

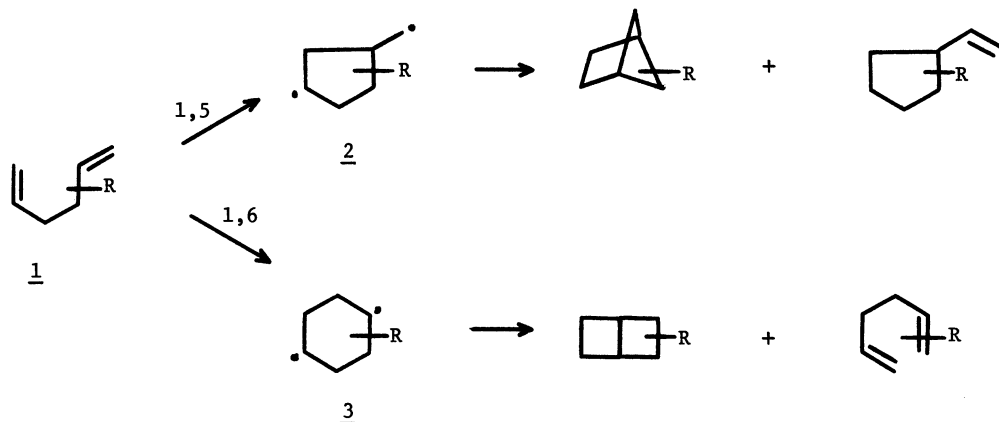
PHOTOCHEMISTRY OF CARBONYL-SUBSTITUTED HEXADIENES

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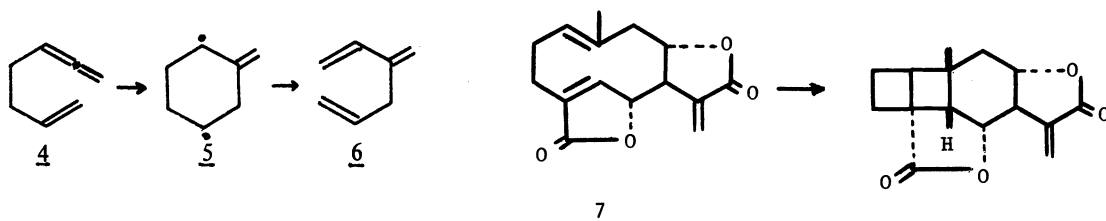
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Abstract - The long-known "rule of five" predicts 1,5 (crossed) cyclization for 1,5-hexadienes, and indeed there have been rather few exceptions to this behaviour reported over the past fifteen years. We have now studied the effect of structure on the regiochemistry of closure in three classes of carbonyl-substituted hexadienes -- 1,5-hexadien-3-ones, 1-acyl-1,5-hexadienes, and 2-acyl-1,5-hexadienes. We find that for the first two of these classes regiochemistry is a function of structure and that this can be controlled to yield predictably regiospecific 1,5 or 1,6 closure or a combination of the two modes. The third class, 2-acyl-1,5-hexadienes, undergoes 1,5 closure regardless of these structural variations. Mechanistic implications and synthetic applications of these findings are discussed.

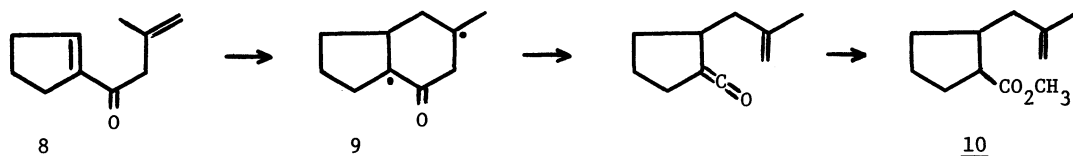
Numerous investigations over the past fifteen years have supported the generalization that ultraviolet irradiation of 1,5-hexadienes (1) leads to preferential 1,5 (crossed) closure, with formation of a biradical intermediate 2 that then proceeds to products such as those shown below (1,2). All indication of the alternative 1,6 (straight) closure (3) is fre-



