acetate–acetic acid (1:1) was placed in a hydrogenator bottle, and after platinum oxide (3 mg) was added, the mixture was stirred at 60 °C for 10 h at 1 atm of hydrogen. The catalyst was removed by filtration, the filtrate was concentrated, and the residual solid was recrystallized from acetone to give **23**: 5 mg (50%); mp 41–42 °C; mass spectrum, *m/e* 292 (M^+); IR (KBr) 2960, 2880, 1475, 1440, 915, 856, 755 cm^{-1}.

Anal. Calcd for $C_{21}H_{40}$: C, 86.22; H, 13.78. Found: C, 86.34; H, 13.74.

Ozonolysis of the Doubly Bridged Allene 5. A stream of ozonized oxygen (ca. 3%, 100 mL/min) was bubbled for 30 min into a chilled (−78 °C) solution of the doubly bridged allene **5** (10 mg, 0.05 mmol) in 5 mL of pentane containing 0.5 mL of methanol. After the flask was flushed with oxygen for 5 min, 30% hydrogen peroxide (0.3 mL) and methanol (5 mL) were added, and the mixture was heated under reflux for 30 min. To the chilled solution was added water to separate an oil which was extracted with ether. Drying with $MgSO_4$ followed by removal of the solvent left an oily residue which solidified to a crystalline mass. Recrystallization from methanol gave **22**: 5 mg (47% yield); mp 51–53 °C (lit.[14] mp 53–54 °C).

Registry No. (±)-**5**, 79203-24-0; (+)-**5**, 79254-41-4; **10**, 10329-90-5; **11**, 38300-49-1; **12**, 80800-19-7; **13**, 80800-20-0; **14**, 80800-21-1; **15**, 80800-22-2; **16**, 80800-23-3; **17**, 80800-24-4; **20**, 16538-98-0; **21**, 64861-65-0; **22**, 14113-56-5; **23**, 79793-22-9.

Solvent and Stoichiometric Effects in the Reactions of Cyclohexanone–Pyrrolidine Enamines with Electrophilic Olefins

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The reaction of the pyrrolidine enamine of tetrahydrocarvone (**2**) with methyl vinyl ketone (MVK) under a variety of conditions has been investigated. With 1 equiv of MVK in a nonpolar solvent (benzene) approximately 50% of the product arises from formal alkylation of the tetrasubstituted isomer of enamine **2**. Similar results are obtained with 1–1.7 equiv of MVK in methanol; however, with 1.8 equiv or more of alkylating agent there is an increase in the amount of abnormal products. With 5 equiv of alkylating agent a single abnormal product, enone **5**, is formed exclusively. Alkylation of dihydrocarvone enamine **3** with 1 equiv of MVK in benzene or methanol affords only the normal product, enone **6**, while with 5 equiv of MVK in methanol, an abnormal product, enone **7**, is the exclusive alkylation product. In an effort to explore the course of these reactions, we carried out the alkylation of enamine **2** with MVK for short periods of time and at reduced temperatures. The alkylation of enamine **2** with ethyl vinyl ketone (EVK) and methyl acrylate was also investigated as was the alkylation of enamine **3** with MVK. Reaction of the enamine of 2-methyl-5-*tert*-butylcyclohexanone (**33**) with MVK in either benzene or methanol affords exclusively the abnormal product, enone **34**. On the basis of distribution of products obtained in these reactions, a mechanism has been suggested for the anomalous alkylation of the enamines of 2-alkylcyclohexanones which does not involve the tetrasubstituted isomer of the enamine.

The reaction of enamines with electrophilic olefins (e.g., methyl acrylate, acrylonitrile, vinyl ketones) is generally considered to be a mild, highly regioselective reaction in which the enamine of a 2-alkylcyclohexanone gives rise to a 2,6-disubstituted product.[1] Although this principle is generally accepted, there have been scattered reports of anomalous reactions in which significant amounts of 2,2-disubstituted products are obtained,[2] and a detailed analysis of these reactions has been presented.[3] A particularly interesting group of these anomalous alkylations is the enamine variation of the Robinson annulation studied by Könst et al.,[2c] in which the reaction of a series of 3-alkyl- and 3,3-dialkyl-6-methyl-1-pyrrolidinocyclohexenes (**1**, Chart I) with methyl or ethyl vinyl ketone afforded varying amounts of the unexpected regioisomeric octalone. Inasmuch as a plausible general synthetic approach to the cadalane group of sesquiterpenes would utilize the normal enamine annulation, employing the pyrrolidine enamines derived from carvomenthone (1-pyrrolidino-3-isopropyl-6-methylcyclohexene (**2**)) and/or dihydrocarvone (1-pyrrolidino-3-isopropenyl-6-methylcyclohexene (**3**)), we undertook a detailed examination of the course of the reactions of enamines **2** and **3** with alkyl vinyl ketones.

At the time this work was initiated, it had been reported that enamine **2** with methyl vinyl ketone (MVK) afforded either exclusively the expected octalone (**4**)[4] or a mixture containing 70% of enone **4** and 30% of material having the gross structure of enone **5**.[2c] Enamine **3** with MVK was reported to afford exclusively the product of normal alkylation of the enamine (**6**).[2c] In view of the discrepancy in the reported course of the reactions of enamine **2** we turned our attention first to a reinvestigation of this annulation.

Repetition of the reaction of enamine **2** with MVK in benzene, duplicating as closely as possible the reported conditions, gave results which were qualitatively in agreement with those described by Könst et al.[2c] (Table I, expt 1) and indicated that this reaction gave rise to a mixture of enones **4**, **5**, and **7** in a ratio of approximately 5:4:1.

Since it had been reported that the pyrrolidine enamine of 2-methylcyclohexanone (**8**) affords exclusively the normal, 2,6-dialkylcyclohexanone on reaction with methyl acrylate in methanol,[3] in contrast to the results observed in less polar solvents,[2a,3] the annulation of enamine **2** was repeated in methanol with 2 equiv of MVK. Although

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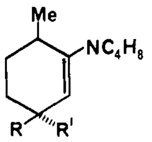
(1) (a) Stork, G.; Brizzolara, A.; Landesmann, H.; Szmuskovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207. (b) Kuehne, M. E. "Enamines"; Cook, A. G., Ed.; Marcel Dekker: New York, 1969. This author has reviewed in depth the use of enamines in organic synthesis.

(2) (a) House, H. O.; Schellenbaum, M. *J. Org. Chem.* **1963**, *28*, 34. (b) Kuehne, M. E.; King, J. C. *Ibid.* **1973**, *38*, 304. (c) Könst, W. M. B.; Witteven, J. G.; Boelens, H. *Tetrahedron* **1976**, *32*, 1415.

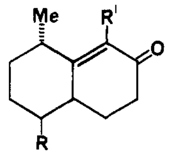
(3) Hickmott, P. W.; Firrell, N. F. *J. Chem. Soc., Perkin Trans. 1* **1978**, 340.

(4) Metge, C.; Bertrand, C. *C. R. Hebd. Seances Acad. Sci. Ser. C* **1975**, *281*, 551.

