water, and dried and solvent removed under reduced pressure to afford 800 mg (80% recovery) of crystalline solid. Glpc analysis on a 10 ft × 0.25 in. column packed with 20% GE-SF-96 silicon oil on 60–80 mesh Chromosorb W-DMCS at 200° and helium flow of 65 cc/min indicated the presence of **2** (96%), trace quantities of **4**, and several unidentified peaks. No evidence for the *endo*-chloro epimer **3** was observed. A sample of **2** collected by preparative glpc showed mp 70–72°. A mixture melting point with an authentic specimen of **2**, mp 67.5–69°, showed no depression, mp 67.5–69.5°.

Treatment of 2 with Aluminum Chloride in Diglyme.—A mixture of 1.00 g (5.8×10^{-3} mol) of **2**, mp 67–69°, and 10 mg (7.5×10^{-5} mol) of aluminum chloride in 3 ml of diglyme was heated under a nitrogen atmosphere at 100° for 16 hr. After work-up as above there was isolated 840 mg (84% recovery) of **2** as colorless crystals, mp 69–71°; there was no depression of melting point on admixture with an authentic specimen of **2**.

Treatment of Olefin 4 with Aluminum Chloride in Diglyme.—A mixture of 1.47 g (1.08×10^{-2} mol) of **4** and 20 mg (1.5×10^{-4} mol) of aluminum chloride in 5 ml of diglyme was heated at 100° for 16 hr. After work-up as above there was isolated 1.37 g (93% recovery) of **4** as colorless crystals, mp 94–98°. A mixture melting point with the starting material **2**, mp 97–99°, showed no depression, mp 94–98°.

Treatment of 4 with Hydrogen Chloride–Aluminum Chloride in Diglyme.—A solution of 1.00 g (7.4×10^{-3} mol) of **4** and 20 mg (1.4×10^{-4} mol) of aluminum chloride in 5 ml of diglyme, saturated with gaseous hydrogen chloride, was heated at 100° for 6 hr. After work-up as above there was isolated 870 mg of soft crystals. Glpc analysis on a 10 ft × $^1/_8$ in. column packed with 20% Reoplex on 60–80 mesh Chromosorb W-DMCS at 200° with a helium flow of 60 cc/min showed **2** (91%, relative retention time 4.3 min), the chloro ketone **3** (2%, relative retention time 10.0 min), four unidentified chloro ketones: relative retention times 11.3 min (2%), 11.7 (2%), 12.8 (1%), 13.0 (0.3%) and **2** (0.4%, relative retention time 18.0 min).

Registry No.—**1**, 15973-61-2; **2**, 16031-45-1; **3**, 16031-46-2; **4**, 4844-11-5; **6a**, 16031-48-4; **7a**, 15973-62-3.

Acknowledgments.—The authors are indebted to Dr. W. Yellin for the PE-421 infrared measurements and to Dr. J. J. McLeskey, III, for the precise nmr decoupling experiments. Informative discussions with Professor William von E. Doering are gratefully acknowledged.

Iron Carbonyl Catalyzed Isomerization of Unsaturated Ethers and Esters. The Effect of Carbomethoxy and Methoxy Groups on Olefin Equilibria[1]

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Equilibrations of the double bonds in methyl *n*-alkenyl- and cyclohexenylcarboxylates and ethers have been studied. Iron pentacarbonyl in hydrocarbon solvents at reflux (125–150°) or with ultraviolet light at 20° was used to catalyze isomerization. Distribution of the double bonds to all possible positions is found with this catalyst system. For example, the equilibrium distribution of methyl octenoate isomers is 2-octenoate, 18%; 3-octenoate, 8%; 4-octenoate, 21%; 5-octenoate, 24%; 6-octenoate, 29%; and 7-octenoate, 1%. Equilibration of methyl pentenyl isomers gave the distribution 1-pentenyl, 86%; 2-pentenyl, 5%; 3-pentenyl, 8%; and 4-pentenyl, 1%. These data are rationalized on the basis of two main effects: (a) the inductive electron-withdrawal destablization effect of the carbomethoxy and methoxy groups and (b) the conjugative stabilization effects of these groups. The net effect of a carbomethoxy group on the stability of an α,β isomer is approximately that of an alkyl group. A methoxy group stabilizes an α,β isomer by a factor of 10 compared to an alkyl group. The relatively low percentages of β,γ isomers found in both series are explained by the inductive destabilization effect of the $-CH_2CO_2CH_3$ and $-CH_2OCH_3$ groups.

Several transition metal compounds have recently been used as extremely efficient isomerization agents of *n*-olefins.[2] For example, Asinger and coworkers[3] have described the double bond isomerization of 1-undecene to an equal distribution of internal isomers by iron pentacarbonyl catalyst at 50° for 1 hr in the presence of ultraviolet light. Other workers[4,5] have shown that the mixture of isomers from iron carbonyl catalyzed isomerizations closely parallels the theoretical thermodynamic equilibrium values. The use of iron carbonyls to catalyze the isomerization of unsaturated alcohols to aldehydes and ketones has been reported.[6,7] Enol alcohols formed in these isomerizations are irreversibly converted into their carbonyl forms, precluding a study of olefin equilibrium in those systems. We wished to use iron carbonyl catalysts for the isomerization of functionally substituted olefins under conditions of reversible equilibrium. By a comparison of the relative percentages of olefin isomers at equilibrium, the effect of the functional group on the relative stability of the various olefin isomers can be ascertained.

Almost four decades ago, Kon and Linstead and collaborators[8] investigated the effects of carbonyl and cyano groups on three carbon atom olefin equilibria as depicted in eq 1. Their results show that the carbonyl

$$\underset{\mathbf{1}}{\mathrm{RCH_2CH_2CH{=}CHX}} \overset{B^-}{\rightleftharpoons} \underset{\mathbf{2}}{\mathrm{RCH_2CH{=}CHCH_2X}} \qquad (1)$$

$$\mathrm{R = alkyl}$$
$$\mathrm{X = CO_2R,\ CO_2H,\ CN,\ COR'}$$

or cyano substituents favor isomer **1** over isomer **2** by a factor of 2–11:1. Under the basic isomerization conditions employed, migration of the double bond further down the chain in **2** is extremely slow due to the low acidity of the unactivated allylic hydrogen atoms compared to the hydrogen atoms adjacent to the substituent in **2**.

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(1) Presented in part at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 9–14, 1967, Abstracts, p O159.

(2) For up-to-date discussions on the mechanism of olefin isomerization by transition metal catalysts, see R. Cramer and R. V. Lindsey, Jr., *J. Amer. Chem. Soc.*, **88**, 3534 (1966), and M. Orchin, *Advan. Catal.*, **16**, 1 (1966).

