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Formation and Synthetic Utility of Dihydro- and Dihydrothiapyrans[1]

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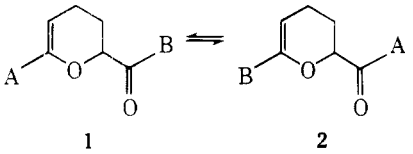
The utility of the Diels–Alder reaction to form 2,3-dihydropyran derivatives and the subsequent incorporation of other functionality by Cope rearrangement have been studied. Brevicomin, the aggregating sex pheromone for *Dendroctonus brevicomis*, has been synthesized, and the mass spectral fragmentation patterns of related bicyclic ketals have been compared. A theoretical prediction of regioselection in the (4 + 2) cycloaddition reactions appears quite consistent with experimental observation, particularly for heterodienes containing sulfur.

The molecular rearrangement of dihydropyran **1** to **2** was first investigated by Roberts.[2] Since then, only Büchi and

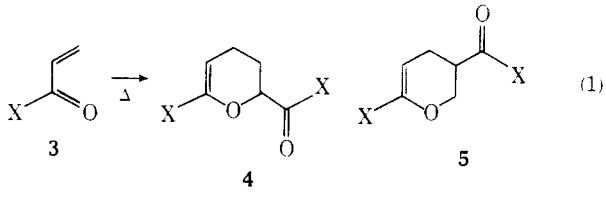


1 **2**

Powell have taken advantage of this [3,3] sigmatropic shift to gain entry into substituted cyclohexene systems.[3] Now we wish to discuss the preparation of these pyranyl systems and their utility as precursors to new compounds. This paper is divided into three sections. Part I discusses theoretical and synthetic aspects of cycloadditions that form dihydropyrans. Included in this section is a new synthesis of brevicomin, the aggregating sex pheromone of the pine bark beetle, *Dendroctonus brevicomis*, and a study of the mass spectral fragmentation patterns of related bicyclic ketals available from dihydropyrans. Part II analyzes the possibility of forming dihydrothiapyrans from either Diels–Alder reactions or Cope rearrangement of substituted dihydropyrans. Part III will focus on our inability to incorporate nitrogen into the molecular framework, and will give details regarding an interesting secondary rearrangement in this work.

Part I

The generation of a suitable ring structure that may be chemically modified before or after rearrangement is a necessity if one is to ensure the generality of a synthetic method. To this end we point out that there may be other routes to dihydropyrans like **1**, but here we shall concern ourselves only with the Woodward–Hoffmann allowed (4 + 2) cycloaddition of heterodienes.[4] Usual problems associated with cycloadditions, such as periselectivity and site selectivity, are of no concern to us in this work. Equation 1 reveals, however, that two possible regioisomers, **4** and **5**, may form upon dimeriza-



3 **4** **5** (1)

tion of enone **3**. In fact, the synthesis of several natural products critically hinges upon the regioselectivity of these cycloadditions, and considerable interest has been expressed in describing the origin of this selectivity.[5]

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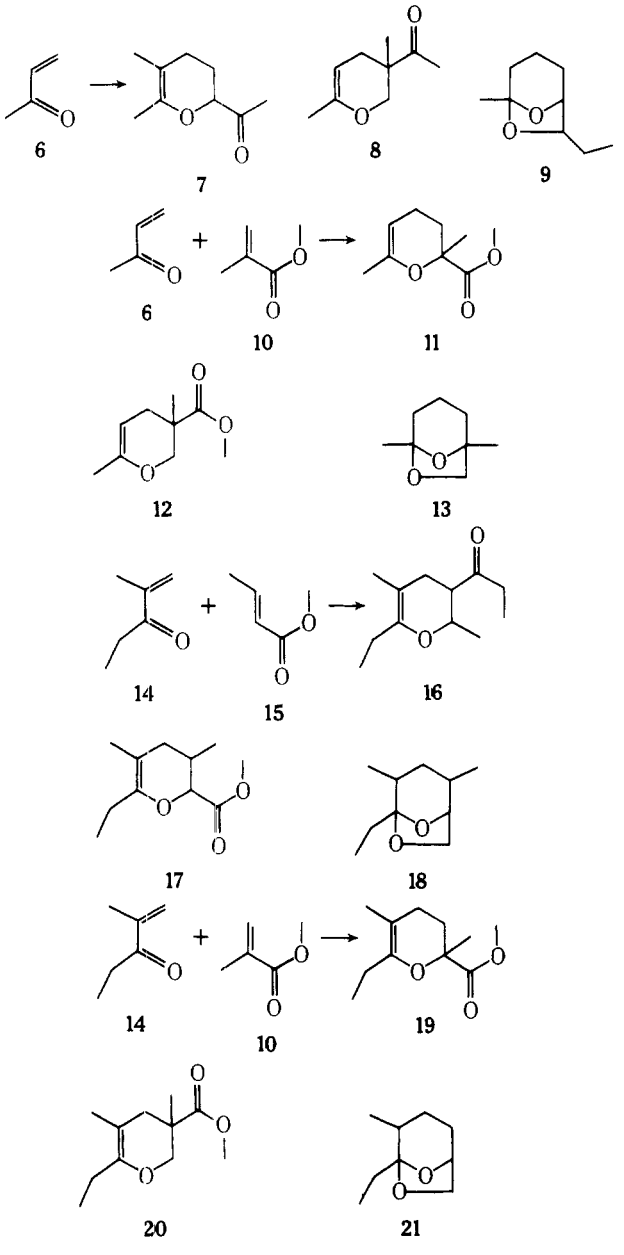
Scheme I. Cycloaddition Reactions of Heterodienes Leading to Pheromones



Spatial and temporal considerations of cycloaddition reactions suggest a mechanism of bond formation that is concerted, yet nonsynchronous.[6] While the exact nature of the transition state remains highly controversial, this nonsynchronous behavior has accommodated a foundation for development of a set of rules with which one may quickly predict a preferred regioisomer.[5a]

A synthetic methodology developed by one of us,[7] and used by other research groups[8] for the synthesis of pheromones possessing the 6,8-dioxabicyclo[3.2.1]octane atomic framework, is dependent on the regioselectivity of the Diels–Alder reaction.[9] This can be graphically illustrated in Scheme I. The product (**7**) resulting from head-to-head dimerization of methyl vinyl ketone is a useful precursor to brevicomin (**9**),[10] whereas the head-to-tail product (**8**) is not. Similarly, the formation of the head-to-head product **11** can serve as a useful entry to frontalin (**13**),[7] while **12** cannot. Recently, the attempted synthesis of multistriatin (**18**) was frustrated because the reaction of **14** and **15** yielded **16**, and not **17** as required.[11] Interestingly, the reaction of **14** and **10** resulted in the head-to-head product **19**, which could be carried on to a multistriatin analogue (**21**).[8a]

In this section we will discuss several aspects of these important reactions from a theoretical point of view. At the outset it must be acknowledged that any procedure based on quantum mechanical calculations which are used to predict the orientation of addition can only be as good as the computed eigenvalues and eigenfunctions. A controversy as to whether simple Hückel or semiempirical wave functions gives better results exists,[5b,c] and in this work we will use CNDO/2[12] wave functions. Due to the enormous amount of computational effort needed to minimize the geometry of molecules, standard bond lengths and bond angles were used.[13] The rules of Alston and Shillady[5a] for determining regioselectivity were utilized in our initial considerations and are summarized as follows: (1) select the HOMO–LUMO gap closest in energy, (2) match eigenvectors for the reacting carbon atoms which are of similar magnitude, and (3) if a regioisomer cannot be selected from application of rule 2, consider secondary orbital interactions.