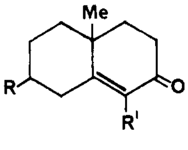
Chart I



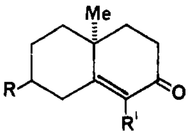
1, R, R′ = alkyl or R = alkyl; R′ = H
2, R = $(CH_3)_2CH$; R′ = H
3, R = $CH_3CH{=}CH_2$; R′ = H
8, R, R′ = H
33, R = $(CH_3)_3C$; R′ = H



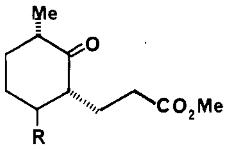
4, R = $(CH_3)_2CH$; R′ = H
6, R = $CH_3CH{=}CH_2$, R′ = H
9, R = $(CH_3)_2CH$; R′ = CH_3
16, R, R′ = H
18, R = $CH_3CH{=}CH_2$; R′ = CH_3



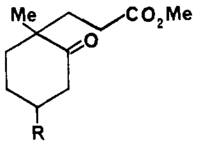
5, R = $(CH_3)_2CH$; R′ = H
10, R = $(CH_3)_2CH$; R′ = CH_3
17, R = $CH_3CH{=}CH_2$; R′ = H
20, R = $CH_3CH{=}CH_2$; R′ = CH_3
34, R = $(CH_3)_3C$; R′ = H



7, R = $(CH_3)_2CH$; R′ = H
11, R = $(CH_3)_2CH$; R′ = CH_3
19, R = $CH_3CH{=}CH_2$; R′ = CH_3



12, R = $(CH_3)_2CH$
14, R = H



13, R = $(CH_3)_2CH$
15, R = H

analogy with the results obtained by Hickmott predicts that these conditions should lead to an increase in the relative amount of octalone **4**,[3] a marked decrease in the relative amount of expected product was observed, and enone **5** now comprised nearly 70% of the product mixture (Table I, expt 2). Several attempts were made to effect the reaction of enamine **2** with 2 equiv of MVK in benzene; however, these reactions invariably gave rise to a mixture of dialkylated products. This same mixture could be obtained by treating the unhydrolyzed dienamine precursors of the mixture of enones **4**, **5**, and **7** with a second equivalent of MVK in benzene.

When the molar ratio of MVK to enamine **2** in methanol was increased to 5 (Table I, expt 3), *enone **5** was the exclusive alkylation product*, while a decrease of the ratio to 1 (Table I, expt 4) gave essentially the same results as those in which benzene was the reaction solvent. From a synthetic standpoint, the exclusive formation of enone **5** constitutes an exceedingly short and direct approach to a bicyclic compound having the relative stereochemistry of the eudesmane group of sesquiterpenes.[5] In terms of solvent effects and stoichiometry these results appeared to be inconsistent with the rationalization presented for the formation of anomalous products in the reaction of enamines with electrophilic olefins,[3] and a detailed study of this reaction was undertaken.

Table I. Reaction of Carvomenthone–Pyrrolidine Enamine (3-Isopropyl-6-methyl-1-pyrrolidinocyclohexene) with Electrophilic Olefins

			products,[b] %		
expt	olefin (equiv)	method[a]	4	5	7
1	MVK (1)	A	53	37	10
2	MVK (2)	B	26	69	5
3	MVK (5)	B		100	
4	MVK (1)	B	58	37	5
5	MVK (0.5)	B	59	35	6
6	MVK (1.3)	B	54	42	4
7	MVK (1.7)	B	62	35	3
8	MVK (1.8)	B	25	72	3
9	MVK (1.9)	B	25	69	6
10	MVK (2)	B (5 s)[c]	48	50	2
11	MVK (2)	B (30 min)	43	53	4
12	MVK (2)	B (1 h)	39	59	5
13	MVK (2)	B (2 h)	22	73	5
14	MVK (2)[d]	B (−78 °C)	66	16	18
15	MVK (2)[e]	B (0 °C)	30	35	35
16	MVK (2)[f]	B (5 s, 25 °C)	60	23	17
17	MVK (2)[g]	B (3 h, 25 °C)	28	42	30
18	MVK (2)[h]	B	19	72	9
19	MVK (1)[h]	A	25	32	40
20	MVK (2)[h]	A	6	32	62

			products,[b] %		
expt	olefin (equiv)	method[a]	9	10	11
21	EVK (1 or 2)[d]	A	100	0	0
22	EVK (1)[d]	B	100	0	0
23	EVK (2)[d]	B	47	40	13
24	EVK (5)[d]	B	31	67	2

			products,[b] %	
expt	olefin (equiv)	method	12[i]	13
25	methyl acrylate (1 or 2)	A	62	38
26	methyl acrylate (1, 2, or 5)	B	100	

[a] A, Benzene, 70–75 °C, 24 h; B, methanol, 65 °C, 3 h, unless other time or temperature specified. [b] Relative percent; all mixtures were analyzed by GLC and GLC/MS with comparison in all cases with authentic materials prepared by independent methods (see Experimental Section). No attempt was made to rigorously assign relative configurations for enones **4** and **9**. For a discussion of steric factors in similar systems see: Wilson, S. R.; Misra, R. N. *J. Org. Chem.* **1980**, *45*, 5079. [c] Aliquot taken at start of reflux. [d] Product mixture contained exclusively diketone precursors to bicyclic enones. For analysis the crude mixture was cyclized with dilute base. [e] Product mixture contained 34% of a mixture of diketones and 66% of a mixture of enones **3**–**5**. For analysis the mixture was cyclized with dilute base. [f] Crude product contained 61% diketones. [g] Crude product contained 39% diketones. [h] With 2 equiv of 4-dimethylaminopyridine. [i] Mixture of stereoisomers.

Since a profound difference had been found in product ratios for the reaction of enamine **2** by increasing the molar ratio of MVK to enamine from 1 to 2, a series of reactions was carried out in which this ratio was increased in increments from 0.5 to 2 (Table I, expts 4–9). These data indicate that with 0.5–1.7 equiv of MVK the reaction affords approximately the same ratio of enones, with octalone **4** as the major product. At molar ratios of vinyl ketone to enamine of 1.8 or larger, (expts 8 and 9) the product distribution becomes essentially that observed with 2 equiv of MVK (expt 2).

These data indicated that as the molar ratio of MVK to enamine approached 2, the relative amount of enone **4** decreased sharply, with a corresponding increase in the amount of enone **5** and suggested that enone **5** was formed via a path which involved, at least formally, two molecules

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(5) The traditional Robinson annulation usually affords a mixture of stereoisomers in which the 10-epieudesmane predominates. (a) Howe, R.; McQuillin, F. J. *J. Chem. Soc.* **1955**, 2423. (b) Barrett, H. C.; Buchi, G. *J. Am. Chem. Soc.* **1967**, *89*, 5665. (c) Humber, D. C.; Pinder, A. R. *J. Org. Chem.* **1966**, *31*, 4188 and many other references.

of MVK and one of enamine. It seemed probable that alkylation of enamine **2** was occurring initially in the normal manner and that this initial alkylation product was then interacting with a second molecule of MVK in some unspecified manner to afford the observed product(s).

In order to test this hypothesis, we carried out the reaction with 2 equiv of MVK, and aliquots were taken at intervals from 5 s to 2 h (expts 10–13). As predicted, the relative amount of enone **4** decreased with time, while the relative amount of enone **5** increased. A similar effect was noted when the temperature was decreased (expts 14–17); however, there was now also an increase in the relative amounts of the epimer of enone **5** (**7**).