(3) (a) F. Asinger, B. Fell, and K. Schrage, *Chem. Ber.*, **98**, 372 (1965); (b) *ibid.*, 381 (1965).

(4) M. D. Carr, V. V. Kane, and M. C. Whiting, *Proc. Chem. Soc.*, 408 (1964).

(5) T. A. Manuel, *J. Org. Chem.*, **27**, 3941 (1962).

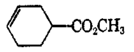
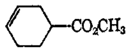
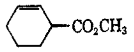
(6) G. F. Emerson and R. Pettit, *J. Amer. Chem. Soc.*, **84**, 4591 (1962).

(7) R. Damico and T. J. Logan, *J. Org. Chem.*, **32**, 2356 (1967).

(8) Recently discussed by D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, pp 201–202.

TABLE I

COMPOSITION OF EQUILIBRIUM MIXTURES FROM OLEFINIC ESTER ISOMERIZATIONS[a]

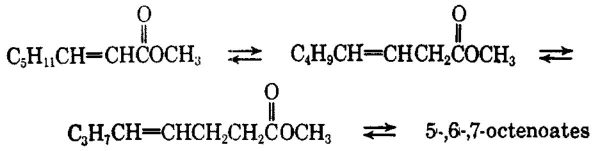
Entry[h]	Substrate	Time,[b] hr	Positional isomer, %[c] 1	2	3	4	5	6	7	Recovery, %	Purity,[d] %
1	$C_5H_{11}CH{=}CHCO_2CH_3$	24	...	18.1 (20.2)	8.1 (9.6)	20.4	23.6	28.5	1.5	92[e]	97
2	$CH_2{=}CH(CH_2)_5CO_2CH_3$	72	...	17.8 (16.5)	7.3 (8.2)	20.8	24.2	28.7	1.2	88[e]	97
3		72[f]	88.8 (87)	3.6 (~5)	7.6	...	...	...	...	95	98
4		48[g]	88.9	3.8	7.3	...	...	...	...	96	98
5		72	86.8	4.4	8.8	...	...	...	...	95	99

[a] Isomerization method A at 125° was used exclusively for these reactions. [b] The reaction time needed to reach equilibrium is reported. [c] Octenoate isomer percentages were determined by oxidative cleavage; cyclohexenyl isomer percentages were determined by quantitative gas chromatography. Values in parentheses for both series were determined by nmr analyses. [d] Per cent purity of samples was determined by gas chromatography. [e] Recovery percentages were calculated after distillation. [f] Addition of 30% excess $Fe(CO)_5$ and continued refluxing for 3 days after this time did not change the isomer percentages reported. [g] A temperature of 150° was used for this reaction. [h] Registry no.: 1, 2396-85-2; 2, 15766-90-2.

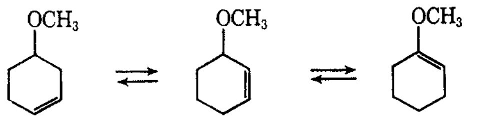
In an equilibrium system of the type shown in eq 1 the difference in stability between **1** and **2** is due to the difference in stabilizing effects of an X group and a $-CH_2X$ group; however, it is difficult to explain this by any one factor. The major problem is that while the α,β isomer is influenced by conjugative and inductive interactions with the functional group, the β,γ isomer is mainly affected by the inductive effect of the $-CH_2X$ moiety. Thus, a question of whether **1** is favored over **2** owing to conjugative stabilization of **2** becomes apparent. To examine this question we have isomerized olefinic ethers[9] and esters with iron pentacarbonyl catalyst to equilibrium mixtures of isomers where the double bonds are distributed to all possible positions. In such systems, the isomers in which the double bonds are located at least two carbon atoms from the functional groups are very similar to unsubstituted internal olefins. Comparison of the relative stability of these isomers with the isomers in which the double bonds are located next to, or one carbon atom removed from, the functional group gives an accurate evaluation of the effect of the functional group on the equilibria in question.

Results

Several acyclic and cyclic unsaturated esters and ethers have been prepared and isomerized with iron pentacarbonyl. Equilibria of the type shown in eq 2 and 3 have been studied.



$$C_5H_{11}CH{=}CH\overset{O}{\overset{\|}{C}}OCH_3 \rightleftarrows C_4H_9CH{=}CHCH_2\overset{O}{\overset{\|}{C}}OCH_3 \rightleftarrows C_3H_7CH{=}CHCH_2CH_2\overset{O}{\overset{\|}{C}}OCH_3 \rightleftarrows \text{5-,6-,7-octenoates} \quad (2)$$



(3)

Two methods of isomerization with iron pentacarbonyl were used. One method consists of refluxing the substrate in octane or nonane solvent at 125–150° with 10–20 mol % of iron pentacarbonyl for periods of 24–96 hr. The catalyst is added in increments of 5–10% during isomerization. We will refer to this isomerization procedure as method A. The alternative method employs iron carbonyl with ultraviolet irradiation, similar to the method developed by Asinger[2] for the isomerization of *n*-olefins. A 200-W high pressure mercury lamp at 20° with 3–5% iron carbonyl in pentane solvent gave complete isomerization within 0.25 to 8 hr with the compounds studied (method B). The results from the isomerization of unsaturated esters and ethers are given in Tables I and II. The effect of alkenyl chain length on the equilibrium mixtures of methyl alkenyl ethers is shown in Figure 1.

The time necessary to reach equilibrium was determined by gas chromatography and infrared spectral analysis of the reaction solutions. For example, gas chromatographic analysis of the isomerization reaction of methyl 2-octenoate (entry 1, Table I) showed four peaks on a 10-ft 20M Carbowax column at 125°. When the relative ratios of these four peaks reached constant values, the isomerization reaction was stopped. Similarly, the isomerization mixture from methyl 7-octenoate (entry 2, Table I) indicated four gas chromatography peaks which attained the same relative ratios as the peaks from the 2-octenoate isomer. Addition of excess iron pentacarbonyl and continued heating did not change the relative ratio of these peaks. Verification that an equilibrium distribution of double bonds had been reached was obtained by oxidative cleavage and nmr analysis of each isomerization mixture.

The isomerization of methyl 1- and 4-pentenyl ethers was followed by gas chromatography in a similar manner and by infrared spectral analyses. Relative intensities of the infrared peaks attributable to *trans* and *cis* α,β-unsaturated ethers[10] at 935 and 1250 cm^{-1}, respectively, compared to *trans* olefin absorption at 965 cm^{-1} were used to determine when equilibrium was established.