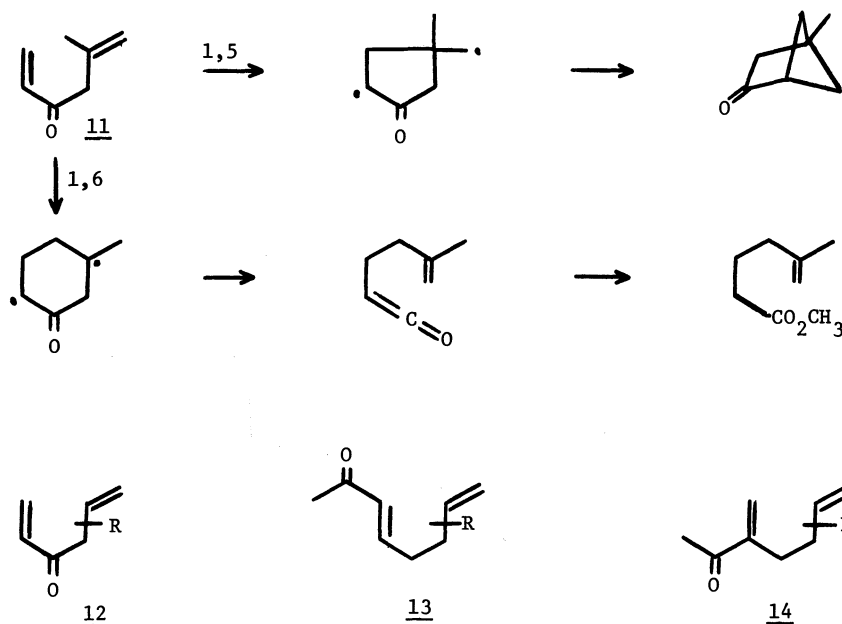
quently completely absent, and little or no change results from incorporation of the hexadiene double bonds into more complex systems such as trienes (2), tetraenes (3), or α,β -unsaturated ketones (4,5) or esters (6). Various authors have called attention to this "rule of five" (1,2,7) and to its broad validity over the years, with one such comment appearing as recently as early 1982 (8). A few exceptions to the generalization have been found, but typically these are understood to result from some unusual structural feature. Photochemical isomerization of allene 4 to triene 6, for example, can be justified because only 1,6 closure can furnish an allylically stabilized intermediate (5) (9). Similarly, the cyclodecadiene ring of isabelin (7) is sufficiently rigid that 1,6, but not 1,5 closure is sterically feasible (10).



In contrast to this pattern of behavior an investigation in our laboratory some ten years ago revealed that photolysis of the cyclopentenyl isobutenyl ketone 8 in methanol gave only the cis and trans isomers of ester 10, a result requiring 1,6 closure (9) (11). Further



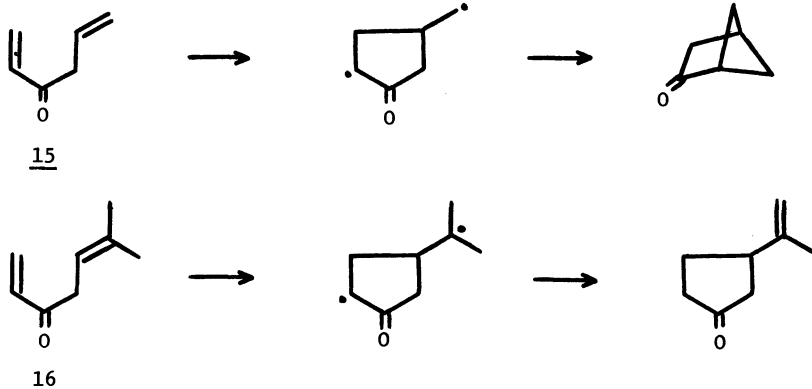
study demonstrated that the simple acyclic analogue of 8, 5-methyl-1,5-hexadiene-3-one (11), yielded products of both 1,5 and 1,6 closure (11). These observations presented two problems. Why do 8 and 11 undergo 1,6 closure, unlike so many other hexadienes? And why does 8 give only 1,6 closure, while 11 follows both pathways?