The highest occupied and lowest unoccupied orbitals for the π bonds were examined for **14, 15, 10,** and **6**. More than one rotamer can exist for the first three, and rather than choose one geometry for the calculation we looked at three distinct rotational conformations, pictorially defined in Table I. The average eigenvectors for the three equally weighted rotamers are also presented in Table I.

Experimental HOMO and LUMO energies are available for **6, 10,** and **15**,[14] and the HOMO and LUMO energies of **14** can be easily approximated from these values. Using these energies, the following conclusions have been reached: **6 + 10,** HOMO dienophile–LUMO diene control; **14 + 15,** HOMO dienophile–LUMO diene control; **14 + 10,** both FMO's are important. With these simplifications the correct regioisomer is predicted in every case using the Alston–Shillady rules with averaged CNDO/2 eigenvectors.[15]

A full frontier orbital treatment that takes into account both HOMO–LUMO interactions and explicitly includes transition state resonance integrals was also considered. Tables II–IV contain interaction energies (ΔE) calculated for head-to-head vs. head-to-tail adducts using eq 2.[16] Eigenvalues and eigenvectors calculated with CNDO/2 and transition state resonance integrals calculated at 3 au[5b] were used.

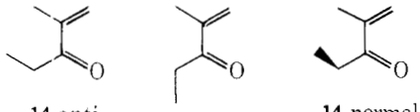
$$\Delta E = \sum_{r}^{occ}\sum_{s}^{unocc} + \sum_{s}^{occ}\sum_{r}^{unocc} \frac{2\left(\sum_{ab} C_{ra}C_{sb}\beta_{ab}\right)^2}{E_r - E_s} \qquad (2)$$

It may be concluded that the choice of transition state geometry is not important. The theoretical results in all three tables consistently predict the same regioisomer regardless of which rotameric pair is used to calculate the interaction energy.

In each example the head-to-head adduct is preferred. For the reaction of **14 + 10** this is experimentally verified, as is the predicted regioisomer from **6 + 10.** However, the predicted and observed regioisomers for the reaction **14 + 10** do not agree. This comes as no great surprise since the electrostatic interactions between reacting species were not considered. Furthermore some of the predictions (**14 + 15**) can be reversed by small changes in the CNDO/2 MO energies and coefficients. Since it is known that the CNDO/2 method can give incorrect MO energies (for instance, the CNDO/2 HOMO of acrolein is higher than the CNDO/2 HOMO of ethylene),[15] the CNDO/2 MO energies and wave functions appear not to be very reliable at this level of sophistication. The correlation of predicted and observed yields in heterocycloadditions (ut infra), particularly for sulfur-containing systems, is, however, surprisingly good.

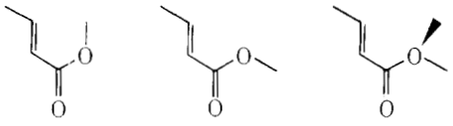
In a review article we indicated that 6,8-dioxabicyclic ketals are found in a wide variety of natural environments.[9] Since

Table I. Average Coefficients for Rotamers of 14, 15, 10, and 6



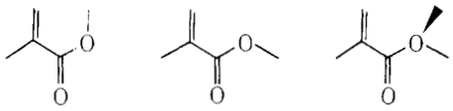
14 anti 14 syn 14 normal

	average eigenvectors	
	HO	LU
C_1	−0.5777	0.5814
C_2	−0.4360	−0.3877
C_3	0.1928	−0.4510
O_4	0.4770	0.4846



15 anti 15 syn 15 normal

	average eigenvectors	
	HO	LU
C_1	−0.3924	0.6125
C_2	−0.3998	−0.4485
C_3	0.1981	−0.3844
O_4	0.5989	0.3935



10 anti 10 syn 10 normal

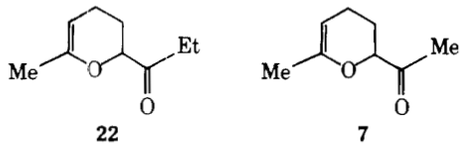
	average eigenvectors	
	HO	LU
C_1	−0.4316	0.6101
C_2	−0.3208	−0.4464
C_3	0.1737	−0.4198
O_4	0.5077	0.4218

6

	HO	LU
C_1	−0.5220	0.5866
C_2	−0.4308	−0.3839
C_3	0.3030	−0.4645
O_4	−0.6350	0.4940

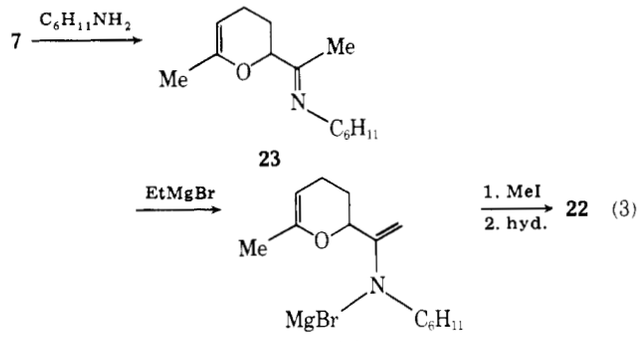
then, new compounds containing the bicyclic ketal moiety have been discovered.[17] It is evident from Table I that substituted dihydropyrans serve as excellent starting material for these natural products. Since the challenge to synthesize brevicomin has been met by several research groups, we wish to report what we believe to be the most conceptually simple and practical synthesis to date. The simplicity of this approach stems from the accessibility of dihydropyranyl systems.

Based on extension of our first effort toward the synthesis of brevicomin,[7] we required the ethyl ketone **22.** This could



22 **7**

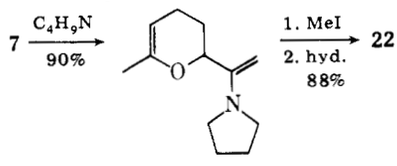
not be obtained in useful quantities from simple enolate methylation of the dimer of methyl vinyl ketone (**7**);[18] however, it was recently prepared[8b] by application of Stork's imine alkylation procedure (eq 3).



23 **24**

(3)

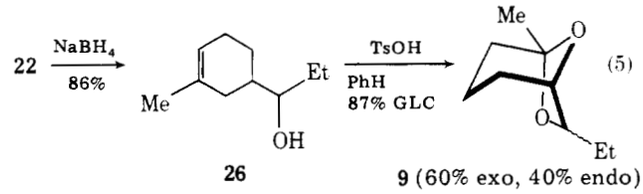
We have, as part of a related study,[19] observed that the pyrrolidino enamine (**25**) of **7** can be readily prepared in high yield. Methylation of **25** followed by hydrolysis gives **22.** The identity of **22** was confirmed by its comparison with the product obtained from the known independent synthesis via the route shown in eq 4.



25

(4)

Reduction of **22** with sodium borohydride in 2-propanol resulted in the epimeric alcohols **26.** Shaking a benzene solution of the alcohols with a trace amount of *p*-toluenesulfonic acid gave *exo*- and *endo*-brevicomin (**9**).[20]

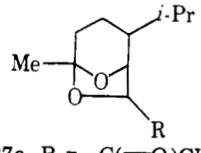


26 **9** (60% exo, 40% endo)

(5)

The easy access to **7** followed by the simple conversions outlined in eq 4 and 5 convincingly shows that this procedure is a useful route to bicyclic ketals. Parenthetically we add that bicyclic acetals of interest to carbohydrate chemists should be available by this route. Indeed, bicyclic acetals have been prepared beginning with substituted pyrans, but this work will be presented at a later date.