During isomerization the change (if any) in iron carbonyl infrared peaks was noted. Under the thermal method of isomerization the bands at 2000 and 2020 cm^{-1}, attributable[11] to $Fe(CO)_5$, did not shift nor did

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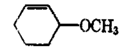
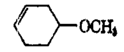
[9] A brief description of isomerization of unsaturated ethers with iron pentacarbonyl has previously been reported. No attempt was made to study the equilibrium distribution in this study. P. W. Jolly, F. G. A. Stone, and K. Mackenzie, *J. Chem. Soc.*, 6416 (1965).

[10] H. R. Warner and W. E. M. Lands, *J. Amer. Chem. Soc.*, **85**, 60 (1963).

[11] C. G. Barraclough, J. Lewis, and R. S. Nyholm, *J. Chem. Soc.*, 2582 (1961).

Table II

Composition of Equilibrium Mixtures from Olefinic Ether Isomerizations[a]

Entry[f]	Substrate	Time,[b] hr	Positional isomer, %[c] 1	2	3	4	Recovery, %	Purity,[d] %
1	$CH_3O(CH_2)_3CH{=}CH_2$	3	85[e]	5	9	1	90	97
2	$CH_3OCH{=}CH(CH_2)_2CH_3$	1	84[e]	6	9	1	91	98
3		6	93.5 (95)	2.9	3.6	. . .	93	98
4		5	95 (95)	2.0	3.0	. . .	96	98

[a] Isomerization method B was used exclusively in these studies. [b] The reaction time necessary to reach equilibrium is reported. [c] Pentenyl isomer percentages were determined by nmr analyses, cyclohexenyl isomers by gas chromatography on a 150 ft × 0.01 in. capillary column coated with polyphenyl ether. This column was purchased from the Perkin-Elmer Corporation. Values in parentheses determined by nmr analyses. [d] Purity percentages were determined by gas chromatography. [e] Approximately equal percentages of *cis* and *trans* 1-pentenyl ethers are present in these mixtures. Nmr and infrared spectral analyses were used to calculate the relative amounts of *cis* and *trans* enol ethers. [f] Registry no.: 1, 1191-31-7; 3, 2699-13-0; 4, 15766-93-5.

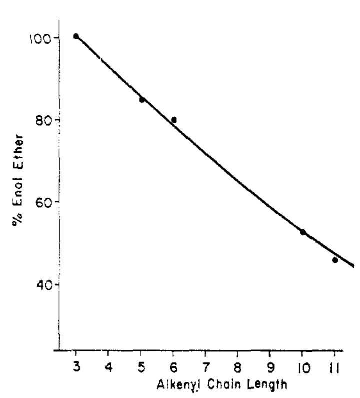


Figure 1.—Effect of alkenyl chain length on the percentages of enol ethers at equilibrium. Terminal alkenyl methyl ethers were isomerized by method B in this study.

new peaks appear. During irradiation, both shifting and new iron carbonyl peaks were discernible in the infrared spectra of the reaction solutions. Under the irradiation conditions, a typical spectrum has carbonyl peaks at 2085, 2055, 2025, and 2005 cm^{-1}. These spectra were independent of the particular ester or ether used.

After isomerization was complete the remaining iron carbonyl was destroyed by one of three methods. With esters, alcoholic ferric chloride oxidation of iron pentacarbonyl to ferrous chloride was effective in removing the last traces of catalyst. Alternatively, prolonged heating of the reaction solution converts essentially all iron carbonyls into elemental iron which is simply removed by filtration. Esters were then analyzed for double bond position, either directly or after distillation. This treatment did not affect the ratios of ester peaks in the gas chromatograms. The alcoholic ferric chloride method could not be used with ethers, due to the lability of enol ethers to acidic alcohol. If, however, irradiation of the ether reactions was continued long enough, insoluble metal carbonyls [$Fe_2(CO)_9$, etc.] were formed and separated by filtration. These isolation methods gave recoveries of 88–95% of esters and ethers which were shown to have purities of greater than 95% by various analyses (Tables I and II).

Evidence that a true equilibrium was reached in each case rests mainly upon the fact that at least two positional isomers were isomerized to the same equilibrium mixture for each type of compound studied. In most instances the two extreme positional isomers (*e.g.*, entries 1 and 2, Table I) were isomerized.

Analyses of the positional isomers was accomplished by oxidative cleavage, quantitative nmr, and gas chromatography analyses. Double bond isomers of esters were cleaved with permanganate–periodate; the resulting acids and acid esters were converted to their methyl esters, which were quantitatively analyzed by gas chromatography.[12] When possible, the percentages of α,β and β,γ isomers were calculated from the nmr spectra of the isomerized reaction mixtures. Olefinic and allylic peaks of the spectra were integrated to obtain these percentages. Good agreement with both oxidative cleavage and gas chromatography analyses was found and is reported in Tables I and II. Quantitative gas chromatography analysis was used when authentic samples of each positional isomer were available and when each isomer was separable. This was only possible in the cyclic series studied.

Discussion

A prime question in this study is the role of the iron carbonyl reagent; *i.e.*, whether it is solely a catalyst for isomerization or is involved in the formation of stable olefin–iron carbonyl complexes. We made several observations that indicate *stable* complexes are not formed under our isomerization conditions. First, careful examination of the infrared spectra of the reaction solutions during the thermal isomerization reactions showed no change occurring in the carbonyl peaks of $Fe(CO)_5$ at 2000 and 2020 cm^{-1}. If a stable olefin–iron carbonyl complex is formed during reaction, a separation of these peaks would be expected.[13] During isomerization method B the carbonyl peaks do shift and new bands are observed, but a similar phenomenon is found when $Fe(CO)_5$ is irradiated alone. This is due to the formation of other iron carbonyl species, such as

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[12] This method has been reported by D. F. Kuemmel of these laboratories [*Anal. Chem.*, **36**, 426 (1964)].

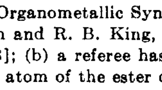
[13] A correlation between the electronic structure of the ligand and the carbonyl stretching frequencies in diene–iron tricarbonyl complexes has been discussed by R. Pettit and G. F. Emerson [*Advan. Organometal. Chem.*, **1**, 11 (1964)].