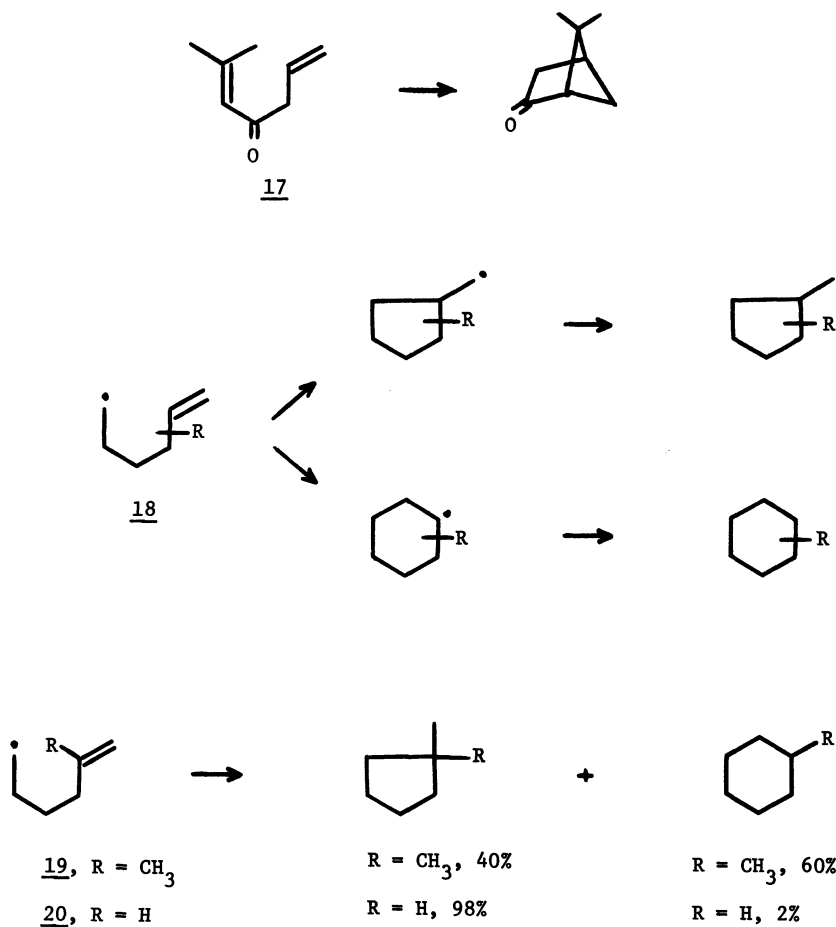
We have now devoted some effort to answering these questions and more broadly to clarification of the photochemical behavior of alkyl-substituted ketones formally related to 1,5-hexadiene. Our aim has been to provide general rules permitting qualitative predication of the photochemistry of these systems, rather than to investigate in physical detail the operative mechanisms. In the following pages we summarize our findings briefly; a more complete account, including details of synthesis and of various assignments of structure and stereochemistry to products, will appear elsewhere. The study began with an examination of 1,5-hexadien-3-ones (12) (12), and was then extended to 1-acyl-1,5-hexadienes (13) and 2-acyl-1,5-hexadienes (14). We typically carried out reactions by direct irradiation using the filtered output (>340 nm) from a medium-pressure mercury arc. Representative members of each group furnished the same products efficiently on triplet sensitization, in keeping with the well-known observation that photocycloaddition and related transformations are generally triplet processes. As we point out below, some members of series 14 undergo other processes on direct irradiation, and for these compounds triplet sensitization was a necessity.

1,5-HEXADIEN-3-ONES

The photochemistry of the simple dienones 15 (4) and 16 (5) has been known for some years; unlike 11 they faithfully follow the "rule of five." It is immaterial to our purposes here that in one case the product arises through collapse of the biradical and in the other, through its disproportionation. Similarly the related ketone 17, although photochemically inert at room temperature (5), is smoothly cyclized to a bicyclo[2.1.1]hexanone on irradiation at elevated temperature (12). From these observations with 11, 16 and 17 it appears then that addition of a methyl substituent to 15 at C(5), but not at C(1) or C(6), leads to increased 1,6 cyclization. This finding is immediately reminiscent of the behavior of alkyl-substituted 5-hexenyl radicals (18). These radicals are relatively insensitive to alkyl substitution at all positions except C(5), generally cyclizing highly preferentially in the



1,5 manner (13). Substitution of a methyl group at C(5), however, introduces a steric effect that dramatically decreases the rate of 1,5 cyclization and concomitantly slightly increases the rate of 1,6 closure. The overall result is that 5-methyl-5-hexenyl (19) closes irreversibly at similar rates to cyclopentane and cyclohexane products, while 5-hexenyl (20) itself gives virtually only the cyclopentane. The parallel between these earlier findings and the photochemistry of 11 and 15-17 is obvious. An additional similarity appeared in comparison of the closure of the cyclohexenyl-substituted radical 21 and dienone 22. The radical furnishes 1,5 and 1,6 products in the ratio 1.2, while we found that photocyclization of 22 to 23-25 gives a 1,5/1,6 ratio of 3.2. Evidence strongly indicating that in the photochemical reaction the effect of C(5) substitution is also primarily steric came from irradiation of the 5-*tert*-butyl analog 26. This yielded 9% of 27 (1,5) and 82% of 28 (1,6). The results with 11, 15, and 26 are summarized in Table 1.