The explanation which has been offered to explain the anomalous regiochemistry in reactions of the enamines of 2-alkylcyclohexanones with electrophilic olefins[3] is based on the assumption that the more stable trisubstituted isomer of the enamine is in equilibrium with the less stable tetrasubstituted isomer. It has been suggested that the more stable isomer of the enamine reacts reversibly with the alkylating agent, while the less stable isomer will effectively react irreversibly.[3] Since it has been shown that the isomerization of enamines is catalyzed by even traces of acid but is suppressed in the presence of base,[6] it would be predicted that the addition of base would greatly attenuate the amount of product arising from the tetrasubstituted isomer of the enamine. However, when the reaction of enamine **2** with MVK was carried out in the presence of 2 equiv of an added strong base [4-(dimethylamino)pyridine, pK_a = 9.70], the product ratios were essentially unchanged when methanol was used as a reaction solvent (expt 18), and in those reactions carried out in benzene (expts 19 and 20) the amount of product formed by direct alkylation of enamine **2** (enone **4**) was considerably decreased relative to that obtained in the absence of base.[7]

The reaction of enamine **2** with ethyl vinyl ketone (EVK) was also investigated (expts 21–24), and as noted by Könst et al.[2c] these reactions afford significantly smaller amounts of the abnormal alkylation products. Also, although the reactions of enamine **2** with MVK under most conditions afford directly enones **4**, **5**, and **7**, alkylation with EVK gave exclusively the diketone precursors to octalones **9–11**. In contrast to the reaction of enamine **2** with 2 equiv of MVK in benzene, reaction with 2 equiv of EVK afforded only monoalkylation products.

Since the prototype reaction for these alkylations utilized methyl acrylate as the electrophilic olefin, the reaction of enamine **2** with methyl acrylate in benzene and methanol was carried out (expts 25 and 26). These reactions follow the same course as those of 1-pyrrolidino-6-methylcyclohexene,[3] with normal alkylation to give keto ester **12** as the only product in methanol with 1, 2, or 5 equiv of alkylating agent. With 1 or 2 equiv of alkylating agent in benzene, a mixture containing 62% of **12** (both stereoisomers) and 38% of **13** was obtained.

Table II. Reactions of Various Substituted Cyclohexanone–Pyrrolidine Enamines with Electrophilic Olefins

enamine	olefin (equiv)	method[a]	products[b] (% yield)
8	methyl acrylate (1)	A	**14** (79), **15** (21)
8	methyl acrylate (2)	A	**14** (85), **15** (15)
8	methyl acrylate (1, 2, or 5)	B	**14** (100)
8	MVK (1 or 2)	A	**16** (100)
8	MVK (1)	B	**16** (100)
3	MVK (1 or 2)	A	**6** (100)
3	MVK (1)	B	**6** (100)
3	MVK (2)	B	**6** (56), **17** (44)
3	MVK (5)[c]	B	**17** (100)
3	EVK (1 or 2)[d]	A	**18** (94), **19** (6)
3	EVK (1)[e]	B	**18** (84), **19** (8), **20** (8)
3	EVK (2)[e]	B	**18** (52), **19** (5), **20** (43)
3	EVK (3)[e,f]	B	**18** (32), **19** (12), **20** (56)
3	EVK (5)[e,g]	B	**18** (48), **19** (9), **20** (42)
33	MVK (2.2)	A	**34** (100)
33	MVK (2.7)	B	**34** (100)

[a] A, benzene, 70–75 °C, 24 h; B, methanol, 65 °C, 3 h. [b] Relative percent; all mixtures were analyzed by GLC and GLC/MS with comparison in all cases with authentic materials prepared by independent methods (see Experimental Section). [c] Product mixture contained 33% uncyclized diketones. For analysis the crude mixture was cyclized with dilute base. [d] Product mixture contained 96% uncyclized diketones. For analysis the crude mixture was cyclized with dilute base. Könst et al.[2c] report enone **18** as the only product with 1 equiv of EVK. [e] Product mixture contained exclusively diketones. For analysis the crude mixture was cyclized with dilute base. [f] Contained 30% dialkylation product. [g] Contained ca. 60–65% dialkylation product.

As a point of reference, the well-documented reactions of the pyrrolidine enamine of 2-methylcyclohexanone (**8**) with both methyl acrylate[2a,3] and MVK[1a] were repeated (Table II). In agreement with the results reported by Hickmott,[3] it was found that enamine **8** with methyl acrylate in methanol afforded exclusively keto ester **14**, while in benzene mixtures of **14** and the 2,2-dialkylated product **15** were obtained. Also, enamine **8** with 1 or 2 equiv of MVK in benzene or 1 equiv of MVK in methanol afforded exclusively the normal alkylation product enone **16**,[8] in agreement with the reported course of this reaction.[1a] The attempted alkylation of enamine **8** with more than 1 equiv of MVK in methanol afforded only polyalkylation products.

By far the most dramatic example of the effect of solvent and stoichiometry on the course of these reactions is found in the reaction of the enamine of dihydrocarvone (1-pyrrolidino-3-isopropenyl-6-methylcyclohexene, **3**) with MVK (Table II). With 1 or 2 equiv of MVK in benzene as described by Könst et al. or 1 equiv of MVK in methanol, the normal product, enone **6**, is formed exclusively. With 2 equiv of MVK in methanol, a mixture of enones **6** and **17** is obtained; however, *with 5 equiv of MVK, enone 17 is the only alkylation product*. With EVK (Table II) enamine **3** gave results which were qualitatively similar to those obtained in reaction of enamine **3** with MVK; how-

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(6) Johnson, F.; Duquette, L. G.; Whitehead, A.; Dorman, L. G. *Tetrahedron* **1974**, *30*, 3241.

(7) Croft, K. D.; Ghisalberti, E. L.; Jeffries, P. R.; Stuart, A. D. *Aust. J. Chem.* **1979**, *32*, 2079. Following the completion of much of this work these authors reported the reaction of enamine **2** with 3 equiv of MVK in dioxane at room temperature to afford the diketone precursor to enone **4**. Base-catalyzed cyclization then afforded **4**, the reported properties of which are in substantial agreement with those of a sample prepared by an alternate route (see Experimental Section). In our hands, reaction of enamine **2** with 1 or 2 equiv of MVK in dioxane at reflux affords mixtures containing approximately equal parts of enones **4**, **5**, and **7**, which is predictable on the basis of solvent polarity. By analogy with the temperature effects cited above it would seem probable that enamine **2** with MVK in dioxane at ambient temperature could well afford predominently the normal alkylation product as reported by Croft et al.

(8) Enone **16** is obtained as a mixture which contains ca. 25% of a nonconjugated regioisomer, presumably with a 9,10 double bond (no vinyl methyl in the NMR).

ever, with more than 2 equiv of vinyl ketone considerable quantities of a mixture of polyalkylation products were obtained.

Discussion

The data summarized in Tables I and II clearly indicate that the explanation described above for the anomalous regiochemistry in the reaction of the enamines of 2-alkylcyclohexanones with electrophilic olefins is not applicable to the enamine variation of the Robinson annulation. The Hickmott mechanism predicts that reactions of enamines carried out in a protic solvent (e.g., methanol) should afford principally, if not exclusively, the product arising from normal, direct alkylation.[3] Yet in the reactions of enamines **2** and **3** with both MVK and EVK significantly more of the abnormal product is formed in methanol than in benzene. Also, it has been shown that enamines **2** and **3** when formed directly from the ketone and pyrrolidine contain no more than 10% of the less stable tetrasubstituted isomer.[2c,6] The equilibrium which exists between these isomers is known to be acid catalyzed and suppressed in the presence of base.[6] However, the reaction of enamine **2** with MVK in benzene affords more abnormal product in the presence of base than in its absence. Finally, the Hickmott mechanism suggests the initial reversible formation of the zwitterion derived from the more stable isomer of the enamine.[3] Thus, it is predicted that increasing the molar ratio of electrophilic olefin to enamine would shift the equilibrium in the direction of the initially formed normal alkylation product, whereas an increase in this ratio in fact decreases the amount of this product.