$Fe_2(CO)_9$ and $Fe_3(CO)_{12}$.[14a] Therefore, the fact that new bands are found cannot be taken as evidence that an iron carbon–olefin complex was formed. Second, the small amount (3–5%) of iron carbonyl necessary to establish equilibrium throughout an olefin molecule with isomerization method B argues against a specific olefin–iron carbonyl species being stable under the isomerization conditions. Third, the addition of amounts up to 30% of iron pentacarbonyl to mixtures which had attained equilibrium did not affect the relative isomer percentages or the high recovery (88–98%) of products with purities of greater than 95%. The latter observation is strong evidence against stable olefin complex formation.[14b]

The ability of $Fe(CO)_5$ to promote isomerization effectively under neutral condition is invaluable. Under the basic conditions of Kon and Linstead,[8] Michael addition of solvent to the α,β isomers was found. Other problems associated with basic catalysis include elimination and cleavage. Thus, Kesslin and Orlando[15] found that treatment of butenyl ethers with potassium *t*-butoxide gives exclusive elimination and no isomerization (eq 4). It is apparent, then, that a real need existed for an isomerization reagent of the type described in this study.

$$ROCH_2CH{=}CHCH_3 + t\text{-BuOK} \longrightarrow CH_2{=}CH{-}CH{=}CH_2 + ROK + t\text{-BuOH} \quad (4)$$

Our studies were concentrated on *n*-alkenyl and cyclohexenyl esters and ethers. The six-membered unsaturated ring system was chosen because this system appears to parallel closely its acyclic analog in isomerization studies.[16] Thus, Boorman and Linstead[17] have reported that 4% of the cyclic α,β isomer **3** was isomerized to the β,γ form, while 10% of its acyclic analog **4** was converted into the unconjugated isomer.



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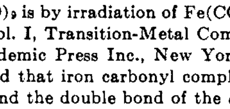

$$CH_3CH_2CH{=}\overset{\displaystyle CH_3}{\overset{|}{C}}{-}CO_2H$$

4

Turning our attention now to the effect of the substituent on the relative double bond stabilities, we wish to discuss two main factors, the resonance and inductive effects of the substituent groups.[18] Conjugative interactions, whether the substituent group is electron releasing (+R) or electron withdrawing (−R), are stabilizing factors. Thus, ether,[19a,b] amine,[19c] and sulfide[19d] substituents (+R groups) strongly favor the vinyl over the propenyl forms in the equilibria of three carbon atom systems, as do the isomerization reactions shown in eq 1 which have −R substituent groups. The role of −I and +I groups on olefin equilibria is less definitive. Electron releasing alkyl groups, especially unbranched groups, have been found to stabilize a double bond isomer when attached to the ethylenic carbon atom.[20] An interesting study[21a] of the effect of electron-withdrawing groups on the equilibria of sulfur-substituted, three carbon atom systems shows an increase in β,γ isomers with increasing −I effect of the groups $-SCH_3$, $-SOCH_3$, and $-SO_2CH_3$. This increase has been rationalized on the basis that an inductive withdrawal of electrons destabilizes the α,β double bonds in these systems.[21b] In our study the $-CO_2R$ group is reported[22] to have a −R and a −I effect, while the $-OCH_3$ group has a +R and −I effect. We have found that the average of equilibrium values from iron carbonyl catalyzed isomerization of methyl octenoate isomers is 18% 2-(α,β), 8% 3-(β,γ), 21% 4-, 24% 5-, 29% 6-, and 1% 7- (terminal) octenoates (entries 1 and 2, Table I). There are several important points to note concerning these isomerization results. The conclusion reached from the base-catalyzed isomerization of

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[14] (a) $Fe_2(CO)_9$ is reported [R. K. Sheline and K. S. Pitzer, *J. Amer. Chem. Soc.*, **72**, 1107 (1950)] to have major infrared peaks at 2034 and 2080 cm⁻¹ while $Fe_3(CO)_{12}$ has major absorptions at 2043, 2020, and 1997 cm⁻¹ [F. A. Cotton and G. Wilkinson, *ibid.*, **79**, 752 (1957)]. Indeed, the recommended preparative method for $Fe_2(CO)_9$ is by irradiation of $Fe(CO)_5$ [R. B. King in "Organometallic Syntheses, Vol. I, Transition-Metal Compounds," J. J. Eisch and R. B. King, Ed., Academic Press Inc., New York, N. Y., 1965, p 93]; (b) a referee has suggested that iron carbonyl complexes with an oxygen atom of the ester or ether and the double bond of the α,β or β,γ isomer and that elimination of hydroiron carbonyl from these complexes controls the relative percentages of α,β and β,γ isomers. This explanation is unacceptable to us for several reasons. If the rate of formation of complexes and elimination of metal hydrides controlled the "equilibria" of α,β and β,γ isomers we would expect changes in relative percentages of these isomers with the addition of different amounts of iron pentacarbonyl and in prolonged reaction times. Neither one of these reaction changes affected the equilibrium values (note entry 3, Table I). A most convincing argument against the referee's suggestion is the observation that all equilibria were established by starting from at least two different positional isomers. It was further established that a stable intermediate is not formed under our isomerization conditions. Therefore, the equilibrium results reported here are the thermodynamic values.

[15] G. Kesslin and C. M. Orlando, Jr., *J. Org. Chem.*, **31**, 2682 (1966).

[16] It is important to choose a ring in which conformational effects are minimal. A study of equilibria between cycloalk-2- and -3-enones shows that for a six-membered ring the equilibrium composition is 99% Δ^2 and 1% Δ^3, while the nine-membered ring is >99.7% Δ^3 and <0.3% Δ^2 [N. Heap and G. H. Whitham, *J. Chem. Soc., Sect. B*, 164 (1966)].

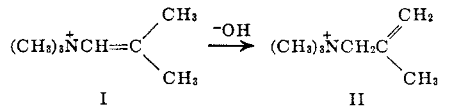
[17] E. J. Boorman and R. P. Linstead, *ibid.*, **258**, 1935.

[18] Other factors that can be considered are steric, solvation, and field effects and the possibility that differences in optical and geometrical isomers may influence the relative stability of positional isomers. Although an investigation of these effects was not undertaken, we do not believe that they are major contributing factors for the following reasons. In molecules of comparable size, such as those under investigation, we would expect small differences in steric factors between difficult positional isomers. Thus, equilibration of *n*-undecene isomers[3] yields the same percentage of 2, 3, 4, and 5 isomers despite the expected differences in steric effects. In our systems conformational effects may be important for double bonds isomers in close proximity to the functional groups, such as the α,β isomers. All reactions were conducted in hydrocarbon solvents in which solvation is unimportant. Comparison of the relative stability of cyclic isomers to acyclic isomers is clouded by the fact that β,γ and γ,δ cyclic isomers have *dl* pairs which contribute an entropy of mixing term (1.38 cal/deg mol) to the equilibrium in question. In addition, each cyclic isomer exists in one geometrical configuration while the acyclic isomer exists in two. Finally, no attempt has been made to distinguish between field effects and σ inductive effects. However, it should be noted that the relative ratios of β,γ and γ,δ isomers in both cyclic and acyclic esters are essentially constant despite the differences in steric and field effects and optical and geometrical isomers of these compounds. Assuming all of these effects are not fortuitously balanced, we can reason that they are not major factors which influence the relative stability of the β,γ and γ,δ isomers.