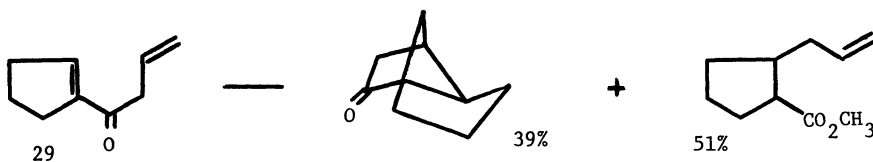
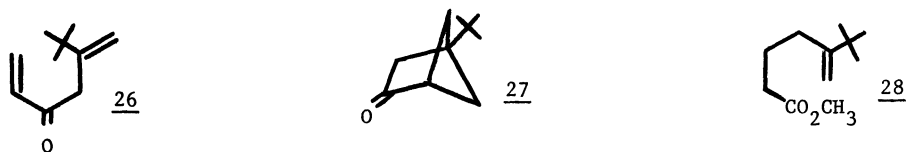
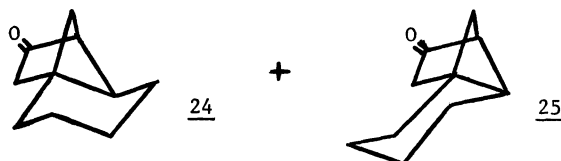
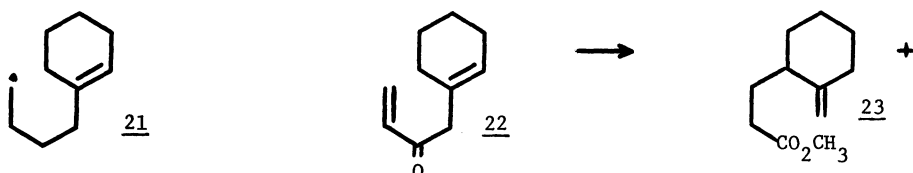


In examining our second question, the cause of the difference in behavior between 11 and its cyclic analog 8, we studied the photochemistry of ketone 29. Despite the absence of alkylation at C(5), irradiation of 29 gave similar amounts of 1,5 and 1,6 cyclization products.

TABLE 1. Effect of C(5) substitution in 1,5-hexadien-3-ones

C(5)-substituent in 1,5-hexadien-3-one		Ratio, 1,5 to 1,6 cyclization
H	(15)	>99 : 1
CH ₃	(11)	65 : 35
(CH ₃) ₃ C	(26)	10 : 90

Incorporation of the conjugated double bond into a five-membered ring is sufficient to cause a significant shift to 1,6 cyclization. The homologous acylcyclohexene shows this same shift to 1,6 closure, but to a much reduced extent. Comparing the behavior of 8 and 29, we conclude that this ring effect is roughly additive with the C(5) substituent effect. These



investigations then answered qualitatively the questions initially posed by the failure of 8 and 11 to follow the "rule of five." We shall return to the nature of this ring effect later, but first we consider the photochemistry of 1- and 2-acyl-1,5-hexadienes.

1-ACYL-1,5-HEXADIENES

We were particularly interested in extending our study to alkyl-substituted 1-acyl-1,5-hexadienes (13) because in these compounds the carbonyl group is formally moved from its position in 1,5-hexadien-3-ones (12) to the other end of the conjugated double bond. That is, in 12 C(1) is the β -carbon atom of an enone, but it has become the α -carbon in 13. An important unsettled issue in the intermolecular [2+2] photocycloaddition reaction between enone and alkene concerns the factors that control the relative orientation of the two addends. One point frequently discussed is whether initial bonding of the alkene occurs selectively to the α - or β -carbon atom of the enone (7, 14, 15). The intramolecular reactions under discussion here are closely related to this intermolecular process, and a