A detailed mass spectral analysis of **9, 13,** and **18** has been reported in which these ketals were noted to give rise to characteristic fragmentation patterns.[21] The modes of fragmentation could not be correlated with the reported mass spectra of **27** isolated from tobacco,[22] which lead Gore and



27a, R = $-C(=O)CH_3$
b, R = $-CH(OH)CH_3$
c, R = $-C(OH)(CH_3)_2$

co-workers to the conclusion that "complex substituents may make a significant contribution to the mass spectra of substituted dioxabicyclo[3.2.1]octanes." Here we substantiate this finding and further discuss the effects of substituents in the 7 position. Particular emphasis is given to the 7,7-disubstituted derivatives of **28,** which are now readily available from dihydropyran **7.**

Table II. FMO Treatment of 14 and 15 [a]

	14 anti/15 anti	14 anti/15 syn	14 anti/15 normal
ΔE	−0.0730	−0.0764	−0.0878
$\Delta E'$	−0.0706	−0.0553	−0.0812
	14 syn/15 anti	**14 syn/15 syn**	**14 syn/15 normal**
ΔE	−0.0612	−0.0652	−0.0764
$\Delta E'$	−0.0546	−0.0588	−0.0697
	14 normal/15 anti	**14 normal/15 syn**	**14 normal/15 normal**
ΔE	−0.0730	−0.0764	−0.0877
$\Delta E'$	−0.0668	−0.0702	−0.0817

[a] ΔE = interaction energy for head-to-head dimer (**17**); $\Delta E'$ = interaction energy for head-to-tail dimer (**16**).

Table III. FMO Treatment of 14 and 10 [a]

	14 anti/10 anti	14 anti/10 syn	14 anti/10 normal
ΔE	−0.0721	−0.0681	−0.0941
$\Delta E'$	−0.0636	−0.0586	−0.0815
	14 syn/10 anti	**14 syn/10 syn**	**14 syn/10 normal**
ΔE	−0.0605	−0.0567	−0.0827
$\Delta E'$	−0.0517	−0.0473	−0.0705
	14 normal/10 anti	**14 normal/10 syn**	**14 normal/10 normal**
ΔE	−0.0726	−0.0708	−0.0944
$\Delta E'$	−0.0637	−0.0594	−0.0660

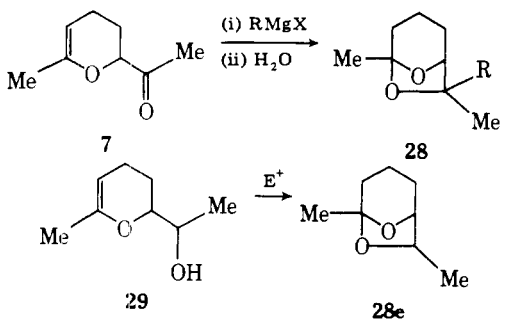
[a] ΔE = interaction energy for head-to-head dimer (**19**); $\Delta E'$ = interaction energy for head-to-tail dimer (**20**).

Table IV. Interaction Energies of 6 and 10 [a]

	6/10 anti	6/10 syn	8/10 normal
ΔE	−0.0702	−0.0658	−0.0892
$\Delta E'$	−0.0661	−0.0619	−0.0834

[a] ΔE = interaction energy for head-to-head dimer (**11**); $\Delta E'$ = interaction energy for head-to-tail dimer (**12**).

All new 7,7-disubstituted bicyclic ketals were prepared by the addition of **7** to the corresponding Grignard reagents in typical fashion. The propensity for alcohols like **29** to ketalize



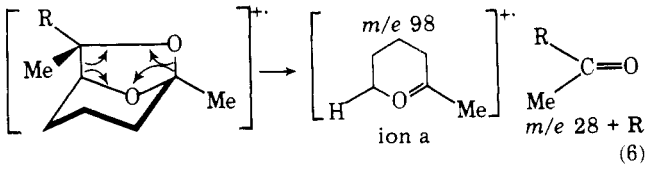
7 **28** **29** **28e**

a, R = Me; **b**, R = *i*-Pr; **c**, R = Et; **d**, R = Ph; **e**, R = H

in the presence of the mildest of electrophilic reagents has been studied, and even with great care to avoid any reagent more acidic than water in the workup of the anticipated tertiary alcohol from **7**, only **28** could be isolated. All new ketals were formed in high yield and were purified as a mixture of exo/endo isomers with the exception of **28b**.[23]

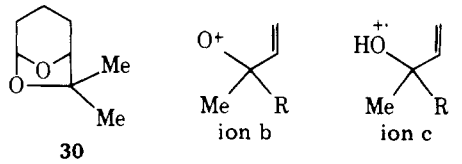
When subjected to electron impact at 70 eV, **28** produced many of the ion fragments recognized from published work.[21] Exo and endo isomers of both 7-methyl (**28e**) and 7-ethyl (**9**) groups indicated that little stereochemical information about the 7 position can be ascertained. In most of the examples, the predicted fragmentations are found and exceptions can be rationalized by other transformations.

For all of the 7,7-disubstituted ketals we note ions for *m/e* 53 + R and *m/e* 81 + R. Examination of the fragmentation for each bicyclic ketal indicates an ion at *m/e* 98 derived from bond rupture shown in eq 6. The complementary ketone may



(6)

serve as progenitor to the $CH_3C{=}O^+$ and $RC{=}O^+$ (*m/e* 28 + R) ions which also were observed for each ketal. We stress here that 7,7 disubstitution significantly enhances this mode of fragmentation. This is exemplified by 7,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane (**30**), which produces ion a as the



30

most abundant species. The relative abundances of ion *m/e* 98 are 64, 83, 51, and 36% for 7,7-disubstituted ketals **28a–d**, respectively, and only 17 and 18% for the two isomeric 7-monosubstituted ketals **28e**. Mass spectra of other unsubstituted or 7-monosubstituted 6,8-dioxabicyclo[3.2.1]octanes follow this pattern.[21]

It was suggested that the presence of alkyl groups at C-1 can be determined on the basis of the relative abundance of ions b and c.[21] We must express our concern over this statement

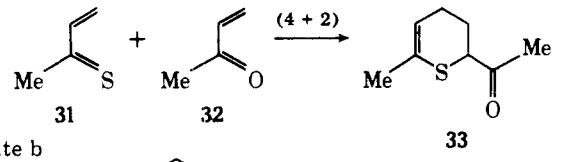
by noting that of the 6,8-dioxabicyclic ketals studied here none possess an alkyl group at C-1, yet most produce ions b and c. Furthermore, the ratios of b/c are **28a** (19:39), **28c** (13:7), *exo*-**28e** (33:21), and *endo*-**28e** (20:28), which demonstrates that a b/c ratio < 1 is not necessarily attributable to an alkyl substituent at C-1.

From these data, we conclude that gross structural information about 6,8-dioxabicyclic ketals can be obtained by mass spectrometry. Stereochemical information, however, generally can not be ascertained by electron impact studies at 70 eV. When used as a definitive tool for structural work, it must be emphasized that bicyclic ketals with substituents at C-7 favor certain modes of fragmentation, and one must exercise caution in spectral interpretation with regard to the position of substituents on the ketal substructure.