[19] (a) T. J. Prosser, *J. Amer. Chem. Soc.*, **83**, 1701 (1961); (b) C. C. Price and W. H. Snyder, *ibid.*, **83**, 1773 (1961); (c) C. C. Price and W. H. Snyder, *Tetrahedron Lett.*, **2**, 69 (1962); (d) D. S. Tarbell and W. E. Lovett, *J. Amer. Chem. Soc.*, **78**, 2259 (1956).

[20] For example, see A. Schriesheim and C. A. Rowe, Jr., *ibid.*, **84**, 3160 (1962), for the equilibrium compositions of 2-methylpentenes.

[21] (a) D. E. O'Connor and W. I. Lyness, *ibid.*, **86**, 3840 (1964); (b) equilibrium constants between I and II at 100 and 161° are 58.1 and 41.8, respectively, with II favored. The inductive electron-withdrawal destablization of I can be used to explain these results. M. Saunders and E. H. Gold,



I II

ibid., **88**, 3376 (1966).

[22] Taft reports the following values of $\sigma_R = -0.50$ and $\sigma_I = +0.23$ for the $-OCH_3$ group, and $\sigma_R = +0.20$ and $\sigma_I = +0.32$ for $-CO_2R$ group. R. W. Taft, Jr. in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 595.

methyl 2- and 3-hexenoates[23] was that the 2 isomer is favored relative to the 3 isomer at equilibrium. Our results, in agreement with this conclusion, indicate a ratio of 2.5:1 of α,β to β,γ octenoate isomers when complete distribution of double bond isomers is found. These results indicate that the relative stability of α,β and β,γ olefinic ester isomers is independent of these two isomerization methods. Surprisingly enough, the α,β isomer is *not* the favored isomer when compared to the other internal isomers. The average olefin per cent of the 4, 5, and 6 octenoate isomers (entries 1 and 2, Table I) is ~25%, slightly higher than the 18% observed for the α,β isomer. Of interest, also, is the small amount of β,γ isomer compared to α,β or to other internal isomers at equilibrium. To explain these data we propose that the carbomethoxy group influences the position of equilibrium by two main factors, conjugative stabilization and inductive electron-withdrawal destabilization effects. These two effects counterbalance one another when the double bond is in the 2 position so that the net result is that the α,β isomer is comparable in stability to the internal isomers not grossly influenced by the $-CO_2CH_3$ group. Inductive effects also appear quite important in influencing the relative stability of the other isomers. Thus, the 4, 5, and 6 isomers are each more stable than the β,γ isomer by a factor of 3 (~25:8). This observation can be rationalized by assuming that the $-$I destabilization effect is transmitted through one methylene unit to the β,γ isomer, while there is little effect of this group on the 4, 5, and 6 isomers.[24] It is evident from these results that a $-CH_2CO_2CH_3$ group is not equivalent to an alkyl group. Finally, the ratio of α,β to β,γ isomers can be explained by the inductive destabilization effect of the $-CH_2CO_2CH_3$ group on the β,γ isomer relative to the net stabilizing influence of the $-CO_2CH_3$ on the α,β isomer.

To test these proposals further we examined the isomerization of methyl cyclohexenyl carboxylate isomers (entries 3, 4, and 5, Table I). In this system the 1 isomer is favored over both the 2 and 3 isomers at equilibrium due to the additional stabilization of a $-CH_2$ unit at the α-carbon atom. Again, the γ,δ (3) isomer is favored over the β,γ (2) isomer. Since these two isomers have comparable alkyl substitution, the difference in stability can be attributed to the destabilization effect of the $>CHCO_2CH_3$ group on the 2 isomer.

The equilibrium isomer distributions of olefinic ethers demonstrate relative resonance and inductive effects. Conjugative stabilization of the $-OCH_3$ group is very important in these systems because a preponderance of the α,β isomer is formed in each case (Table II and Figure 1). In the acyclic compounds the equilibrium amount of enol ether varied between 46 and 100% depending on chain length, while 95% enol ether is formed during isomerization of the cyclohexenyl ethers. Examination of the relative amounts of 2 and 3 isomers from the isomerization of *n*-pentenyl and cyclohexenyl isomers (Table II) indicates that the inductive destabilization of the $>CHOCH_3$ group is important. The ratio of 3 isomer to 2 isomer is 1.5 to 1 in both series of compounds. Although the percentages of 3 and 2 cyclohexenyl isomers are small (3–3.6:2–2.9) it is significant that, starting with the 2 isomer (entry 3, Table II), more 3 than 2 was present when the equilibrium was reached.

Figure 1 shows the effect of alkenyl chain length on the per cent of α,β (enol) isomer at equilibrium. An increase in percentage of internal isomers and a decrease in α,β isomer with increasing number of possible internal isomers is evident from the graph. A ratio of enol ether to each internal ether (excluding β,γ) of ~10:1 can be obtained from these data and from the pentenyl ethers' equilibrium values. Therefore, replacement of an alkyl group with a methoxy group at a vinyl carbon atom increases the stability of this isomer by 1.5 kcal.[25]

Qualitatively, the inductive and resonance effects of the carbomethoxy and methoxy groups on olefin stability, as determined from this work, can be summarized. A carbomethoxy group influences the stability of an α,β isomer by opposing conjugative stabilization and inductive destabilization; the net effect of the $-CO_2CH_3$ unit is comparable to the inductive stabilization of an alkyl group. A $-CH_2CO_2CH_3$ group inductively destabilizes an olefin isomer by a factor of ~3 compared to an alkyl group. A methoxy group stabilizes an α,β isomer by a factor of 10, while a $-CH_2OCH_3$ destabilizes a β,γ isomer by ~1.5:1 compared to an alkyl group.[26]

Experimental Section[27]

Methyl 2-Octenoate.—This compound was prepared by methanol-sulfuric acid esterification of 2-octenoic acid (Aldrich Chemical Co.). After the normal work-up, distillation at 42–44° (1.4 mm) afforded the product in 98% purity by gas chromatography analysis. Oxidative cleavage analysis[12] of the double bond positions of this product showed that 89% was in the α,β form and 11% was in the β,γ form.

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.9; H, 10.2.

An nmr spectrum has peaks centered at τ 3.3 (1 H, β vinyl proton), 4.4 (1 H, α vinyl proton), 6.4 (3 H, $-CO_2CH_3$), 7.9 (2 H allylic CH_2), 8.7 (8 H, alkyl CH_2), and 9.1 (3 H, alkyl CH_3). In addition, a small peak at τ 7.15, characteristic of the allyl protons adjacent to the carbomethoxy group in the β,γ isomer, was discernible.