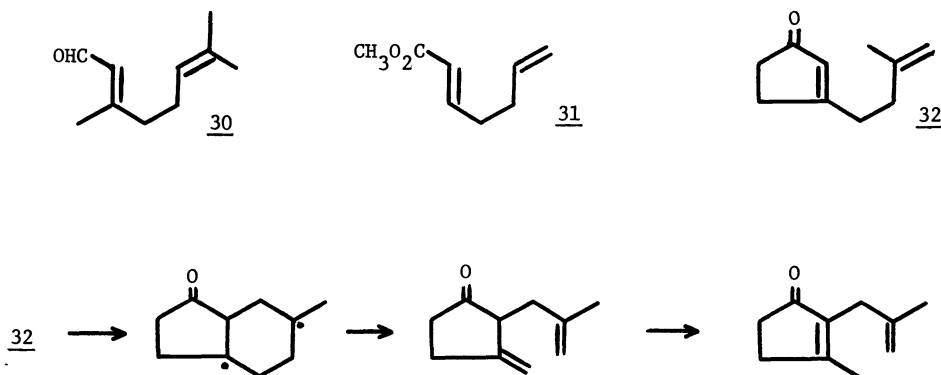
comparison of the photochemistry of representatives from series 12 and 13 should reveal whether reversal of the polarity of the enone double bond influences the regiochemistry of these transformations.

TABLE 2. Photoproducts from 1-acyl-1,5-hexadienes

Substrate	Ratio, 1,5/1,6	1,5 Products	1,6 Products
	22:78	 5% 8%	 17% 30%
	74:26	 20% 49%	 22% ~2%
	13:87	 11%	 76% <2%
	10:90	 7%	 56% 8%
	only 1,6		 84% 4%

There are numerous examples of operation of the "rule of five" in 1-acyl-1,5-hexadienes. Perhaps the best known is citral (30), which closes only 1,5 to form a biradical that collapses, disproportionates, or undergoes a formyl shift, depending on the temperature of photolysis (16). The simplest representative of this series for which photochemical studies have been reported is the 1-carbomethoxydiene 31; acetone-sensitized photolysis of this ester yields the epimeric 5-carbomethoxybicyclo[2.1.1]hexanes indicative of 1,5 cyclization (17). With these and other examples supportive of the "rule of five" in mind, and in light of our experience with 1,5-hexadien-3-ones sketched above, we turned immediately to examination of systems incorporating the conjugated double bond in a ring and/or possessing a substituent at C(5).

Our results with representatives of series 13 are summarized in Table 2. The enones listed as minor 1,6 products, such as 2-allyl-3-methylcyclopentenone and the corresponding cyclohexenone, are regarded as the results of 1,6 closure and fragmentation with subsequent shift of the β,γ -double bond into conjugation. This sequence is illustrated below for 3-(3-methyl-3-butenyl)-2-cyclopentenone (32).



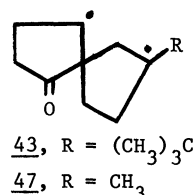
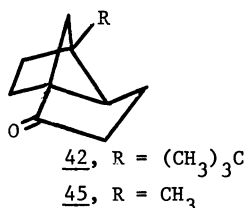
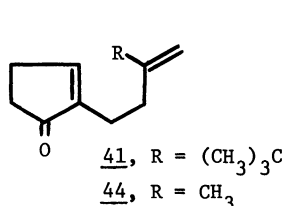
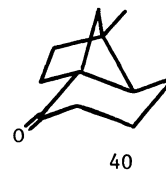
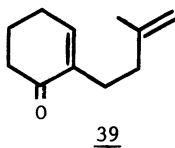
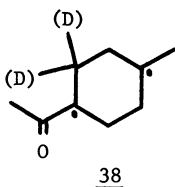
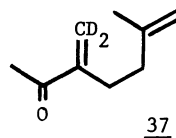
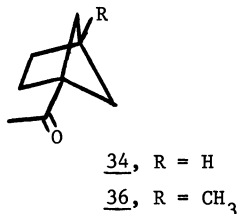
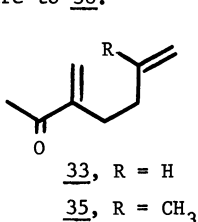
The pattern of isomerization in Table 2 demonstrates that series 13 behaves just like 12. The presence of a C(5) methyl group or a ring once again causes a shift to 1,6 closure, with a five-membered ring more effective than a six. The substrate with both a cyclopentene ring and a substituent at C(5) (32) furnishes only products of 1,6 cyclization, just as did the corresponding 1,5-hexadien-3-one (8). The reversal of position of the carbonyl group on the double bond has no effect on the regiochemistry of these reactions.