Part II

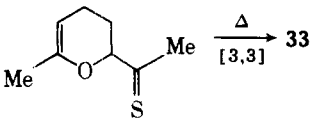
With our success in the pyran series, we next turned our attention to the sulfur analogues. These can, in principle, be realized from two routes:

route a



31 32 33

route b

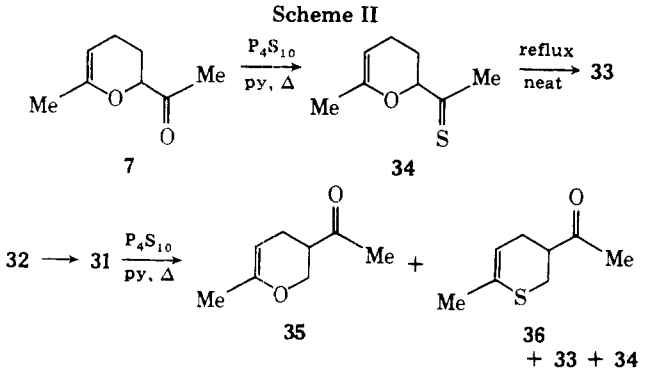


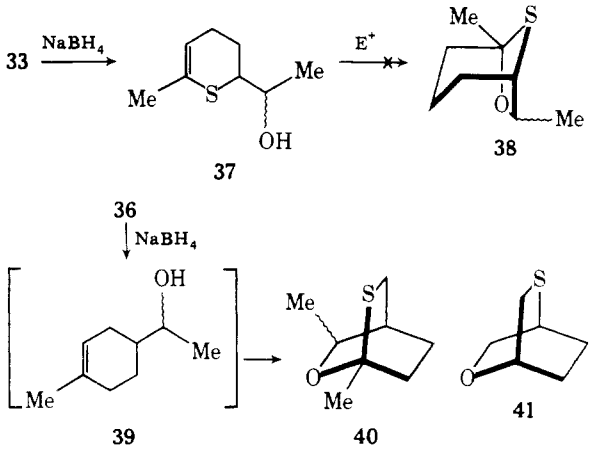
34

The second route (b) should clearly be the more regioselective; however, the temperature required for the rearrangement might also result in a retro-Diels–Alder reaction, in principle resulting in scheme a. With no literature precedence upon which to make a priori predictions, we embarked upon an analysis of reactions a and b with the intent of placing sulfur in the ring. A preliminary account of our efforts has been reported[24] and is summarized in Scheme II. The cycloaddition process a clearly affords a much more complex reaction mixture and, in terms of a tactical synthesis of thiapyrans like **33**, is undesirable.

With several unique thiapyran derivatives available to us, it seemed appropriate to examine the methodologies which might lead to sulfur analogues of bicyclic ketals—particularly those such as **38**, which are structurally similar to the insect pheromones. To achieve this, a GLC mixture of **33** and **36**, available from route a, was reduced with sodium borohydride. A mixture of diastereomeric alcohols **37** resulting from reduction of **33** was prepared. Reaction of **37** with electrophilic reagents was unsuccessful in cyclization to **38**. The diastereomeric alcohols expected from reduction of **36** were not found, but rather a novel heterocyclic system (**40**) was obtained as a mixture of exo and endo isomers. A structurally

Scheme II

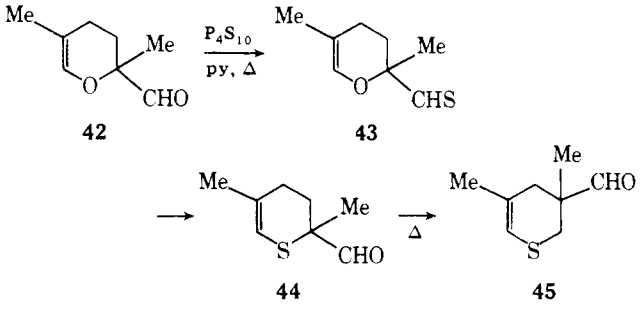




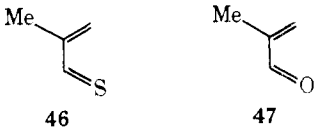
related heterocycle (**41**) is known.[25] The inability of **37** to cyclize with reagents that readily ketalize its oxygen counterpart is perplexing and is being investigated.

Further investigation of the preparation of thiapyranyl systems was attempted with acrolein. Unfortunately, the instability of acrolein dimer precluded our investigation of route b, and the reaction of acrolein monomer with P_4S_{10} via route a resulted in polymerization.

The chemistry of methacrolein, however, behaved quite well. Methacrolein dimer **42**, when treated with P_4S_{10} in refluxing pyridine, did not give pyran **43** upon workup. Aldehyde **44** though was obtained. It is apparent that the activation energy for Cope rearrangement of **43** is much lower than for isomer **34** since **34** must be refluxed neat (~210 °C) to induce the [3,3] sigmatropic shift. Significant amounts of isomeric aldehyde **45** are also found. The ratio of **45**/**44** can be increased



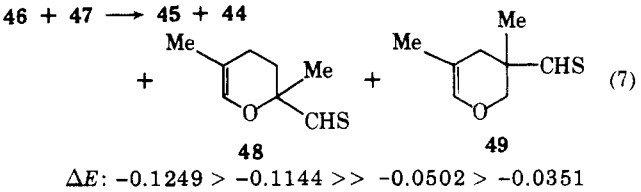
by increasing the reaction time. Heating **44** neat under a nitrogen blanket for 10 min completely converts it to **45**. This is only possible by a retro-Diels–Alder reaction that forms **46**



46 47

and **47** followed by recombination to **45**. A theoretical treatment of this recombination follows.

One can expect that methacrolein and thiomethacrolein could react to produce four possible isomers. A frontier molecular orbital treatment using CNDO/2 eigenvalues and eigenvectors[26] is presented in eq 7. The calculated interaction



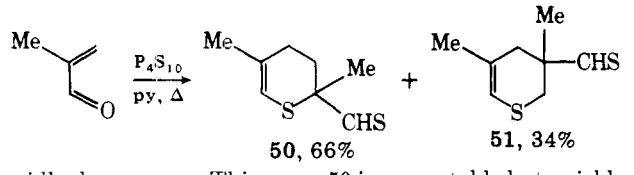
(7)

ΔE: −0.1249 > −0.1144 >> −0.0502 > −0.0351

energies (ΔE) for the thiapyrans **44** and **45** are much larger than for the pyrans **48** and **49**. This is consistent with the expected behavior of the sulfur system to act as the diene due

to the softness of the sulfur. It is also borne out by our experiment since no pyrans are found in the reaction mixture. Given that there are two possible thiapyran regioisomers, we see that frontier molecular orbital theory correctly predicts the observed regioisomer **45**. It is evident from previous experience[24] and from this work that frontier orbital theory is very useful in assessing product mixtures from Diels–Alder reactions of heterodienes. In fact, an excellent correlation can be seen between the theoretical prediction of $C_8H_{12}OS$ isomer formation and the relative percent yield found experimentally (Figure 1).

The reaction of methacrolein monomer behaves quite differently from the isomeric methyl vinyl ketone. Only two products are obtained when methacrolein is treated with P_4S_{10}, neither of which appears to contain oxygen. The thiapyran tentatively assigned structure **51** is very unstable and

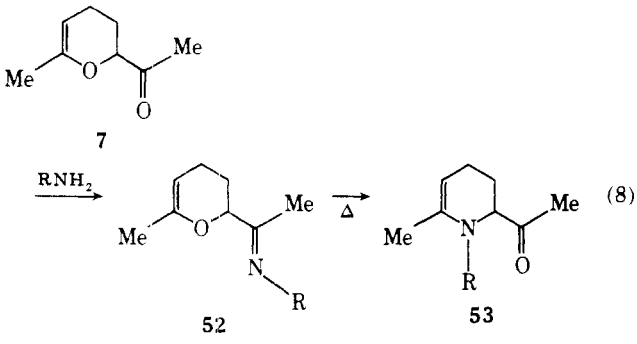


50, 66% **51**, 34%

rapidly decomposes. Thiapyran **50** is more stable but quickly discolors, as do most of the sulfur-containing heterocycles mentioned in this paper. Studies focused around the regioselectivity of heterodienes containing sulfur and thermal rearrangements into the thiapyranyl ring system are being pursued experimentally and theoretically.