Methyl 7-Octenoate.—A solution of 20.0 g (0.089 mol) of 8-bromooctanoic acid (Sapon Laboratories, Oceanside, N. Y.) and 32 g (0.29 mol, 50% excess) of potassium *t*-butoxide in 250 ml of *t*-butyl alcohol was refluxed for 3 hr. The mixture was

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[23] G. A. R. Kon, R. P. Linstead, and G. W. G. Maclennan, *J. Chem. Soc.*, 2452, 2454 (1932).

[24] The distribution of the 4, 5, and 6 isomers indicates that a progressive diminishing of the $-CO_2CH_3$ inductive effect is in evidence. Although we favor this explanation, other factors, such as the change in the alkyl substituent, may cause this isomer distribution.

[25] Calculated from $\Delta F = -RT \ln K$. A value of 5.75 kcal conjugative stability (*ca.* 2.25 kcal relative to methyl) has been assigned to the methoxy group (see footnote 27 in C. D. Broaddus, *J. Amer. Chem. Soc.*, **87**, 3706 (1965)).

[26] These generalizations agree well with the reported σ_I and σ_R effects of these groups (*cf.* ref 22). They are also consistent with the σ_I reported values [M. Charton, *J. Org. Chem.*, **29**, 1222 (1964)] of the $-CH_2CO_2CH_3$ and $-CH_2OCH_3$ groups which are +0.17 and +0.07, respectively. Using these values we are tempted to make more quantitative comparisons of our results with these reported σ values. However, the recent literature describes the influence of substrate [M. Charton, *J. Org. Chem.*, **30**, 557 (1965)], solvent [R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *J. Amer. Chem. Soc.*, **85**, 709 (1963)], and other factors on both σ_R and σ_I values which may make such comparisons invalid.

[27] Boiling points are uncorrected. Infrared spectra were obtained on hydrocarbon solutions in a 0.015-mm cell with a Perkin-Elmer Infracord or a Model 21 spectrophotometer. Gas chromatographic separations were made on a 10 ft × 0.25 in. column packed with 20% Carbowax 20M on 60–80 mesh, acid-washed Chromosorb W, unless otherwise indicated. Nuclear magnetic resonance spectra were determined in carbon tetrachloride or deuterated chloroform solutions with a Varian Model HA-100 or A-60 spectrophotometer using tetramethylsilane as an internal standard.

cooled, acidified with sulfuric acid, diluted with water, and extracted with ether. The ether layer was evaporated under reduced pressure and the residue acid esterified with a solution of 2 ml of sulfuric acid and 35 ml of methanol. Distillation at 43–45° (0.45 mm) afforded 7.3 g (43%) of product which was 98% of one component by gas chromatography analysis; the nmr spectrum showed peaks at τ 4.3 (1 H, =CH—), 5.1 (2 H, =CH_2), 6.4 (3 H, —CO_2CH_3), 7.8 (2 H, —CH_2CO_2—), 8.2–8.7 (8 H, allylic CH_2 and C—CH_2), and 9.1 (3 H, C—CH_3).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.0; H, 10.2.

Methyl 1-Cyclohexene-1-carboxylate.—The method of Bailey and Baylouny[28] was used to prepare the ester in 57% yield: bp 47–50° (2 mm) (lit.[28] bp 86° (15 mm)); nmr spectrum, τ 3.2 (1 H, =CH—), 6.5 (3 H, —CO_2CH_3), 7.9 (4 H, allylic CH_2), and 8.5 (4 H, C—CH_2).

Methyl 2-Cyclohexene-1-carboxylate.—Metalation[29] of cyclohexene with *n*-butylsodium followed by carbonation and diazomethane esterification afforded the ester: bp 65–67° (7.5–8.0 mm) (lit.[29] bp 78–80° (20 mm)); nmr spectrum, τ 4.3 (2 H, CH=CH), 6.4 (3 H, —CO_2CH_3), 7.0 (1 H, C=C—CH—CO_2—), and 7.9–8.6 (6 H, allylic CH_2 and C—CH_2).

Methyl 3-Cyclohexene-1-carboxylate.—A stirred mixture of 22 g (0.2 mol) of 3-cyclohexene-1-carboxaldehyde (Columbia Organic Chemicals Co., Inc.) and 57 g (0.25 mol) of silver oxide[30] was heated at 50° for 2 hr and then maintained at room temperature for 12 hr. The mixture was acidified with concentrated hydrochloric acid, filtered to remove silver chloride, extracted with ether, and the ether layer evaporated to yield unpurified 2-cyclohexene-1-carboxylic acid. The acid was esterified with methanol–sulfuric acid and, after work-up, distilled at 48–49° (4.5 mm) (lit.[28] bp 80–82° (23 mm)). A total of 14 g (50%) of ester was recovered; the nmr spectrum gave signals at τ 4.4 (2 H, CH=CH), 6.4 (3 H, —CO_2CH_3), 7.55 (1 H, —CH—CO_2—), and 7.7–8.3 (6 H, allylic CH_2 and C—CH_2).

***n*-Hexyl allyl ether** was purchased from Peninsular Chem-Research Inc., Gainesville, Fla.

Methyl 1-Decenyl Ether.—Using the procedure of Warner and Lands[31] for the preparation of a similar compound, the alkenyl ether was prepared from decanal, methanol, and hydrogen chloride to produce methyl 1-chlorodecyl ether followed by elimination of hydrogen chloride with dimethylaniline. The product mixture was distilled at 45–55° (0.45 mm) to yield a mixture of dimethylaniline and methyl 1-decenyl ether. Final purification of the ether was accomplished by column chromatography on neutral alumina (Alupharm Chemicals, New Orleans, La., activity grade 2) using pentane as an eluent.[31] A gas chromatogram of the product showed 50% *cis*-, 50% *trans*-decenyl ethers; the nmr spectrum[32] gave signals at 3.8 and 4.3 (1 H, α-vinyl H of *trans* and *cis* isomers), 5.55 and 5.8 (1 H, β-vinyl H of *trans* and *cis* isomers), 6.55 and 6.80 (3 H, —OCH_3 of *cis* and *trans* isomers), 8.15 (2 H, allylic CH_2), 8.4–8.8 (12 H, C—CH_2), and 9.1 (3 H, C—CH_3).

Methyl 1-Pentenyl Ether.—Methyl 1-chloropentyl ether was prepared from pentanal, methanol, and hydrogen chloride according to the procedure of Warner and Lands.[31] The chloro ether was dehydrochlorinated by reaction with *sym*-collidine. Removal of *sym*-collidine hydrochloride by filtration, followed by distillation of the ether at 99–114° (760 mm), afforded the product which was purified by column chromatography on alumina using pentane as an eluent. A gas chromatogram showed the product was approximately 90% pure and consisted of 52% *cis* and 42% *trans*-methyl 1-pentenyl ether. The product contained pentanal (~8%) as the major impurity. An nmr spectrum was in accord with the structure.