Now, most of the photoproducts from 12 and 13 that we have designated "1,5 products" are derivatives of bicyclo[2.1.1]hexane and, as such, have two new carbon-carbon bonds, C(1) to C(5), and C(2) to C(6). There are two observations strongly suggesting that in all these isomerizations the initial bond is indeed formed C(1) to C(5) and not C(2) to C(6). In the first place, in appropriately substituted compounds there are also obtained disproportionation products (as from both 16 and 30), where only one new carbon-carbon bond exists. In most cases this bond is C(1) to C(5); analogous products with a single new C(2) to C(6) bond are unusual and are formed only in quite low yield. Second, the steric effect of an alkyl substituent at C(5) (Table 1) is readily interpretable only if the initial bonding is either 1,5 or 1,6. Initial 2,6 bonding seems to occur only rarely in 12 or 13. Our conclusion above that the regiochemistry of these processes is insensitive to reversal of the enone double bond then is tantamount to stating that it is immaterial whether C(1) be the α (13) or the β (12) carbon atom of an enone for initial bonding to occur at this site. Insofar as these findings with 12 and 13 are relevant to the intermolecular [2+2] cycloaddition reaction, they suggest that initial intermolecular bonding can also occur at either position of the conjugated double bond. This conclusion is in agreement with some of the evidence from direct study of the intermolecular reaction (7, 14, 15). We shall see shortly, however, that the third group of dienones under discussion here appears not conform to this pattern.

2-ACYL-1,5-HEXADIENES

Rather fewer members of this third class, the 2-acyl-1,5-hexadienes (14), had been the subject of prior investigation. In an earlier examination of the photochemistry of α -methylene ketones in our laboratory Cormier had found that, although direct irradiation of 33 leads largely to hydrogen abstraction, triplet sensitization gives only the bicyclo[2.1.1]hexane 34 (18). A few other examples were known to us, all in accord with the "rule of five." Seeking evidence for the steric effect delineated above, we examined first the simple C(5)-methyl derivative 35. In contrast to our previous experience, however, the only product was 36; the methyl group had caused no shift to 1,6 closure. This unanticipated result led us to prepare and irradiate the deuterated substrate 37, on the hypothesis that perhaps the bis-tertiary biradical 38 resulting from the expected 1,6 closure was too hindered to proceed to

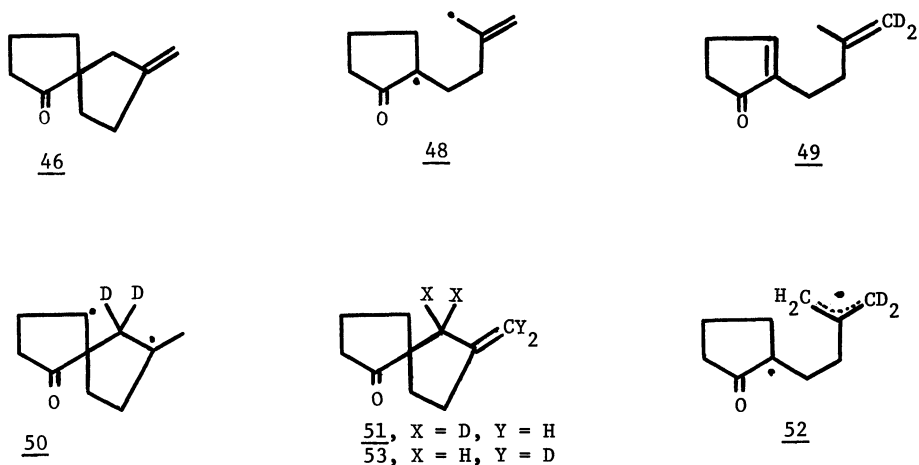
products and merely reverted. If this were correct, the reversion should scramble the label of 37, since apart from the label 38 is a symmetrical species. Irradiation to partial conversion of the deuterated ketone and recovery of starting material yielded 37 with the label intact. No scrambling had occurred; there was no evidence for reversible, non-productive 1,6 closure to 38.