It has been tacitly assumed that the anomalous products in these reactions arise *via* the less stable, tetrasubstituted isomer of the enamine.[2b,c,3] However, this explanation seems a priori to be improbable for it is known that there is considerably less overlap of the unshared electrons on nitrogen with the π system of the double bond in this isomer relative to the more stable trisubstituted isomer,[6,9] thereby greatly decreasing the rate of alkylation via this isomer. Also, alkylation of the tetrasubstituted isomer of the enamine results in a very energetically unfavorable $A^{(1,3)}$ interaction in the product zwitterion,[10] causing a considerable increase in the energy of activation for alkylation of a tetrasubstituted enamine relative to its trisubstituted isomer.

We suggest an alternative rationale for these reactions which does not involve alkylation of the tetrasubstituted isomer of the enamine, which accommodates the published data, and which explains the solvent, stoichiometric, and temperature effects described above. A consideration of the data summarized in Tables I and II indicates several trends in the course of the enamine variation of the Robinson annulation: formation of the abnormal, 2,2-dialkylation products is favored by the use of a polar, protic solvent (methanol), greater than 1.8 equiv of vinyl ketone, elevated temperatures, and prolonged reaction times.

These data suggest that the abnormal products result from the net reaction of 2 equiv of vinyl ketone with 1 equiv of enamine, and the effects of reaction time and temperature suggest that these reactions occur by the relatively rapid formation of a normal alkylation product, followed by reaction with a second molecule of vinyl ketone to afford the abnormal product.

For enamines similar to **1** there are two possible stereoisomers, the more stable of which is the cis isomer in which the methyl group is quasi-axial. The energetically less favorable trans isomer is an equilibrium mixture of conformers in which the methyl group is quasi-equatorial or quasi-axial; however, the exact composition of this mixture will vary as a function of the conformational free energy of the alkyl substituent.[11] Direct alkylation of any of these isomers via the usual axial approach of the vinyl ketone would give rise to a normal alkylation product; however, it has been found that if there is severe steric interference with axial attack, the alkylation of enamines affords predominently the product of equatorial attack, presumably via a boatlike transition state.[12] Direct axial attack of reagent on the isomers of enamines similar to **1** in which there is a quasi-axial methyl group results in an axial–axial interaction in the transition state, while in those isomers which have a quasi-equatorial methyl there is an incipient $A^{(1,3)}$ interaction in the transition state. Therefore, it is probable that the reactions of enamines of 2-alkylcyclohexanones (**1**) with electrophilic olefins proceed via a twistlike transition state, thus avoiding these very energetically unfavorable $A^{(1,3)}$ or diaxial interactions.

A reaction path incorporating this suggestion and which agrees with the solvent, stoichiometric, and temperature effects summarized in Tables I and II, as well as the results described by others,[2,3] is outlined in Scheme I (G = COR, $R_2 = C_4H_8$). Alkylation of the more stable cis isomer of enamine **1** (**1a**), through any one of several possible half-twist conformers, may proceed by attack of vinyl ketone from either face to afford zwitterions **21** or **22**.[13] However, examination of models indicates that all possible twist conformers of ion **21**, and by extension the transition states leading to them, have either $A^{(1,3)}$ interactions or flagpole-type interactions between R′ and the methyl group. Consequently, this path may be considered to be of little importance, except in that case in which R′ = H. Reaction of the thermodynamically less favorable trans isomer of enamine **1** (**1b**), again through half-twist transition states, can give rise to zwitterions **23** and **24**. These zwitterions, in various twist conformations, have no $A^{(1,3)}$, flagpole, or axial–axial interactions, and ion **24** is sterically able to undergo a facile intramolecular proton shift to afford enamine **25**.[14] Zwitterions **22** and **23** may be stabilized by conversion to the corresponding dihydropyrans (**26** and **27**)[12,15] or may be protonated to the corresponding iminium ions. Ultimately the zwitterion–dihydropyran pair **22** $\rightleftharpoons$ **26** will lead to enamine **25**, while the pair **23** $\rightleftharpoons$ **27** will

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(9) Gurowitz, W. D.; Joseph, M. A. *J. Org. Chem.* **1967**, *32*, 3289.

(10) (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. (b) Johnson, F.; Malhotra, S. K. *J. Am. Chem. Soc.* **1965**, *87*, 5492. (c) For a recent concise discussion of $A^{(1,3)}$ and $A^{(1,2)}$ interactions see: Narula, A. S. *Tetrahedron Lett.* **1981**, 2017.

(11) Although conformational free energies of many alkyl groups are known, to the best of our knowledge, few if any have been determined for those in allylic positions on a cyclohexene. It is reasonable to assume that the $A^{(1,2)}$ interactions involving the methyl group are unaffected by the nature of the other alkyl substituent.

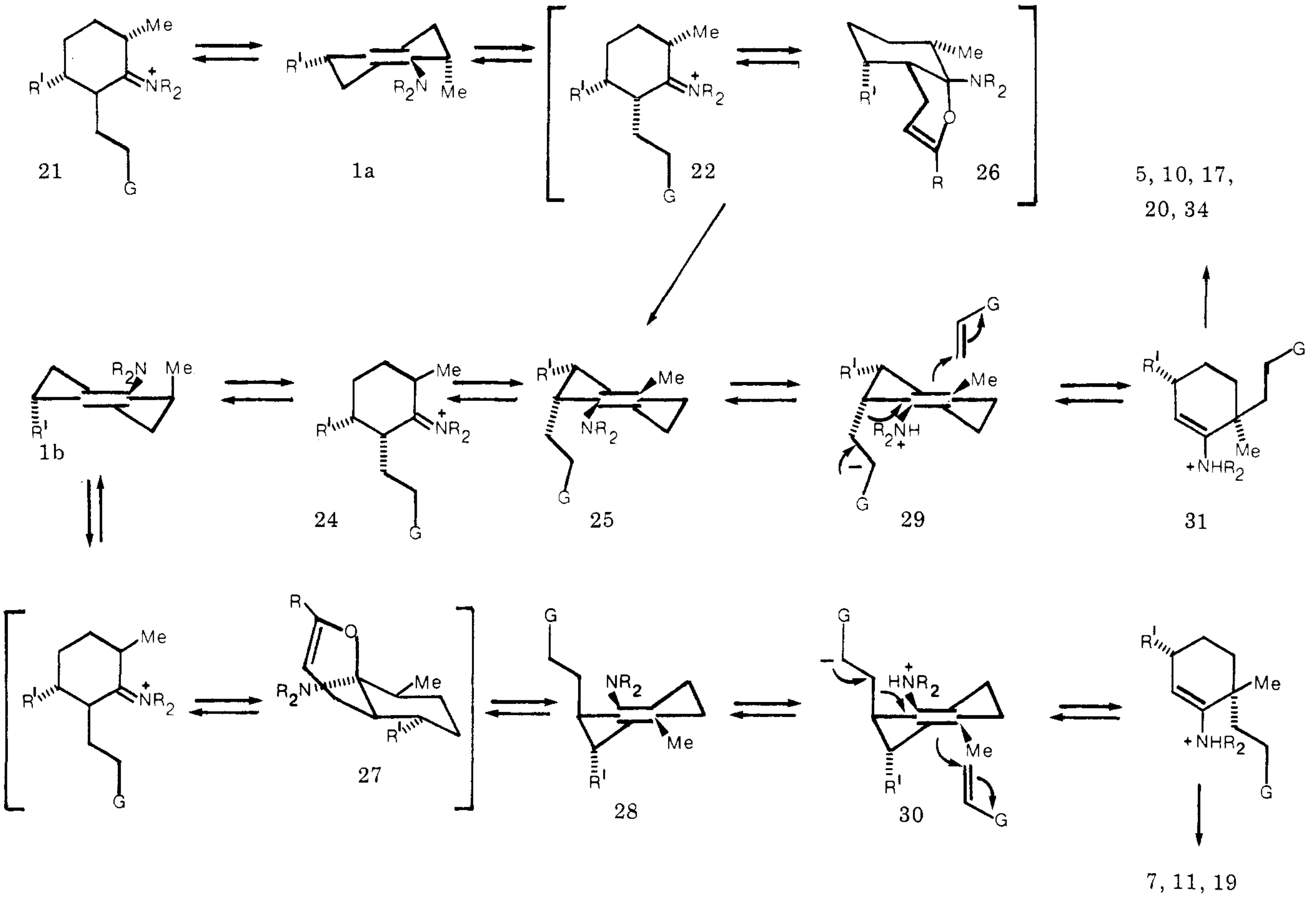
(12) (a) Fabrissin, S.; Fattuta, S.; Risaliti, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 109. (b) Fabrissin, S.; Fattuta, S.; Malusa, N.; Risaliti, A. *Ibid.* **1980**, 686. (c) Forchiassin, M.; Risaliti, A.; Russo, C.; Calligaris, M.; Pitacco, G. *Ibid.* **1974**, 660 and other papers in this series. (d) Forchiassin, M.; Risaliti, A.; Russo, C. *Tetrahedron* **1981**, *37*, 2921. These authors cite several examples in which enamines react with electrophiles via equatorial attack in the absence of steric interference to axial attack.

