. This not only demonstrates the relative unimportance of steric and torsional constraints brought about by the alkyl groups in **2**, but emphasizes the role of conjugation in affecting reactivity. When steric factors were made approximately equivalent (entry 5, Table I), the conjugated enone **7** could not compete with the nonconjugated enone **2**.

One factor reducing reactivity in the *conjugated* enone system is a generally lower ground-state energy.[10] However, kinetic studies will have to be carried out in order to evaluate transition-state energy differences for these substrates. While transition states in metal hydride reductions have been assumed to be "reactant-like,"[6a] we cannot as yet define transition-state energy

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(9) For a discussion of steric approach control and rate data on attack of substituted cyclohexanones from the equatorial and axial positions, see ref 6b.

(10) See, for example, K. G. Lewis and G. J. Williams, *Tetrahedron Lett.*, 4573 (1965).

differences for these intermolecular competition reactions.[11]

β-Phorone is less reactive than the saturated ketones **3**, **4**, and **5**. A comparison between **2** and **5** is the most instructive, since they both contain geminal methyl groups. If the conformation of **2** is taken as a half-chair, with carbons 2, 3, 4, and 5 coplanar, it appears from an inspection of Dreiding models that steric hindrance to axial attack due to the methyl group is certainly no worse than analogous hydride attack on ketone **5**. Equatorial attack on **2** may involve a somewhat greater extent of eclipsing with an adjacent hydrogen than similar attack on **5**, but it is difficult to draw a definite conclusion about this from the models, which are obviously approximations. Compound **2** in a boat form would minimize steric effects arising from interactions with methyl groups.

We draw the tentative conclusion that the difference in reactivity between **2** and the saturated ketone **5** is not due to steric or torsional effects primarily, but rather to an electronic effect of the C=C double bond.[12]

Control Experiments.—The fact that unreacted **2** was partially or completely converted to **8** raised the possibility that **2** was rapidly converted to **8**, which is known to undergo very slow reduction by LATH.[5] This was shown not to be the case when **2** was readily reduced by LATH at room temperature.

In another experiment, **2** was stirred in THF overnight. The solution was divided in half, and one portion was concentrated in the same manner as in the competition experiments. Analysis (glpc) showed that no isomerization occurred. The other half was treated with aqueous alkali and analysis showed that **2** had completely isomerized to **8**. Therefore unreacted **2** in the reductions isomerized to **8** during hydrolysis. Reduction of conjugated enones to saturated ketones was not encountered as a problem, as expected.[13]

Experimental Section

β-Phorone (**2**)[14] was prepared by fractional distillation of isophorone at atmospheric pressure through a helix-packed column.[15] A small pellet of sodium hydroxide was added, and the reflux ratio was maintained at about 30:1. The best sample of **2** had bp 170°, n^{23}_{D} 1.4620 (lit.[16] n^{20}_{D} 1.4626). Analysis by glpc using an 8-ft 10% silicone rubber SE-30 acid-washed and silanized column at 110° showed a purity of 99.1% with 0.9% isophorone (**8**). Convenient analyses of **2** were also obtained with a 5-ft 10% diethylene glycol succinate column, acid-washed and silanized, at 135°. The carbonyl stretching absorption of **2** (*ca.* 1704–1709 cm^{-1}) is readily distinguished from that of **8** (1664 cm^{-1}); nmr spectrum of **2**, δ 1.04 (6 H), 1.73 (3 H), 2.25 (2 H), 2.67 (2 H), 5.50 (1 H).

In the preparation of **2**, water sometimes codistilled with the product. This was apparently due to condensation side reactions of isophorone. In these cases **2** was dried (Na_2SO_4) and stored in a refrigerator.

Ketones **3** and **4** were commercial materials which were distilled, **6** was obtained from Aldrich Chemical Co., **7** was prepared by the $LiAlH_4$ reduction of 3-isobutoxy-5,5-dimethylcyclohex-2-enone,[17] and **5** was prepared from **7** by hydrogenation over 5% Pd/C in absolute ethanol, bp 68.5–70° (15 mm), n^{23}_{D} 1.4435.