We next incorporated both a C(5) substituent and a six-membered ring in the substrate. Direct irradiation of cyclohexenone 39 gave a small amount of hydrogen abstraction (~7%) and the "rule of five" product 40 in 71% yield. It appeared then that neither of the rules established in the two earlier series of dienones holds for these 2-acyldienes. A most dramatic illustration of this divergence came from the photochemistry of 41. Here both a five-membered ring and a C(5) *tert*-butyl group are present. Nonetheless, the only volatile photo-product found (37%) was 42. The low yield and formation of an unusually large proportion of polymeric material is not surprising, since this reaction requires over one week's irradiation under conditions giving complete conversion of substrate from series 12 or 13 in about two days. This slow rate of reaction was typical of the series 14 ketones.

This invariable regiochemistry and generally slower reaction of the 2-acyl-1,5-hexadienes strongly suggest that we have encountered some mechanistic difference here. The simplest explanation in accord with our observations is that for these compounds the initial bonding must occur from C(2) to C(6), rather than C(1) to C(5) as we discussed above for the other classes of dienones. This provides the necessary rationalization for formation of 42. If the first bond made is C(2) to C(6) (see 43), then no change of regiochemistry is expected on substitution at C(5). For some time we believed that the photochemistry of 44 provided independent evidence to support this hypothesis of 2,6 closure. In addition to the expected [2+2] product 45 (50%), photolysis of 44 furnishes ~6% of spiroketone 46. Since a plausible pathway to 46 is 2,6 closure to 47, followed by disproportionation, this minor product appeared to offer direct evidence for this mode of cyclization. We were cognizant, however, of an alternative mechanistic pathway to 46. Transfer of hydrogen from the side chain methyl group to the β -carbon atom of cyclopentenone 44 would give biradical 48, and this could collapse directly to 46. Such intramolecular abstractions in cyclopentenones are well documented (19). It is true that they are disfavored when a seven-membered cyclic transition state is required (20), as would be the case here, but 46 was found in only low yield. If this hydrogen abstraction is responsible for 46, then the spiroketone is only an irrelevant concomitant of 45, and its formation contributes nothing to our problem. For this reason we felt obliged to probe the origin of 46 with some care. This we did through photolysis of the deuterated cyclopentenone 49. Direct 2,6 closure of 49 would lead to biradical 50 and thence 51. On the other hand, a hydrogen abstraction mechanism would furnish the allylicly delocalized biradical 52, which then could close to a mixture of 51 and 53. In the event 49 was

isomerized to an approximately equal mixture of 51 and 53. Both the deuterated 45 formed simultaneously and also the recovered starting ketone 49 were cleanly labeled, indicating that scrambling of deuterium took place specifically in formation of the spiroketone. Thus, contrary to appearances, the isomerization to 46 does not provide support for the hypothesis



of initial 2,6 cyclization in the [2+2] products of this series. We continue to favor this explanation for the photochemistry of 2-acyl-1,5-hexadienes, but it requires independent experimental verification.

MEASUREMENT OF QUANTUM YIELDS

In Table 3 are recorded quantum yields for product formation from several of these ketones. They were measured at ~ 313 nm, using the known conversion of valerophenone to acetophenone as a chemical actinometer (21). Ketones 8, 32, and 44 represent the three different series of dienones under investigation; they share a common carbon skeleton and differ only in location of the carbonyl group. The similarity of structure should minimize steric effects in these three ketones. The lower quantum yield for 44 once again suggests a fundamental difference in the 2-acylhexadiene series. Comparison of 32 and 46 indicates that the regiochemical effect of the C(5) methyl group is referable largely to a five-fold increase in quantum yield for 1,6 cyclization. Similarly, the data for 32 and 45 show that the increased regioselectivity imposed by a five-membered ring in comparison with its six-membered homologue is accompanied by a small decrease in quantum yield. The cyclohexenone is both less selective and more efficient.

DISCUSSION

Examination of these dienones has permitted us to formulate three rules that amplify the long standing "rule of five" in predicting the photochemical behavior of 1,5-hexadienes.

Rule 1: For 1,5-hexadien-3-ones (12) and 1-acyl-1,5-hexadienes (13) substitution at C(5) causes a shift from 1,5 (crossed) to 1,6 (straight) cyclization. This is a steric effect and the larger the alkyl substituent, the greater the shift to 1,6 closure. Alkyl substitution elsewhere in the hexadiene has no comparable effect. The situation appears similar to that already studied in depth for alkyl substitution in 5-hexenyl radicals (13).