Part III

A strategy for facile entry into the piperidine series by the general scheme delineated in eq 8 was next investigated.[27] The

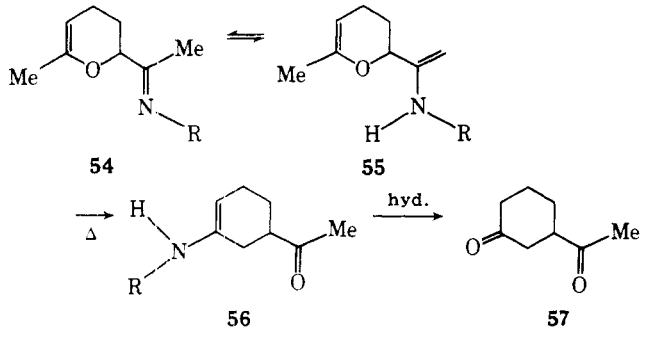


(8)

requisite imine **52** was obtained by stirring an ether solution of **7** with an appropriate amine over molecular sieves. The imines (R = Me, Et, Pr, Bu) could be purified by distillation, and heating at 250 °C resulted in formation of a product which was an enamine. However, hydrolysis of the rearrangement product resulted in 3-acetylcyclohexanone (**57**). This observation can only be rationalized by Scheme III. Imine–enamine tautomerism has literature precedence, even when followed by Cope rearrangement (eq 9).[28]

The details relating to the two steps of the reaction (tautomerism, [3,3] sigmatropic shift) have not been investigated.

Scheme III



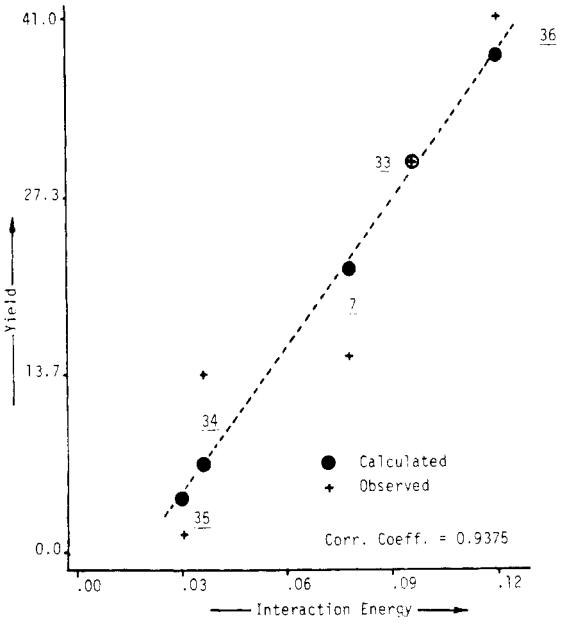
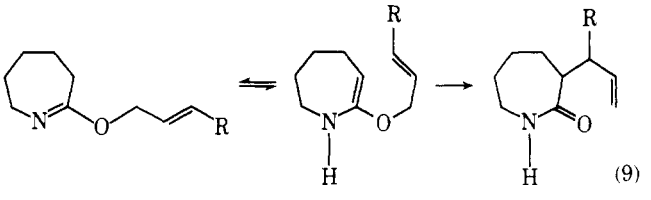


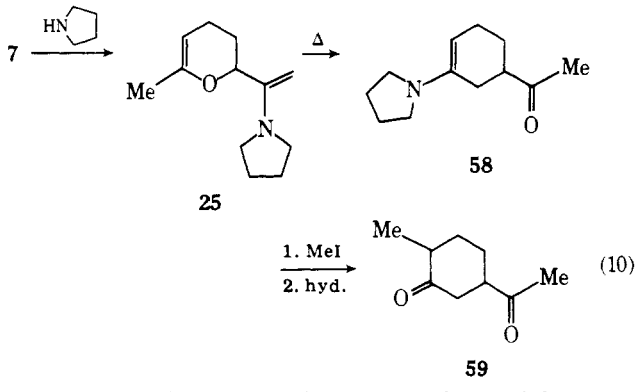
Figure 1. Correlation of predicted and observed yields in heterocycloaddition reactions.



(9)

However, we have noted a temperature dependence on the reaction (Table V).

Although the desired entry into the piperidine series was not achieved, the procedure offers an excellent entry into an activated 3-acetylcyclohexanone derivative. This was buttressed by the scheme shown in eq 10. The enamine of **7** was



(10)

readily prepared by stirring the ketone with pyrrolidine over molecular sieves. Thermal rearrangement of **25** → **58** occurred in high yield,[19] and conversion to **59** was accomplished by standard procedure. Thus, the preestablished functionalization of the cyclohexanone carbonyl group allows for regioselective alkylation of the molecule. Other than alkylation, the many specialized reactions which can be carried out with enamine allow a wide selection of additional functionalities to be included.

Conclusion

The utility of the cycloaddition reaction to form dihydropyran derivatives and the subsequent incorporation of other functionality by Cope rearrangement have been studied. Brevicomin, the aggregating pheromone of the western pine

Table V. Rearrangement of the Methylimine 52

temp, °C	% 52	% 56[a]
150	100	
175	100	
200	82	18
225	29	71
250		100
275		*b*
300		*b*

[a] Relative GLC areas (10% SE-30 on Chromosorb W, 160 °C). [b] Although only **52** was observed, there was extensive decomposition, thus suggesting product deterioration at higher temperature.

bark beetle *Dendroctonous brevicomis*, was synthesized along with other bicyclic ketals, and the mass spectral fragmentation patterns of these molecules have been analyzed. A theoretical prediction of regioselection in the (4 + 2) cycloadditions appears quite consistent with experimental observations, particularly for heterodienes containing sulfur. Our inability to incorporate nitrogen into the ring is accounted for by an imine–enamine tautomeric shift prior to the Cope rearrangement. The unexpected product offers an excellent entry into substituted cyclohexanone derivatives.

Experimental Section

All NMR spectra were recorded at 60 MHz in $CDCl_3$ or CCl_4 and are reported in δ units relative to Me_4Si as an internal standard. Mass spectra were recorded on either a Varian CH-5 or CH-7 mass spectrometer. High-resolution spectra were obtained with an AEI-MS-9 spectrometer. Analytical samples were provided by Midwest Analytics Inc., Indianapolis, Indiana, and Chemalytics Inc., Tempe, Ariz.

Preparation of the Cyclohexylimine Derivative 23. A 20-g amount of **7** and 14.2 g of cyclohexylamine were placed in 200 mL of benzene and allowed to reflux for 10 h. Water was removed from the reaction using a Dean-Stark water separator, and after the theoretical amount had been collected the benzene solution was reduced in volume. The residue was distilled ($bp_{8\ mm}$ 95–96 °C) to yield 29.2 g (92%) of the required imine. This was used directly in the next step.

Preparation of 2-Propionyl-6-methyl-2,3-dihydro-4*H*-pyran (22). Method A. The imine (14 g) was dissolved in 150 mL of anhydrous THF and added to an equivalent of ethyl Grignard. The reaction mixture was refluxed under nitrogen for 5 h, and after cooling to 0 °C 8.9 g of methyl iodide in 50 mL of THF was added. After the addition was complete, the reaction mixture was allowed to come to room temperature and stir for 24 h. At this time, it was cooled to 0 °C and 1 equiv of glacial acetic acid as a 5% aqueous solution was added. After stirring for 0.5 h, the reaction mixture was extracted with ether (4 × 100 mL) and the combined extracts were washed with brine and dried over magnesium sulfate. Excess solvent was removed, and the residue was distilled at aspirator pressure (84 °C) to give 7.8 g of product. This was identical with the product made by method B.

Method B. The pyrrolidine enamine (15 g) of **7**, whose preparation is discussed in a later portion of the Experimental Section, was placed in benzene and cooled to 0 °C. To this solution, maintained under nitrogen atmosphere, was added 11 g of methyl iodide. The reaction mixture was stirred for 1 h and then refluxed for 24 h. After this time, the reaction mixture was cooled to 0 °C and hydrolyzed with 1 equiv of acetic acid (5% aqueous solution). The reaction mixture was stirred for 45 min and then extracted (4 × 100 mL) with ether. Workup and distillation were the same as in method A: NMR δ 4.4 (multiplet, 1 H), 4.16 (multiplet, 1 H), 2.5 (quartet, J = 7.2 Hz, 2 H), 1.92 (multiplet, 4 H), 1.7 (singlet, 3 H), 1.03 (triplet, J = 7.2 Hz, 3 H).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.14. Found: C, 70.07; H, 9.35.