(13) By analogy with a similar reaction, it is assumed that the formation of the zwitterion is reversible. Risaliti, A.; Valentin, E.; Forchiassin, M. *Chem. Commun.* **1969**, 233.

(14) The conformations indicated for enamines **25** and **28** are those in which the carbonyl containing side chain is quasi-axial. While this is almost certainly the more stable conformation for enamine **25** in which R′ is equatorial, enamine **28** will contain a significant amount of the alternate half-chair conformer, in which R′ is equatorial but in which there exists an $A^{(1,2)}$ interaction involving the side chain plus a gauche interaction between R′ and the side chain.

(15) (a) Fleming, I.; Harley-Mason, J. *J. Chem. Soc.* **1964**, 2165. (b) Fleming, I.; Karger, M. H. *J. Chem. Soc. C* **1967**, 226. For convenience only, the most stable conformers of dihydropyrans **26** and **27** are shown.

Scheme I



afford enamine **28**. At this stage, cyclization of either enamine **25** or **28** will afford the enone expected from the normal enamine variation of the Robinson annulation.[16]

The abnormal products arise from conversion of enamines **25** and **28** to the corresponding enolates (**29** and **30**), effected either by external base or the relatively strongly basic tetrasubstituted enamine,[6] followed by reaction with a second molecule of vinyl ketone to afford isomeric enolates **31** and **32**.[17] Enolate **31** on protonation would afford the enamine precursor to those enones in which R′ and the methyl group are cis (e.g., **5**, **10**, **17**, **20**), while enolate **32** is the precursor to those in which they are trans (**7**, **11**, **19**). All of the transformations of enamines **25** and **28**, with the exception of cyclization to the dienamine precursors of the product enones, are assumed to be reversible.

This reaction path also provides an explanation for the observation that the anomalous annulation products are principally those isomers in which the angular methyl group and R′ are cis. The preferred conformation of enamine **25** is that depicted in which R′ is equatorial and the oxobutyl or oxopentyl side chain is quasi-axial, while enamine **28** is a mixture of the conformation depicted and an alternative conformer in which R′ is equatorial. The composition of this mixture will be a function of the conformational free energy of R′ and the magnitude of the $A^{(1,2)}$ interaction in the other half-chair conformer of **28**. The rate of conversion of enamine **25** to ion **31** is predictably faster than the rate of conversion of enamine **28** to ion **32**, leading to the preferential formation of annulation products derived from ion **31**. In the presence of an added, external base, the reversion of enamine **28** to its precursor, dihydropyran **27** (or zwitterion **23**), will be suppressed, and the formation of more of the product derived from ion **32** under these conditions is explained.

The overall product distribution in the reactions of the enamines of substituted 2-alkylcyclohexanones with vinyl ketones then becomes a function of the position of the equilibria involving enamines **25** and **28** as well as ions **29**, **31** and **30**, **32** and of the relative rates at which these equilibria are established combined with the relative rates of conversion of these ions, or the derived enamines, to the bicyclic enones or their precursors. These equilibria are in turn profoundly affected by the reaction time, solvent, temperature, and stoichiometry as well as the structure of the substrate enamine.

The effect of stoichiometry is quite straight forward. The suggested reaction path requires a step incorporating two molecules of vinyl ketone per molecule of enamine, and on the assumption that the initial alkylation is rapid compared to the alkylation–dealkylation equilibrium, the necessity of a second equivalent of vinyl ketone becomes apparent. While greater than 2 equiv of vinyl ketone will

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(16) It has been observed that reaction of the enamine of 2,5,5-trimethylcyclohexanone with a variety of electrophilic olefins affords 60–100% of the abnormal annulation product.[2c] In this case geminal substitution at C-5 causes the alternate half-chair conformer of enamine **28** to be destabilized by an additional gauche interaction between a methyl group and the oxygen. If the reversibility of all steps in Scheme I is assumed, reaction would then be favored via enamine **25** and ion **31**, affording a preponderence of the abnormal product as is observed.

(17) It is known that dihydropyrans which can cyclize to the dienamine precursors of enones (e.g., **26** and **27**) are stable at low temperature but are rapidly coverted to dienamines at room temperature.[15] The details of this conversion are, however, not known with certainty, but it has been suggested that this step is initiated by traces of water or pyrrolidine. (a) Spencer, T.; Schmiegel, K. V. *Chem. Ind. (London)* **1963**, 1765. (b) White, J. D.; Ruppert, J. F.; Avery, M. A.; Torii, S.; Nokami, J. *J. Am. Chem. Soc.* **1981**, *103*, 1813. These authors describe a related reaction.

not affect the position of the equilibria involving ions **29** through **32**, it will affect the initial equilibrium between the enamine and the zwitterions and the rates at which the various steps occur.

Relatively short reaction times and lower temperatures would favor the formation of the normal reaction products, while longer reaction times would afford increasing amounts of products derived from ions **31** and **32**. In those cases in which the reaction proceeds without cyclization to the dienamine, the overall product distribution becomes a function of the relative position of the equilibria outlined in Scheme I, while if cyclization occurs, the relative rates of cyclization of the various intermediates are superimposed on the equilibria.