Methyl 4-Pentenyl Ether.—A mixture of 4.8 g (0.2 mol) of sodium hydride and 20.0 g (0.2 mol) of 4-penten-1-ol (Chemical Samples Co., Columbus, Ohio) in 30 ml of hexane diluent was stirred at reflux under an argon atmosphere for 3 hr. After the mixture was cooled, 37 g (0.26 mol, 30% excess) of methyl iodide was added dropwise (exothermic reaction) over 25 min and then heated to reflux for 2 hr, cooled, poured into water, and extracted with ether. The separated ether layer was dried with 3-Å molecular sieves and distilled at 41–42° (35 mm) to yield 12.4 g (54%) of methyl 4-pentenyl ether which had a gc purity of 98%; the nmr spectrum showed peaks at τ 4.3 (1 H, =CH—), 5.1 (2 H, H_2C=), 6.7–6.9 (5 H, CH_2—O— and —O—CH_3), 7.95 (2 H, allylic CH_2), and 8.4 (2 H, C—CH_2).

Methyl 5-hexenyl, 9-decenyl, and 10-undecenyl ethers were prepared in essentially the same manner as the 4-pentenyl ether. Gc purities were in each case greater than 98%. Nmr spectra were in accord with the indicated structures.

Methyl 2-Butenyl Ether.—This compound was prepared to determine the nmr position of an allylic methylene group adjacent to a methoxy function in an *n*-alkenyl ether. Preparation in the normal manner afforded a product of bp 78–78.5° (760 mm) which had a gc purity of ~99%; the nmr spectrum showed peaks at τ 4.4 (2 H, CH=CH), 6.2 (2 H, —O—CH_2—C=C), 6.7 (3 H, —OCH_3), and 8.3 (3 H, =C—CH_3).

1-Cyclohexen-1-yl methyl ether was prepared in 73% yield and 95% gc purity by acid-catalyzed elimination of methanol from cyclohexanone dimethyl ketal using the method described[33] for the preparation of 1-cyclohexen-1-yl ethyl ether. The enol ether distilled at 39–42° (15 mm); the nmr spectrum gave signals at τ 5.7 (1 H, vinyl H), 6.65 (3 H, —OCH_3), 8.05 (4 H, allylic CH_2), and 8.5 (4 H, C—CH_2).

2-Cyclohexen-1-yl Methyl Ether.—Using the procedure described for the preparation of methyl 4-pentenyl ether, this compound was prepared in 60% yield: bp 129–139° (760 mm); gc purity of 91% with a major impurity of 5% methyl cyclohexyl ether; the nmr spectrum gave signals at τ 4.32 (2 H, vinyl H), 6.4 (1 H, =C—CH—O—), 6.75 (3 H, OCH_3), 8.05 (2 H, allylic CH_2), and 8.4 (4 H, C—CH_2).

3-Cyclohexen-1-yl Methyl Ether.—Prepared from 3-cyclohexen-1-ol (Columbia Organic Chemicals Co., Inc.,) by the sodium hydride–methyl iodide method, this compound was distilled at 37–43° (18 mm) and shown to have a gc purity of only 71%. The mixture contained 24% of methyl cyclohexyl ether that was formed due to the starting alcohol containing 30% cyclohexanol impurity. Distillation of the alcohol did not separate cyclohexanol from 3-cyclohexen-1-ol. This impurity did not interfere with gc or nmr analyses of isomerized 3-cyclohexen-1-yl methyl ether. A gc collected sample of the ether had the following nmr spectrum: τ 4.5 (2 H, vinyl H), 6.6–6.75 and —O—CH—, (4 H, —OCH_3), and 7.8–8.7 (6 H, allylic CH_2 and C—CH_2).

Thermally Induced Iron Carbonyl Catalyzed Isomerizations of Alkenyl Esters.—These isomerization reactions were all conducted in a similar manner. The isomerization of methyl 2-octenoate (entry 1, Table I) is given as an example. A solution of 5 g (0.032 mol) of methyl 2-octenoate and 0.32 g (0.22 ml, 0.0016 mol, 5 mol %) of iron pentacarbonyl in 30 ml of octane was refluxed (~125°) under argon in a three-necked, 50-ml Bantamware (Kontes Glass Co., Vineland, N. J.) flask equipped with a rubber septum in one side arm. The reaction mixture turned dark within minutes after it reached 125° and black deposits of metallic iron were soon noted. Samples (1 ml) were withdrawn at 2, 5, 17, and 22 hr reaction times by the use of a hypodermic needle through the rubber septum. Infrared spectra of these samples were examined for peaks in the regions of iron carbonyl (1950–2050 cm), ester carbonyl (1720–1740 cm^{-1}), and vinyl CH deformation (890–1000 cm^{-1}) frequencies. During the course of the reaction no changes in the iron pentacarbonyl peaks (2000, 2020 cm^{-1}) were noted; the conjugated carbonyl peak (1740 cm^{-1}) decreased and a *trans* olefin peak[34] at 965 cm^{-1} became visible. After 17 hr of refluxing, the carbonyl and olefin peaks did not change in position or intensity. The iron pentacarbonyl peaks diminished noticeably in intensity during the 17 hr of reflux, and additional (10%) catalyst was added. Refluxing for 5 hr more did not change the infrared peaks. The samples were also analyzed by gas chromatography. Four peaks were separable on the gas chromatograph. After 22 hr

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(28) W. J. Bailey and R. A. Baylouny, *J. Amer. Chem. Soc.*, **81**, 2126 (1959).

(29) Using the procedure of A. A. Morton and R. A. Finnegan, *J. Polymer Sci.*, **38**, 19 (1959). We thank Dr. D. Muck of these laboratories for providing us with a sample of 2-cyclohexene-1-carboxylic acid.

(30) Prepared by the method of E. Campaigne and W. M. LeSuer in "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, pp 919–921.

(31) H. R. Warner and W. E. M. Lands, *J. Amer. Chem. Soc.*, **85**, 60 (1963).

(32) The nmr spectra of alkenyl ethers have been analyzed by Warner and Lands,[31] T. J. Prosser [*ibid.*, **83**, 1701 (1961)], and C. D. Broaddus [*ibid.*, **87**, 3706 (1965)].

(33) A. Johannissian and E. Akunian, *Bull. Univ. État R.S.S. Arménie*, *No. 5*, 235, 245 (1930); *Chem. Abstr.*, **25**, 921, 922 (1931).