Sodium Borohydride Reduction of 22. To a solution containing 14 g of **22** and 100 mL of isopropyl alcohol, cooled to 0 °C, was slowly added (over ~1 h) 3.45 g of sodium borohydride. After the addition had been completed, the solution was stirred for an additional 2 h and 15 mL of 20% sodium hydroxide was added. The solution was then warmed to 45 °C and after 2 h was poured into 200 mL of H_2O. The aqueous solution was extracted (4 × 100 mL) with ether, the combined ether layers were dried over magnesium sulfate and reduced in volume, and the residue was distilled. The product, 12.2 g, had $bp_{10\ mm}$ 84 °C.

Anal. Calcd for $C_9H_{16}O_2$: C, 69.20; H, 10.31. Found: C, 69.01; H, 10.61.

Synthesis of *exo*- and *endo*-Brevicomin (9). A benzene solution of **26** was shaken with a trace of *p*-toluenesulfonic acid. Neutralization of the acid with bicarbonate left a benzene solution of the brevicomin isomers.

Synthesis of 7,7-Disubstituted-5-methyl-6,8-dioxabicyclo[3.2.1]octanes 28a–e. Typically, 0.007 mol of Grignard reagent was prepared in a round-bottom flask equipped with a magnetic stirring bar. A 1-g (0.07-mol) amount of methyl vinyl ketone dimer **7** in ethyl ether was slowly added. The precipitated salts were stirred and hydrolyzed with water. Extraction with methylene chloride, drying over anhydrous magnesium sulfate, and removal of solvent provided the desired compounds. Structural identification follows.

28a: IR 1380 (geminal dimethyl), 1200–1040 (cyclic ketal) cm^{-1}; NMR δ 3.88 (broad singlet, 1 H), 1.65 (methylene envelope, 6 H), 1.40 (singlet, 3 H), 1.38 (singlet, 3 H), 1.28 (singlet, 3 H); MS calcd and found, *m/e* 156.

Anal. Calcd for $C_9H_{16}O_2$: C, 69.20; H, 10.20. Found: 69.08; H, 9.91.

28b: 71.2% yield, isolated on a 5% SE-30 column; IR 1200–1040 cm^{-1} (cyclic ketal); NMR δ 3.88 (broad singlet, 1 H), 2.0–1.3 (methylene envelope, 7 H), 1.28 (singlet, 3 H), 1.10 (singlet, 3 H), 0.83 (two overlapping doublets, 6 H, J = 7 Hz); MS calcd and found, *m/e* 184.

28c: 82.4% yield, exo and endo isomers could not be resolved with 5% SE-30, 10% UCON-50, 20% Carbowax 20M, or Apiazon columns; IR 1200–1050 cm^{-1} (cyclic ketal); NMR δ 3.95 (singlet, 1 H), 1.7 (methylene envelope, 6 H), 1.4 (singlet, 3 H), 1.3 (singlet, 3 H), 0.05 (broad ethyl multiplet, 5 H); MS calcd and found, *m/e* 170.

Anal. Calcd: C, 70.59; H, 10.59. Found: C, 70.68; H, 10.38.

28d: described in ref 24.

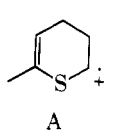
28e: this was a well-characterized substance described in ref 30.

Synthesis of 2-Thioacetyl-6-methyl-2,3-dihydro-4H-pyran (34). Methyl vinyl ketone dimer **7** (5.6 g) and an excess of phosphorus pentasulfide (3.0 g) were stirred at reflux in 40 mL of pyridine for 12 h. Upon cooling, 50 mL of petroleum ether was added and the black-brown solution was washed (2 × 100 mL) with water, followed by enough dilute hydrochloric acid washings to remove the pyridine. Drying the petroleum ether layer over anhydrous magnesium sulfate, filtration, and removal of solvent yielded a crude black product which was immediately distilled, $bp_{0.25\ mm}$ 37 °C, to yield 2.0 g of an orange product in 32% yield. This product is >95% pure by GLC: IR 3000–2850 (broad CH stretch), 1625 (sharp), 1220, 1155, 1035, 1018, 797 (shape unknown) cm^{-1}; NMR δ 5.0 (singlet, 2 H), 1.91 (singlet superimposed on a methylene envelope, 10 H); MS calcd and found, *m/e* 156.

Anal. Calcd for $C_8H_{12}OS$: C, 61.54; H, 7.69; S, 20.51. Found: C, 61.71; H, 7.70; S, 20.73.

This sulfur heterocycle was by far the most stable sulfur-containing molecule in this investigation. Nevertheless, it will slowly decompose upon standing overnight. GLC pure samples were collected using 5% SE-30 and 15% Apiazon columns.

Synthesis of 2-Acetyl-6-methyl-2,3-dihydro-4*H*-thiapyran (33). Dihydropyran **34** was stirred at reflux under a nitrogen blanket. Serious decomposition was observed. Short-path distillation ($bp_{0.18\ mm}$ 59 °C) produced a mixture of **33** and **34** which can be separated on 10% OV-101 or 10% Carbowax 20M columns. In both cases, **33** had a shorter retention time than **34**: IR 3010–2840 (C–H stretch), 1705 (C=O), 1640, 1430, 1358, 1284, 1216, 1155, 1105 (sharp unknown) cm^{-1}; NMR δ 5.53 (methine singlet, 1 H), 3.77 (vinyl triplet, J = 3.5 Hz, 1 H), 2.27 (singlet, 3 H), 2.10 (methylene envelope, 4 H), 1.90 (doublet, J = 1 Hz, 3 H); MS calcd and found, *m/e* 156; intense ions at *m/e* 113 and 43 correspond to structure A and $CH_3C{\equiv}O^+$ respectively. Elemental analysis: two attempts consistently gave low carbon and low sulfur, suggesting an oxidative decomposition.



A

Synthesis of 2,3-Dihydropyran 35 and 2,3-Dihydrothiapyran 36. Methyl vinyl ketone (3.5 g) and phosphorus pentasulfide (2.37 g) were refluxed for 12 h in 20 mL of pyridine. Upon cooling, 50 mL of petroleum ether was added and the solution was washed with water, hydrochloric acid until excess pyridine was removed, and water once more. Drying over anhydrous magnesium sulfate, filtration, and reduction in volume yielded 0.50 g of brown-orange oil as a mixture of **33, 34, 35,** and **36**. The percent yields have been presented in a communication.[24] Attempted distillation at reduced pressure resulted in decomposition to black tar. The structural identification of **36**

follows: IR 3010–2830 (C–H stretch), 1710 (C=O), 1645, 1430, 1345, 1290, 1235, 1165, 1122 (unknown) cm^{-1}; NMR δ 5.50 (broad vinyl singlet, 1 H), 2.91 (methine and methylene multiplet, 3 H), 2.37 (methylene envelope, 2 H), 2.22 (singlet, 3 H), 1.87 (multiplet, 3 H). MS calcd and found, *m/e* 156 with an intense ion at *m/e* 43 similarly observed in **33**. Elemental analysis: serious decomposition precluded our obtaining a correct analysis. The structure of **35** was assigned by analogy. Mass spectral data indicated this as a $C_8H_{12}OS$ isomer of **33, 34,** and **36**. The intense ion at *m/e* 43 was not present, indicating the lack of an acetyl moiety. Low yield (1%) and serious thermal decomposition did not permit GLC collection of this component.