In terms of solvent effects, it would be expected that ionic intermediates are stabilized, and reactions via these intermediates are facilitated in a polar solvent. In a nonpolar solvent (benzene) the equilibrium between zwitterions **22** and **23** and the corresponding dihydropyrans (**26**, **27**) would favor the dihydropyrans,[2b] while the intramolecular proton transfer to afford enamine **25** should be relatively unaffected by solvent polarity. The result of this sequence would be the relatively slow generation of low concentrations of enamines **25** and **28**, which would favor the formation of the normal annulation products.

The structure of the substrate enamine will also affect the various equilibria depicted in Scheme I and the relative rates of cyclization of the various product enamines. The presence of an alkyl group at C-3 (R′) destabilizes enamine **28** relative to enamine **25**.[14] On the other hand, dihydropyran **27** in which R′ is equatorial will be more stable than **26** in which this group is axial and in a diaxial relationship to the oxygen of the heterocyclic ring. Of the four possible isomeric enamines (**25**, **28**, and those derived from ions **31** and **32**), the enamine derived from **31** should cyclize most rapidly. Of all the possible enamines depicted, this is the only one in which the principal conformation will have both the oxobutyl side chain and R′ quasi-equatorial and equatorial, respectively. Also, the derived bicyclic products (e.g., enones **5** and **17**) have the substituent alkyl group equatorial, while those derived via ion **32** have an axial alkyl substituent. The other half-chair conformer of enamine **28** would also be expected to cyclize readily to an enone in which the alkyl group and oxobutyl side chain are both equatorial. As the steric bulk of R′ is increased, not only is the conformer of enamine **28** in which R′ is axial destabilized but the other half-chair conformer also is destabilized by gauche interactions between R′ and the side chain.[16] In the case in which R′ = H (the enamine of 2-methylcyclohexanone), not only should the cyclization of any intermediate enamine be facile but an alternative overall reaction path through zwitterion **21** with intramolecular proton transfer to a product enamine also is available.

This explanation predicts that a bulky group at C-5 (cf. *tert*-butyl) would preclude reactions via either half-chair conformer of enamine **28** or dihydropyran **26**. Also, enamine **25** would be destabilized by gauche interactions between R′ and the side chain, thus favoring reaction via ion **31**. In accordance with this prediction, the enamine of 2-methyl-5-*tert*-butylcyclohexanone (**33**) with MVK in either methanol or benzene gave enone **34** as the exclusive annulation product.

The lack of cyclization observed in alkylations with ethyl vinyl ketone is most readily explained if it is assumed that the cyclization step is initiated by formation of the enamine of the side-chain carbonyl[17] and that this step is less facile with the ethyl than the methyl ketone.[18]

The solvent effects described by Hickmott[3] for the reactions of enamine **8** with methyl acrylate may also be rationalized according to Scheme I. The zwitterions derived from methyl acrylate (Scheme I, G = CO_2CH_3) will be considerably more basic than those derived from vinyl ketones, and in methanol they would be expected either to protonate, as suggested by Hickmott[3], or to undergo intramolecular proton transfer to give a new enamine.[19] Protonation would be expected to be essentially irreversible in this case due to the difference in acidity between the α-protons of an ester and a ketone.

It is known that the zwitterions derived from the reactions of an enamine and an acrylic ester exist in equilibrium with a carbalkoxycyclobutane, and this equilibrium should favor the cyclobutane in nonpolar solvents.[2b] The abnormal products observed in the reactions of enamines such as **1** with methyl acrylate in benzene would then proceed from a cyclobutane intermediate to an enolate ion and undergo an alkylation–dealkylation step as described for the vinyl ketone reaction.

Experimental Section

Microanalyses were performed by Atlantic Microlab, Atlanta, GA. Infrared spectra, reported in reciprocal centimeters, were measured as liquid films between sodium chloride plates on a Perkin-Elmer Model 137 spectrophotometer. Proton magnetic resonance spectra were recorded in deuteriochloroform or, where specified, benzene-d_6 solutions at 90 MHz by using a JEOL FX-90 Q spectrometer or at 60 MHz by using either a Varian A-60A (60 MHz) or a Hitachi Perkin-Elmer R-24 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane as an internal standard. Gas chromatographic analyses were performed on an F&M Model 810 instrument utilizing a hydrogen flame-ionization detector. Columns employed were 2 m × 3.3 mm with a stationary phase of 10% SE-30 on a solid support of 80–100-mesh Chromosorb W, 3 m × 3.3 mm OV-17 on 80–100-mesh Chromosorb W, and 3 m × 3.3 mm 10% Carbowax 20M on 80–100-mesh Chromosorb WHP. Product ratios were determined by relative GLC peak areas by using authentic samples of product bicyclic enones for calibration and identification. Product ratios for a given run are accurate to within ±1%, and product ratio reproducibility for duplicate runs is 4% or less for duplicate runs unless noted otherwise. Mass spectral measurements were performed on a Hewlett-Packard 5985 GC/MS system using a 0.6 m × 3.3 mm column of 2% OV-101 on 100–120-mesh Chromosorb WHP. Electron ionization was used in all cases for mass spectral determinations. Melting points, which were uncorrected, were obtained by using a Mel-Temp apparatus or a Kofler hot-stage apparatus.

Reagents. The ketones used as substrates for the formation of the enamines were either commercial samples or were prepared by published procedures. The bicyclic enones used for comparison were synthesized as described below or were prepared by Swain.[20]

Preparation of Pyrrolidine Enamines. The enamines of carvomenthone (2-methyl-5-isopropylcyclohexanone) and 2-methylcyclohexanone were prepared from the ketone and pyrrolidine by using published procedures[1a,6] and possessed physical and spectral properties in agreement with those reported. In contrast to the results reported by Könst et al.[2c] the enamine of dihydrocarvone (2-methyl-5-isopropenylcyclohexanone) could not be formed by the direct interaction of the reagents in benzene. The enamine was formed, however, by using the procedure of Szmuskovicz[21] in which a solution of 10.0 g (0.07 mol) of ketone, 12 mL of pyrrolidine, and a crystal of *p*-toluenesulfonic acid were

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[18] Not only would reaction of pyrrolidine as a nucleophile be slower with an ethyl than with a methyl ketone, but the monosubstituted enamine derived from the methyl ketone should be more reactive than that derived from the ethyl ketone.

[19] Pandit, U. K.; Huisman, H. O. *Tetrahedron Lett.* **1967**, 3901. These authors have demonstrated that intramolecular proton transfer occurs in the reaction of an enamine with a substituted acrylate with methanol as a reaction solvent.

[20] Swain, W. E. Ph.D. Dissertation, Clemson University, 1979.

[21] Szmuszkovicz, J. *Adv. Org. Chem.* **1963**, *4*, 1.

heated at reflux in 50 mL of toluene for 96 h under a Soxhlet apparatus in which the thimble was packed with 3A molecular sieves. The toluene and excess pyrrolidine were removed at reduced pressure, and the residue was fractionally distilled to give 10.5 g of enamine [bp 96–97 °C (0.40mm)], the spectral properties of which agreed with those reported.[5]

General Procedure for the Alkylation of an Enamine with an Electrophilic Olefin. Enamines were alkylated by using the procedures of Könst et al.[2c] or Hickmott[3] in which a sample of 0.100–0.400 g of the appropriate purified enamine under nitrogen was dissolved in 0.435 mL of solvent (benzene, methanol, or dioxane)/mol of enamine. The desired number of molar equivalents of electrophilic olefin was added rapidly, with stirring, to the reaction mixture which was heated to the desired temperature for the appropriate length of time. When benzene was used as the solvent, the electrophilic olefin was first dissolved in 0.109 mL of benzene/mmol of enamine before the olefin was added to the reaction mixture. After the designated alkylation period, a solution of 25 mL of acetic acid, 25 mL of water, and 12.5 g of sodium acetate was added to the reaction mixture in the amount of 0.217 mL/mmol of starting enamine. The mixture was then brought to reflux for 1 h, cooled, poured into water, and extracted three times with ether. The combined ethereal extracts were washed with saturated bicarbonate, water, and brine and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The crude product was then analyzed by GLC and, in most cases, distilled and reanalyzed by GLC and IR, NMR, and mass spectrometry.