(34) K. Nakanishi, "Infrared Absorption Spectroscopy—Practical," Holden-Day, Inc., San Francisco, Calif., 1962.

the ratios were 3.84:3.00:1.00:1.22. The reaction mixture was cooled, filtered to remove metallic iron, and treated with 2.9 g (0.0182 mol) of ferric chloride in 20 ml of 95% ethanol. Gas evolution (CO) was noticed. This mixture was stirred for 2 hr, poured into salt water, and extracted with pentane. Distillation of the pentane extract, with tridecane added as a chaser solvent, yielded a fraction of bp 71–85° (18–20 mm) which contained octane, ester isomers, and tridecane. This mixture weighed 5.1 g, of which 4.1 g (92% recovery after correction for aliquot samples) was ester isomers as determined by quantitative gc. The ratio of gc peaks remained constant before and after ferric chloride treatment and distillation. An nmr spectrum showed peaks at 3.2 (β-vinyl H, 2 isomer), 4.35 (α-vinyl H, 2 isomer), 4.7 (vinyl H, internal isomers), 6.45 ($-CO_2CH_3$), 7.15 ($C{=}C{-}CH_2{-}CO_2{-}$), and other normal peaks of olefin ester internal isomers. Integration of the aforementioned peaks showed 20.2% of the 2 isomer and 9.6% of the 3 isomer. The mixture was analyzed by oxidative cleavage (Table I) to obtain the per cent of other internal isomers and to substantiate the nmr result.

An alternative in the work-up involved leaving out the ferric chloride treatment and destroying most of the $Fe(CO)_5$ catalyst by heating. In these cases the product was analyzed directly after filtration to remove metallic iron. Analyses of isomerized mixtures by gas chromatography were checked by preparing known molar concentration solutions of standards. For example, a prepared mixture of methyl cyclohexene carboxylate isomers containing 43.8% of the 1, 22.7% of the 2, and 34.5% of the 3 isomer was shown by gas chromatography to have 46.2% of 1-, 21.3% of 2-, and 32.5% of 3-cyclohexene carboxylates.

Irradiation Induced Iron Carbonyl Catalyzed Isomerization of Alkenyl Ethers.—An example of these reactions is the isomerization of methyl 4-pentenyl ether. To a solution of 1.0 g (0.01 mol) of methyl 4-pentenyl ether in 135 ml of deoxygenated pentane, was added 0.1 g (0.07 ml, 5×10^{-4} mol, ∼5 mol %) of iron pentacarbonyl. The solution was irradiated with a 200-W high pressure mercury lamp (Type S, 654A-36 Hanovia lamp, Engelhard Hanovia, Inc., Newark, N. J.) with argon bubbling through the solution for a 3-hr period. At 1-hr intervals, the irradiation was stopped and 3-ml samples were withdrawn and analyzed by infrared and gas chromatography after removal of most of the pentane by distillation. Infrared bands at 6.0, 8.0, and 10.7 μ indicated that within 1 hr most of the starting material had been converted into methyl *cis* and *trans* 1-pentenyl ethers. Analysis by gas chromatography showed two peaks of relative area 1:2.66. After 3 hr, an additional 5% of iron pentacarbonyl was added and the solution irradiated for 3 more hr. No change in infrared or gas chromatography analyses was detected after this period. The mixture was filtered to remove insoluble metal carbonyls and pentane solvent was removed by distillation. The total of 900 mg (∼97%) of unpurified product was recovered. Gas chromatography analysis of this product indicated 97% of this mixture was methyl pentenyl ether isomers.

During some of the reactions a dark film was deposited on the immersion well of the reactor, decreasing the transmittance of ultraviolet light. The isomerization reactions were stopped when this occurred, the well was cleaned with sulfuric acid, and the reactions were continued.

Registry No.—Iron pentacarbonyl, 13463-40-6.

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The Total Synthesis of (±)-1-Deaza-1-thiareserpine[1a]

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The potential antihypertensive, (±)-1-deaza-1-thiareserpine (**10**), is described by way of its seven-step synthesis from the methyl ester of (±)-2α-methoxy-3β-hydroxy-5-ene-7-keto-1,2,3,4,7,8-*cis*-9α,10α-octahydro-1β-naphthoic acid, 4,3,4,5-trimethoxybenzoyl chloride (**5**), and 6-methoxy,3-(2-aminoethyl)benzo[*b*]thiophene (**3**).

Reserpine, isolated from *Rauwolfia serpentina* Benth, has been used clinically for a number of years as an antihypertensive. Its adverse side effects, together with our continuing interest in the field of sulfur-containing pharmaceuticals, has prompted our synthesis of a modified reserpine in which the indole nitrogen is replaced by the thianapthyl sulfur, *viz.* 1-deaza-1-thiareserpine (**10**).

The brilliant total synthesis of the natural reserpine molecule by Woodward and his coworkers[2] formed the basis of our synthetic development. Advantage was taken of other more recent work[3] to reduce the number of individual steps in our total synthesis of thiareserpine.

Since the benzo[*b*]thiophene molecule follows closely much of the electrophilic substitution chemistry of indole,[4] it was anticipated that the reactions to effect condensation of the molecules shown in Scheme I would proceed without difficulty and yield intermediates of unambiguous structures.

Thus, our initial synthetic attempts were directed toward the preparation of the previously unknown 6-methoxy-3-(2-aminoethyl)benzo[*b*]thiophene (**3**). Earlier work in our laboratories indicated that a feasible synthesis of this amine would be difficult by direct replacement of intermediate substituents on the thianapthene nucleus.[5] Therefore, the desired precusor, **3**, was formed by building the thiophene ring onto the benzene ring (Scheme II). Ethyl 4-chloro-3-ketobutyrate was treated with *m*-methoxybenzenethiol in pyridine to form the sulfide, **1**, which on ring closure with polyphosphoric acid and subsequent ammonolysis gave a mixture of 6-methoxy- and 4-methoxythianapthenes in a 20:1 ratio. Separation of the isomers was accomplished by fractional crystallization. The structure of the desired amide, **2**, 6-mehtoxy-3-thianaphthyl acid, was established by hydrolysis to its corresponding acid, followed by Raney

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(1) (a) Presented in part at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967. (b) To whom all correspondence should be addressed at the Institute of Biology and Medicine, Department of Chemistry. (c) Abstracted in part from the Master's Dissertation of G. P. Nilles and the Doctoral Dissertation of R. L. Titus.

(2) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958).

(3) For examples see E. Schlittler in "The Alkaloids," Vol. 8, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1965, Chapter 13.

(4) G. V. Zyl, C. J. Bredeweg, R. H. Rynbrandt, and D. C. Neckers, *Can. J. Chem.*, **44**, 2283 (1966).

(5) R. L. Titus, Doctoral Dissertation, Michigan State University, East Lansing, Mich., 1964.