Synthesis of 1,3-Dimethyl-2-oxa-6-thiabicyclo[2.2.2]octane (40). A 250-mg amount of **33** and **36** (3:4 ratio, freshly isolated on a 5 ft × 0.25 in. column of 20% Carbowax on Chromosorb W) was added to excess sodium borohydride in 2 mL of ethanol and stirred for 2 h. Addition of water, extraction with methylene chloride followed by drying of the organic layer over anhydrous magnesium sulfate, and removal of solvent yielded approximately 250 mg of a mixture containing **40** and **37** (3:4 ratio) as a light orange oil. GLC analysis on a 5 ft × 0.25 in. 5% Carbowax 20M column indicated one short and two long retention peaks. The short retention isomer was a mixture of *exo* and *endo*-**40** (1:1 mixture, see below), while the two long retention peaks were a 1:1 mixture of diastereomeric alcohols **37**. The structure proof of **40** follows: IR 3000–2800, 1445, 1370, 1190, 1165, 1050, 1042, 972 (all strong and sharp), 830 (broad and strong) cm^{-1}; NMR δ 4.17 (multiplet, 1 H), 3.00 (multiplet, 1 H), 2.00 (multiplet, 6 H), 1.38 (singlet, 3 H), 1.25 (singlet, 3 H). Incremental addition of $Eu(fod)_3$ split the upfield methyl absorption into a doublet which integrated as a 1:1 mixture of *exo*- and *endo*-**40**. The methyl singlet centered at δ 1.25 was broadened but not shifted. MS: calcd and found, *m/e* 158. Elemental analysis: not consistent due to decomposition, but high-resolution mass spectral data are available (calcd 158.0766, found 158.0753).

Synthesis of Hydroxythiapyran 37. Sodium borohydride reduction of **33** was described above. A 50:50 mixture of diastereomeric alcohols was separated by GLC on a Carbowax 20M column. The structure proof of the short retention diastereomer follows: IR 3600–3200 (O–H), 3000–3800 (C–H), 1648, 1440, 1375, 1085 (unknown) cm^{-1}; NMR δ 5.56 (vinyl singlet, 1 H), 3.83 (unassigned pentet, J = 4 Hz, 1 H), 3.03 (hydroxyl multiplet, 1 H), 2.10 (methylene envelope, 5 H), 1.73 (vinyl methyl singlet, 3 H), 1.26 (hydroxyl methyl doublet, J = 4 Hz, 3 H); MS calcd and found, *m/e* 158; high-resolution mass spectrum calcd 158.0766, found 158.0777. Elemental analysis: none.

The structure proof of the long retention diastereomer follows: IR 3600–3200 (O–H), 3000–2800 (C–H), 1648, 1440, 1380, 1110, 1070 cm^{-1}; NMR δ 5.53 (vinyl multiplet, 1 H), 3.87 (pentet, J Hz, 1 H), 3.03 (hydroxyl multiplet, 1 H), 2.16 (methylene envelope, 5 H), 1.85 (vinyl methyl singlet, 3 H), 1.31 (hydroxyl methyl doublet, J = 4 Hz, 3 H); MS calcd and found, *m/e* 158; high-resolution mass spectrum calcd 158.0766, found 158.0764. Elemental analysis: none.

An unusually high degree of thermal decomposition of these alcohols tends to plug the chromatograph injector port at 190 °C.

Synthesis of 2-Formyl-2,5-dimethyl-2,3-dihydro-4*H*-thiapyran (44). Methacrolein dimer **42** (2.80 g) and phosphorus pentasulfide (1.30 g) were refluxed for 12 h in 30 mL of pyridine. Workup as described for **34** yielded 1.00 g of brown oil. GLC analysis on a 10% SE-30 column demonstrated four peaks. In order of increasing retention time, we found 9.9% $C_8H_{12}OS$ isomer **45**, 25.7% unreacted starting material, 58.8% $C_8H_{12}OS$ isomer **44**, and ~5.5% unidentified compound, whose mass spectrum indicated two sulfurs ($C_8H_{12}S_2$, *m/e* 172 and 174). An increase in reflux time from 12 to 42 h changed the relative percent yields to 37.4% **45**, 15.0% unreacted starting material, and 47.4% **44**. The structure determination of **44** follows: IR 3000–2820 (C–H stretch), 2800 (aldehyde C–H),[29] 2720 (aldehyde C–H),[29] 1720 (C=O), 1440 and 1350 (aliphatic aldehyde absorption) cm^{-1};[29] NMR δ 9.65 (aldehyde singlet, 1 H), 3.10 (vinyl, 1 H), 2.1–1.55 (methyl singlet centered over a methylene envelope at δ 1.65, 10 H), 1.30 (singlet, 3 H); MS calcd and found, *m/e* 156; high-resolution mass spectrum calcd 156.0619, found 156.0624.

Synthesis of 3-Formyl-3,5-dimethyl-2,3-dihydro-4*H*-thiapyran (45). A 5.45-g amount of the mixture described above was gently refluxed under nitrogen for 10 min. Distillation under high vacuum resulted in serious decomposition. Flash distillation, however, yielded 0.20 g of orange oil which contained the desired thiapyran. Separation was achieved on a 10% SE-30 column (10 ft × 0.25 in.). This $C_8H_{12}OS$ regioisomer (**45**) was very unstable and quickly decomposed. Structural identification follows: IR 3000–2820 (C–H), 2800 (aldehyde C–H),[29] 2700 (aldehyde C–H),[29] 1717 (C=O), 1440 and 1375 (aliphatic aldehyde absorptions) cm^{-1};[29] NMR δ 9.40 (singlet, 1 H), 5.05 (quartet, J = 0.75 Hz, 1 H), 2.45–2.10 (methylene envelope, 4 H), 1.80 (doublet, J = 0.75 Hz, 3 H), 1.15 (singlet, 3 H); MS calcd and found, *m/e* 156.

Synthesis of 2-Thiaformyl-2,5-dimethyl-2,3-dihydrothiapyran (50) and 3-Thiaformyl-3,5-dimethyl-2,3-dihydro-4*H*-thiapyran (51). These molecules were prepared by reacting methacrolein with phosphorus pentasulfide in pyridine. The procedure parallels that for formation of **35** and **36** using 3.5 g of aldehyde and 2.37 g of phosphorus pentasulfide. Typical workup followed by flash distillation at reduced pressure yielded 0.3 g of orange oil. GLC analysis on 10% SE-30 indicated a two component mixture. The short retention isomer accounted for 34% of the mixture and was tentatively assigned structure **51**. The major product, 66%, was thiapyran **50**. The minor product quickly decomposed, while the major component appeared to be moderately stable. Structural identification of **50** follows: IR 3000–2820 (C–H), 1430, 910–975 (intense) cm^{-1}; NMR δ 6.05 (multiplet, 1 H), 4.95 (singlet, 1 H), 4.75 (singlet, 1 H), 3.45 (triplet, J = 3.25 Hz, 1 H), 2.36 (doublet, J = 3.25 Hz, 2 H), 1.87 (singlet, 3 H), 1.83 (singlet, 3 H); MS calcd and found, *m/e* 172. A large P + 2 peak (17.78% relative abundance) was present as expected for a molecule with high percent sulfur content.

The structural identification of thiapyran **51** follows: IR 3000–2820 (C–H), 1430, 825, 795, 758 cm^{-1}; NMR δ 5.50 (multiplet, 2 H), 3.33 (singlet, 1 H), 2.83 (doublet, J = 3.50 Hz, 2 H), 1.81 (multiplet, 6 H); MS calcd *m/e* 172, found *m/e* 174. This is a source of confusion since this peak is 1.21% relative abundance.