As a reference compound, 3,5,5-trimethylcyclohex-3-en-1-ol was prepared from **2** by reduction with $LiAlH_4$ using alkaline hydrolysis; the product had bp 68° (2.5 mm), n^{25}_{D} 1.4704 [lit.[16] bp 71–73° (3 mm), n^{20}_{D} 1.4737], crystallized when refrigerated but melted at room temperature. 5,5-Dimethylcyclohex-2-en-1-ol was prepared from **7** by $LiAlH_4$ reduction, bp 84–85° (15 mm), n^{26}_{D} 1.4660. The product was contaminated with some starting ketone, but was satisfactory as a standard for glpc analysis.

Gas chromatographic analyses were carried out with a Hewlett-Packard 5750 gas chromatograph. Columns used were a 10-ft 10% Carbowax 20M acid-washed and silanized column, and a 5-ft 10% diethylene glycol succinate acid-washed and silanized column. Nmr analysis was done with a JEOL MH-100 instrument. THF was dried and distilled from $LiAlH_4$.

Competition Reduction of 2 and 3.—This reduction is described in some detail as a typical example. A solution of **2** (4.1555 g, 0.030 mol, 99% by glpc analysis) and **3** (2.9471 g, 0.030 mol, distilled and stored over anhydrous Na_2SO_4) was dissolved in 70 ml of THF and placed in a 250-ml Ace reactor equipped with a stirrer, condenser, and addition funnel. A solution of LATH (3.8 g, 0.015 mol) in 50 ml of THF was added dropwise to the rapidly stirred solution. Stirring was continued for several hours and the reaction mixture was kept overnight (about 15 hr). The reaction mixture was then cooled and hydrolyzed with water and 15% sodium hydroxide,[18] and dried ($MgSO_4$). The filtered solution was concentrated by fractional distillation through a 12-in. helix-packed column (oil bath, maximum bath temperature 102°), bp 63.5–66.5°. The concentrated residue was analyzed by glpc.

Registry No.—**2**, 471-01-2; **3**, 108-94-1; **4**, 591-24-2; **5**, 2979-19-3; **6**, 930-68-7; **7**, 4694-17-1; LATH, 17476-04-9.

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[11] For a discussion of the stereochemical course of hydride reductions of conjugated enones, see T. Toromanoff in "Topics in Stereochemistry," Vol. 2, N. L. Allinger and E. L. Eliel, Ed., Interscience, New York, N. Y., 1967.

[12] The effect of "remote" unsaturation on carbonyl groups has been observed before. For example, the carbonyl group of Δ^3-cyclohexenic aldehydes is much less active than that of cyclohexanic aldehydes. See G. P. Kugatova-Shemyakina and Y. A. Ovchinnikov, *Tetrahedron*, **18**, 697 (1962). A similar explanation to the one given by these authors is conceivable, which would amount to a form of homoconjugation of the two double bonds.

[13] M. R. Johnson and B. Rickborn, *J. Org. Chem.*, **35**, 1041 (1970).

[14] M. S. Kharasch and P. O. Tawney, *J. Amer. Chem. Soc.*, **63**, 2308 (1941); **67**, 128 (1945).

[15] This distillation method, which displaces the equilibrium between **2** and **8**, was suggested by Dr. W. Wellman, Esso Research and Engineering Co., Linden, N. J. For an alternate method of preparation see J. Meinwald and L. Hendry, *J. Org. Chem.*, **36**, 1446 (1971).

[16] R. Bonnett, A. K. Mallams, A. A. Spark, J. L. Tee, B. C. L. Weedon, and A. McCormick, *J. Chem. Soc. C*, 429 (1969).

[17] H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **33**, 956 (1968).

[18] See L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 584.