General Procedure for the Cyclization of Enamine Alkylation Products. In those cases in which the enamine alkylation was carried out by using a vinyl ketone and the hydrolysis product contained uncyclized diketone precursors to the bicyclic enones, the distilled hydrolysis product was cyclized with dilute base according to the following procedure. The distilled hydrolysis product from the alkylation was dissolved in 0.65 mL of freshly prepared 5% ethanolic potassium hydroxide/mmol of starting enamine. The stirred mixture was heated at reflux under dry nitrogen for 1 h, cooled, neutralized with 10% acetic acid, poured into water, and extracted three times with ether. The products were isolated and characterized as described above.

***ent*-14-Nor-10-epicadin-1-en-3-one (4).** To 1.01 g (0.005 mol) of 2-(3-oxobutyl)-3-isopropyl-6-methylcyclohexanone[22] was added, with stirring, 3 mL of 5% ethanolic potassium hydroxide. The reaction mixture was stirred at reflux under nitrogen for 1 h. After cooling, the mixture was neutralized by the addition of 10% aqueous acetic acid, poured into water, and extracted twice with ether. The combined ethereal extracts were washed with water, dried, and filtered, and the solvent was removed at reduced pressure. Distillation afforded 0.582 g (63%) of enone 4, bp 150 °C (air bath; 0.01 mm). Analysis by GLC (SE-30, 190 °C) indicated a 68:32 ratio of the conjugated enone to a nonconjugated isomer which had a shorter retention time: IR 1710 (sh), 1675, 1620, 887; NMR δ 0.83 (d, 3 H, J = 6.5 Hz, CH_3CH), 0.94, (d, 3 H, J = 6.5 Hz, CH_3CH), 1.07 (d, 3 H, J = 6.3 Hz, CH_3CH), 5.76 (m, 1 H, $={CH}$); mass spectrum, m/e (relative intensity) 206 (79), 163 (20), 137 (30), 135 (67), 124 (100), 121 (40), 82 (31), 79 (34), 78 (75), 77 (38).[23] The 2,4-dinitrophenylhydrazone gave red needles, mp 142–144 °C (from ethanol).

Anal. Calcd for $C_{20}H_{26}N_4O_4$: C, 62.18; H, 6.74; N, 14.51. Found: C, 62.11; H, 6.81; N, 14.46.

2-(3-Oxopentyl)-3-isopropyl-6-cyclohexanone. This material was obtained from 2-methyl-5-isopropylcyclohexanone by using the general procedure of Corey and Nozoe[22] as a colorless liquid [bp 125 °C (air bath; 0.04 mm)] which was homogeneous by GLC (OV-17, 180 °C) and TLC: IR 1720; NMR δ 0.84–1.22 (6 peaks, CH_3CH); mass spectrum, m/e (relative intensity) 238 (4), 195 (100), 111 (28), 95 (15).

***ent*-2-Methyl-14-nor-10-epicadin-1-en-3-one (9).** Enone 9 was prepared by cyclization of 2-(3-oxopentyl)-3-isopropyl-6-methylcyclohexanone by the procedure described above. From 0.338 g (0.001 mol) of diketone there was obtained 0.285 g (91%) of enone 9 as a pale yellow oil [bp 110 °C (air bath; 0.025 mm)] which was homogeneous to GLC (SE-30, 163 °C): IR 1675, 1620; NMR δ 0.83 (d, 3 H, J = 6 Hz, CH_3CH), 0.93 (d, 3 H, J = 6.0 Hz, CH_3CH), 1.08 (d, 3 H, J = 7.2 Hz, CH_3CH), 1.78 (s, 3 H, $CH_3C{=}$); mass spectrum, m/e (relative intensity) 220 (99), 149 (31), 138 (57), 136 (100), 135 (35), 93 (31). The 2,4-dinitrophenylhydrazone was obtained as red needles, mp 182–183 °C (from ethanol).

Anal. Calcd for $C_{21}H_{28}N_4O_4$: C, 62.98; H, 7.05; N, 13.99. Found: C, 62.87; H, 7.07; N, 13.94.

2-(3-Oxobutyl)-3-isopropenyl-6-methyl-cyclohexanone. This diketone was obtained from dihydrocarvone and methyl vinyl ketone by the general procedure of Corey and Nozoe[22] as a colorless oil: bp 145 °C (air bath; 0.01 mm); IR 1710, 1640, 890; NMR δ 0.99 (d, 3 H, J = 6 Hz, CH_3CH), 1.70 (d, 3 H, J = 1 Hz, $CH_3C{=}$), 2.06 (s, 3 H, CH_3CO), 4.68 (m, 2 H $C{=}CH_2$); mass spectrum, m/e (relative intensity) 222 (86), 180 (32), 179 (53), 164 (36), 152 (53), 151 (100), 149 (62), 137 (77), 123 (49).

***ent*-14-Nor-10-epicadin-1,11-dien-3-one (6).** Enone 6 was obtained by cyclization of the corresponding diketone by the procedure described above. From 0.980 g (0.004 mol) of diketone there was obtained 0.723 g (80%) of enone 6 as a pale yellow oil, bp 105 °C (air bath; 0.05 mm). GLC (SE-30, 190 °C) indicated that this material contained 23% of a nonconjugated regioisomer: IR 1710 (sh), 1680, 1625, 887; NMR δ 1.10 (d, 3 H, J = 6 Hz, CH_3CH), 1.70 (d, 3 H, J = 1 Hz, $CH_3C{=}C$), 4.74 (d, 2 H, J = 1 Hz, $CH_2{=}C$), 5.78 (m, 1 H, $C{=}CH$); mass spectrum, m/e (relative intensity) 204 (100), 162 (88, 161 (42), 147 (77), 133 (44), 119 (41), 107 (34), 105 (62), 95 (55).

Anal. Calcd for $C_{14}H_{22}O$: C 82.30; H, 9.87. Found: C, 82.12; H, 9.85.

2-(3-Oxopentyl)-3-isopropenyl-6-methylcyclohexanone. This diketone was prepared from dihydrocarvone and ethyl vinyl ketone by using the general procedure of Corey and Nozoe[22] as a colorless oil, bp 105 °C (air bath; 0.01 mm). GLC (SE-30, 180 °C) indicated that it was an equimolar mixture of two stereoisomers: IR 1710, 1640, 890; NMR (C_6D_6) δ 0.99–1.02 (6 peaks, 6 H, CH_3CH and CH_3CH_2), 1.58, 1.66 (br, s 3 H, $CH_3C{=}$, each isomer), 4.80 (m, 2 H, $CH_2{=}C$); mass spectrum, m/e (relative intensity) 236 (63), 152 (33), 151 (60), 149 (38), 137 (43), 121 (34), 109 (43).