Preparation of the *N*-Methylimine of 2-Acetyl-6-methyl-2,3-dihydro-4*H*-pyran (52, R = Me). A solution of **7** (19 g) and 100 mL of anhydrous diethyl ether containing 15 g of Linde 4Å molecular sieves was cooled to 0 °C, after which 2.48 g (~20% excess) of methylamine was added. The solution was allowed to stir and come to room temperature. After stirring overnight, the molecular sieves were filtered off and washed with ether. The combined ether solution was reduced in volume to leave a residue which was distilled (bp 37 °C) to give 9.7 g of product. The spectral data for this and other imines have been reported elsewhere.[27]

Preparation of 5-Acetyl-1-(methylamino)cyclohexene (56, R = Me). The imine **52** (5 g) was placed in a 15-mL round-bottom flask and heated to reflux temperature. Instead of a cooling condenser, the flask was fitted with a glass-filled column heated at 250 °C. The boiling imine, after passing through the column, rearranged and gave a crude pyrolysis product. Distillation (bp 125 °C) gave 3.3 g of product. The spectral data for this and other alkyl enamines have been reported elsewhere.[27]

Preparation of 3-Acetylcyclohexanone (57). A 3-g amount of **56** was dissolved in 50 mL of benzene to which was added 10 mL of 5% sulfuric acid. The entire solution was refluxed under nitrogen for 24 h, after which time the benzene layer was separated. Extraction of the aqueous layer (2 × 25 mL) with benzene was followed by three washings (50 mL) of the combined benzene fractions with saturated bicarbonate. The benzene solution was dried over magnesium sulfate and reduced in volume. Distillation of the residue at aspirator pressure gave 1.9 g of product (bp 124 °C).[30] The preparation of **25** and **58** has been reported elsewhere.[27]

Preparation of 2-Methyl-5-acetylcyclohexane (59). A 3-g amount of **58** was dissolved in 50 mL of dry benzene, and the solution was placed under a nitrogen atmosphere. To this stirred solution was added 2.12 g of methyl iodide. The resulting solution was heated to reflux, and after 24 h 10 mL of 5% sulfuric acid was added. After an additional 5 h at reflux, the solution was extracted (3 × 100 mL) with ether. The combined extracts were washed with saturated bicarbonate, dried over magnesium sulfate, and reduced in volume. The residue was distilled at aspirator pressure (bp 131–132 °C) to give 1.81 g of product: NMR δ 2.55–1.15 (multiplet, 8 H), 2.18 (singlet, 3 H), 0.92 (multiplet, both isomers present, 3 H). The mass spectrum gave a molecular ion at *m/e* 154 (19.6) with major fragments of *m/e* 43 (100), 55 (72), 96 (66), 111 (58), and 139 (16).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.12, H, 9.09. Found: C, 69.82; H, 8.53.

Registry No.—**7,** 28450-02-4; *exo*-**9,** 20290-99-7; *endo*-**9.** 22625-19-0; **22,** 62255-24-7; **23,** 68378-81-4; **25,** 67236-47-9; **26** (isomer 1), 68378-82-5; **26** (isomer 2), 68378-83-6; **82a,** 16566-96-4; *exo*-**28b,** 68378-84-7; *endo*-**28b,** 68378-85-8; *exo*-**28c,** 68378-86-9; *endo*-**28c,** 68378-87-0; *exo*-**28e,** 56057-15-9; *endo*-**28e,** 56057-16-0; **33,** 65818-69-1; **34,** 65818-67-9; **35,** 65818-68-0; **36,** 65818-66-8; **37** (isomer 1), 68378-88-1; **37** (isomer 2), 68378-89-2; *exo*-**40,** 68378-90-5; *endo*-**40,** 68421-52-3; **42,** 1920-21-4; **44,** 68378-91-6; **45,** 68378-92-7; **50,** 68378-93-8; **51,** 68378-94-9; **52,** 67654-02-8; **56,** 67654-06-2; **57,** 15040-97-8; **58,** 67175-85-5; **59,** 56893-77-7; cyclohexylamine, 108-91-8; methyl vinyl ketone, 78-94-4; methacrolein, 78-85-3; pyrrolidine, 123-75-1.

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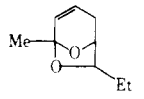

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Syntheses of Some Furans and Naphtho[2,3-*c*] Derivatives of Furan, Pyrrole, and Thiophene

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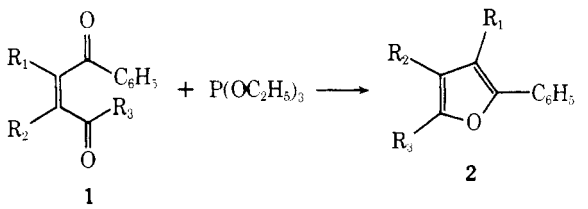
Treatment of aryl-substituted 2-butene-1,4-diones with triethyl phosphite caused ring closure reactions to furan derivatives. Simple routes to the preparation of 1,3-diphenylnaphtho[2,3-*c*]furan, 1,3-diphenyl-2-methylnaphtho[2,3-*c*]pyrrole, and 1,3-diphenylnaphtho[2,3-*c*]thiophene are described.

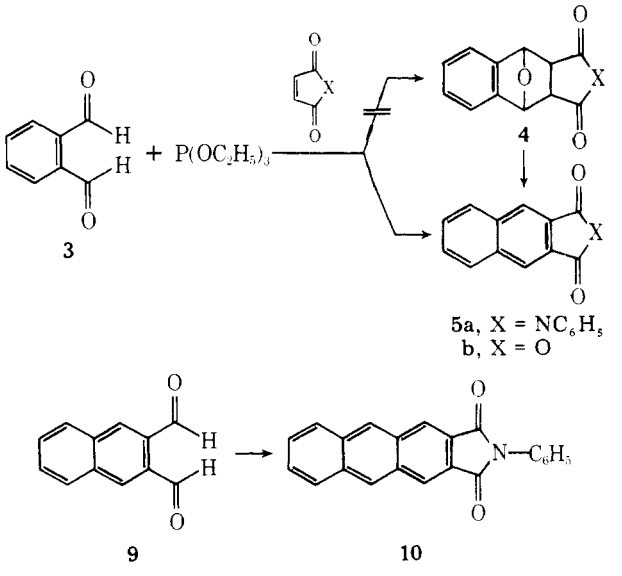
The reaction of aromatic aldehydes with hexaalkylphosphorus triamides to give aryl-substituted oxiranes has been reported by Mark.[1,2] Ramirez and co-workers[3] showed that the reaction of trimethyl phosphite with *trans*-1,2-dibenzoylethylene afforded 2,5-diphenylfuran. We planned to test the generality of the reaction of trialkyl phosphites with precursors that possess a 2-ene-1,4-dione functional group as a route to furans and isobenzofurans.[4]

It was found that the heating of a triglyme solution of 2-butene-1,4-diones **1a–e** with triethyl phosphite resulted in the formation of furans **2a–e**. These results encouraged us to examine the reaction of triethyl phosphite with aromatic *o*-diketones and *o*-dialdehydes. Treatment of o-dibenzoylbenzene, under various conditions, failed to produce any isolable quantity of 1,3-diphenylisobenzofuran although the latter was detected in traces by TLC. It was expected that the replacement of *o*-dibenzoylbenzene by *o*-phthalaldehyde (**3**) would improve the yield of the reaction and lead to the generation



1 **2**

a, $R_1 = R_3 = C_6H_5$; $R_2 = H$
b, $R_1 = R_2 = R_3 = C_6H_5$
c, $R_1 = C_6H_5$; $R_2 = H$; $R_3 = p\text{-}CH_3C_6H_4$
d, $R_1 = C_6H_5$; $R_2 = H$; $R_3 = p\text{-}CH_3OC_6H_4$
e, $R_1 = C_6H_5$; $R_2 = H$; $R_3 = p\text{-}BrC_6H_4$



9 **10**

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