Rule 2: Incorporation of the conjugated double bond of 12 or 13 into a five-membered ring causes a shift from 1,5 to 1,6 cyclization. A six-membered ring has a similar but reduced effect. In view of the steric effect just discussed, it is natural to inquire whether this ring effect also has a counterpart in the chemistry of 5-hexenyl radicals. The behavior of 2-(3-butenyl)cyclohexyl (54) was already on record (22), and the six-ring radical undergoes overwhelming 1,5 (98%), rather than 1,6, closure. If there is any parallel with dienone photochemistry, the corresponding cyclopentyl radical 55 would have to show a dramatic shift to 1,6 cyclization. We found, however, that this was not the case; cyclization of 55 was even more selective than 54 for the 1,5 mode. The only cyclization products obtained were isomeric 2-methylbicyclo[3.3.0]octanes (56), with an upper limit of $\sim 0.5\%$ for the unobserved 1,6 products (perhyrindanes) (23). The photochemical ring effect has no analogy in the behavior of 5-hexenyl radicals. It presumably reflects a steric requirement for overlap in the initial 1,5 or 1,6 bonding, taken together with the geometry of the excited state of the

TABLE 3. Quantum yields for products

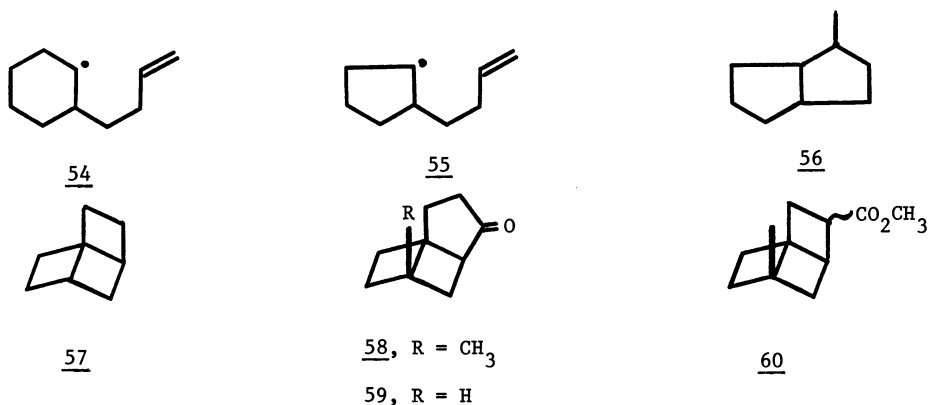
Substrate	Product, quantum yield	
<u>8</u> 	 0.59	
<u>32</u> 	 0.34	
<u>44</u> 	 0.055	
<u>45</u> 	 0.067	 0.48
<u>46</u> 	 0.010	 0.076

enone. Although there has been discussion of this geometry (15, 24), there is no clear agreement or definitive information on this point yet available. It is well known that incorporation of an enone double bond in a ring can introduce constraints on the geometry of the triplet that are responsible for alteration of excited state reactivity (25).

Rule 3: The effects just described do not influence the regiochemistry of photocyclization in 2-acyl-1,5-hexadienes (14). The "rule of five" is followed in a reaction that is relatively slow. The quantum yield is about an order of magnitude lower, and the available evidence suggests that initial bonding in this series is 2,6.

We have limited our attention here to alkyl and cycloalkyl derivatives of three classes of ketones related to 1,5-hexadienes and have avoided substituents that would introduce major inductive or electronic effects. We have been able to codify the behavior of these simple compounds under three straightforward rules. Nonetheless, a picture of some subtlety and complexity emerges, and it is apparent that even these simple dienones are not free of mechanistic complications.

In closing we note that incident to our photochemical survey is the very simple preparation of several new tricyclic ring systems incorporating either a bicyclo[2.2.0]- or a bicyclo[2.1.1]hexane. Virtually nothing is yet known about these new structures in detail, although



we have exploited one such series to provide convenient access to tricyclo[4.2.0.0^{1,4}]octane (57) and some of its derivatives (26). Tricyclic ketones 58 and 59 are the major photo-products from cyclopentenone 32 and its desmethyl lower homologue (Table 2). Ring contraction of 58 through Wolff rearrangement of the derived α -diazoketone furnished epimeric esters 60. Similarly, 59 had previously been transformed through ring contraction and subsequent decarboxylation into the parent hydrocarbon 57 (27).

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