2-Methyl-11-norcadina-1,12-dien-3-one (18). The base-catalyzed cyclization of 4.31 g (0.018 mol) of diketone afforded 1.54 g (39%) of enone 18 as a colorless oil [bp 110 °C (air bath; 0.05 mm)] which was homogeneous to GLC (SE-30, 190 °C): IR 1670, 1620, 883; NMR δ 1.13 (d, 3 H, J = 6.9, CH_3CH), 1.71, 1.77 (br s, 3 H each, $CH_3C{=}C$), 4.70 (br s, 2 H, $CH_2{=}C$); mass spectrum, m/e (relative intensity) 218 (55), 203 (47), 147 (33), 136 (47), 109 (63), 93 (44), 81 (100).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.46; H, 10.18.

2-[2-(Carbomethoxy)ethyl]-3-isopropyl-6-methylcyclohexanone (12). To a stirred solution of 1.81 g (0.009 mol) of 1-pyrrolidino-3-isopropyl-6-methylcyclohexene in 3.8 mL of dry methanol was added 1.50 g (0.012 mol) of methyl acrylate. The solution was heated at reflux for 3 h, 1.9 mL of the buffered acetic acid hydrolysis mixture (see above) was added, and the mixture was heated at reflux for an additional hour, poured into water, and extracted three times with ether. The combined ethereal extracts were washed with saturated aqueous sodium bicarbonate, water, and brine and dried, and the solvent was removed under reduced pressure. Chromatography on Woelm silica gel and elution with 15% ethyl acetate in benzene afforded 1.44 g (69%) of clear colorless oil, homogeneous to GLC (SE-30, 180 °C): IR, 1740, 1705; NMR (C_6D_6) δ 0.71, 0.73 (pair of d's, 6 H, J = 7 Hz, $(CH_3)_2CH$), 0.94 (d, 3 H, J = 6.6 Hz, CH_3CH of 2,6-trans isomer), 0.97 (d, 3 H, J = 6.1 Hz CH_3CH of 2,6-cis isomer; integration of these signals showed a 71:29 ratio of cis to trans isomer), 3.37 (s, 3 H, OCH_3); mass spectrum, m/e (relative intensity) 240 (3), 197 (42), 165 (100), 137 (30), 111 (43), 55 (38). A small portion of the chromatographed product was distilled for analysis; bp 90 °C (air bath; 0.035 mm).

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.93; H, 10.09.

1-Pyrrolidino-3-*tert*-butyl-6-methylcyclohexene (33). A mixture of 10.1 g (0.060 mol) of 2-methyl-5-*tert*-butyl cyclohexanone, 10.0 g (0.14 mol) of pyrrolidine, and 20 mL of dry benzene was heated at reflux under helium with continuous re-

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[22] Corey, E. J.; Nozoe, S. *J. Am. Chem. Soc.* **1965**, *87*, 5728.

[23] Subsequent to our preparation of this material, it was described by Croft et al.[7]

moval of water for 116 h. The benzene and excess pyrrolidine were removed by distillation, and the residue was fractionally distilled to give 1.40 g (10%) of enamine **33** [bp 112–114 °C (0.7 mm)] which contained 20% of the starting ketone (NMR): IR 1630, 1710 (residual C=O); NMR δ 0.86 (s, 9 H, *tert*-butyl), 1.09 (d, J = 7.1 Hz, CH_3CH), 4.15 (d, J = 1.5 Hz, vinyl H of major isomer), 4.41 (br s, vinyl H of minor isomer).

The lower boiling fractions from the reaction mixture consisted of recovered ketone and mixtures of the ketone and enamine.

11-Methyl-14-noreudesm-4-en-3-one (34). To a solution of 0.469 g (0.0021 mol) of enamine **33** in 1.0 mL of dry methanol, under nitrogen, was added rapidly, with stirring, 0.389 g (0.0056 mol) of MVK. The reaction mixture was heated at reflux for 5 h and then hydrolyzed, and the products were isolated by the procedure described above. The combined crude products from five runs of approximately this scale using a total of 2.44 g (0.012 mol) of enamine were combined and distilled [bp 136–146 °C (air bath; 0.01 mm)] to give 0.426 g (18%) of enone **34** as a yellow oil, contaminated with 18% of the starting cyclohexanone (GLC), which was dissolved in hexanes and chromatographed on silica gel. Elution with hexanes–ether mixtures gave 0.187 g of enone **34** as a white crystalline solid which was homogeneous to GLC. Repeated crystallization from pentane at −15 °C afforded material with the following: mp 78–78.5 °C; IR 1645, 2910; NMR δ 0.90 (s, 9 H, *tert*-butyl), 1.21 (s, 3 H, CH_3), 5.73 (s, 1 H, C=CH); mass spectrum, *m/e* (relative intensity) 221 (13), 220 (70), 149 (80), 136 (44), 135 (47), 124 (38), 123 (48), 122 (62), 121 (100).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.68; H, 10.97.

GLC analysis of the crude reaction mixture indicated that enone **34** and 2-methyl-5-*tert*-butylcyclohexanone were the only volatile substances present.

Acknowledgment. The JEOL FX-90 Q NMR spectrometer was obtained through an NSF Support of Research Equipment grant.

Geminate-Substituted Cyclopentadienes. 1. Synthesis of 5,5-Dialkylcyclopentadienes via 4,4-Dialkylcyclopent-2-en-1-ones[1]

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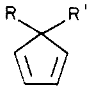
A synthetic route for the preparation of 5,5-dialkylcyclopentadienes (1) via 4,4-dialkylcyclopent-2-en-1-ones (3) is described. Beginning with ketones (in which the two carbonyl substituents will become the two alkyl groups in the title compounds), the route traverses the Guareschi imides **5**, 3,3-dialkylglutaric acids **4** and their ethyl esters **7**, masked acyloins **8**, cyclopentenones **3**, alcohols **9**, and bromides **10** to reach the dienes **1**. Physical properties of five such derivatives **1** and **3** (dimethyl, methylethyl, diethyl, methyl-*n*-propyl, and methylisopropyl) are presented.

Introduction

It is possible to formulate a number of mechanistic problems which could be addressed if even small quantities of geminate-substituted cyclopentadienes (1) were readily available. Indeed, a few such studies already have been carried out, using materials synthesized rather laboriously by a number of procedures. For example, Brown et al.[3] needed apobornene and made it by a circuitous method not involving a Diels–Alder reaction of 5,5-dimethylcyclopentadiene since "the synthesis of the diene appeared to offer severe difficulties". Apobornene and apobornadiene were subsequently prepared from 5,5-dimethylcyclopentadiene,[4] available from a route essentially the same as that outlined by us earlier[1] and reported in detail in this paper.



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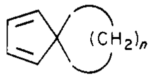
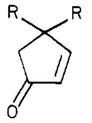


2



3

Most of the relevant mechanistic work already described involves the thermal sigmatropic rearrangements of trimethylcyclopentadienes,[5-8] pentamethylcyclopentadiene,[9] 5,5-diphenylcyclopentadiene,[10] and various spirocyclic derivatives **2**,[11-19] some of which can be prepared relatively easily.

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[1] Preliminary results were presented as a paper: Holder, R. W.; Daub, J. P.; Baker, W. E.; Gilbert, R. "Abstracts of Papers", 175th National Meeting of the American Chemical Society, Anaheim, CA, March 1978; American Chemical Society, Washington, DC, 1978; ORGN 80.

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